Basic Study on a Lower-energy Defibrillation Method Using Computer Simulation and Cultured Myocardial Cell Models

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***Abstract*—Computer simulation and myocardial cell models were used to evaluate a low-energy defibrillation technique. A generated spiral wave, considered to be a mechanism of fibrillation, and fibrillation were investigated using two myocardial sheet models: a two-dimensional computer simulation model and a two-dimensional experimental model.**

A new defibrillation technique that has few side effects, which are induced by the current passing into the patient's body, on cardiac muscle is desired. The purpose of the present study is to conduct a basic investigation into an efficient defibrillation method. In order to evaluate the defibrillation method, the propagation of excitation in the myocardial sheet is measured during the normal state and during fibrillation, respectively. The advantages of the low-energy defibrillation technique are then discussed based on the stimulation timing.

I. Introduction

VENTRICULAR fibrillation is a condition that is marked by unsynchronized contraction of cardiac muscle cells, which causes the heart to cease pumping blood. The most reliable treatment for ventricular fibrillation is electrical defibrillation, during which a large current is delivered to the cardiac muscle through paddles. However, sufficiently strong defibrillation shocks can cause temporary or even permanent damage to the heart, including myocardial necrosis, and burns to the surface of the body. Therefore, a less invasive method of defibrillation shock is desired.

In a recent study, a spiral wave was considered as a mechanism of fibrillation. Fibrillation is considered to be generated by breakups, fusions and disappearances of spiral waves.

II. Purpose

The purpose of the present study is to perform a basic investigation into an efficient defibrillation method using computer simulation and experimental models. Due to the complicated multi-layer structure of the heart, evaluation and estimation of low-energy defibrillation methods are difficult. In order to remove the multi-layer elements from the structure of the actual heart, two myocardial sheet models (a computer simulation model and a cultured myocardial cell model) are developed as two-dimensional models. The mechanism of generation/disappearance of fibrillation was investigated in the myocardial sheet models, and an efficient defibrillation method was considered by changing the stimulation timing.

In processing the computer simulation, electrocardiograms (ECGs) were obtained from the calculation results of potential propagation, and the characteristics of cell excitation were then evaluated on the basis of the excitation vector on a myocardial sheet.

Although a number of studies have examined the mechanism of fibrillation based on the spiral wave theory, an efficient defibrillation method using both computer simulation and cultured myocardial cell models has not yet been reported.

III. Methods

A. Computer Simulation Model

1) Spiral Wave Reentry Simulation

Computer simulations were performed using the two-dimensional FitzHugh-Nagumo (FHN) model. The FHN model is able to represent the vibratility and excitability properties of cardiac cells.

When the interaction is homogeneous and the cells have isotropic conduction properties, as defined as following equation:

$$\frac{dx_{ij}}{dt} = c\left(y_{ij} + x_{ij} - \frac{x_{ij}^{3}}{3} \right) + z_{ij} + g\sum_{ad=1}^{4}\left(x_{ad} - x_{ij} \right) \quad (1)$$

$$\frac{dy_{ij}}{dt} = \frac{\left(-by_{ij} + a - x_{ij} \right)}{c} \quad (2)$$

where i and j indicate the locations of cells in two dimensions, x_{ij} is the magnitude of the action potential of a cell (negative indicates depolarization of the cardiac cell), y_{ij} is a refractory variable, x_{ad} is the magnitude of the potential of adjoining cells, a, b, and c are parameters, z_{ij} indicates the exterior stimulation, and g is the coupling constant with adjoining cells.

A rectangular waveform with a pulse duration of 0.7 was used for defibrillation. Stimulation was applied with increasing x and y coordinates.

Moreover, Z is the magnitude of stimulation for

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defibrillation, as expressed by following equation:

$$Z = -z - \left(\frac{j}{20} \right) (3)$$

where j is the row number and z is a constant.

The excitability condition ($1-2b/3<a<1$, $0<b<1$, $b<c2$, $0<c$) was used. Here, $a=0.7$, $b=0.8$, $c=5.0$ and $g=6.25$ were selected as the standard parameters in the model. Moreover, 98×98 cells coupled with each other around the four cells were assumed as the myocardium sheet. The term "cell" does not indicate an actual myocardial cell but rather the unit volume of the myocardium [1].

A spiral wave was generated by the cross-field stimulation technique. A conditioning planar wave was initiated by a stimulus *S1* ($5.5< T <7.0$) applied to the entire bottom border of the array. A premature planar wave stimulus *S2* ($25.0< T <26.5$) was applied to the left half plane (i.e., perpendicular to *S1*) of the array. Here, T is the unit of time in the computer simulation. Fibrillation was induced by additional stimulation applied to the entire region when a spiral wave was generated.

2) Calculation of ECG during Fibrillation

Figure 1 shows a schematic diagram of the relative location between the myocardial sheet and ECG measurement electrodes [2], [3]. The ECGs during the spiral wave and the fibrillation were obtained using equations (4) and (5), respectively, where Φ and Φ_{in} are the electrical potentials, σ and σ_0 are the electrical conductivities, J_{in} is the current density, and r is the interelectrode distance. The ECGs of the vertical and horizontal components were obtained from two paired electrodes (E1-E4 and E2-E3), respectively. The subscript "in" indicates the inside of the myocardial sheet. The four electrodes used for measurement of the ECG, E1 to E4, as shown in Fig. 1, were placed with a certain distance r from the myocardial sheet.

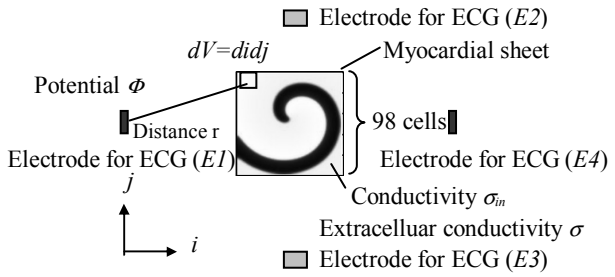


Fig. 1. Computer simulation model.

$$\Phi = \frac{1}{4\pi\sigma} \int_V \mathbf{J}_{in} dV \cdot \nabla \left(\frac{1}{r} \right) = \frac{1}{4\pi\sigma} \int_V \mathbf{J}_{in} dV \cdot \left(-\frac{\mathbf{r}}{r^3} \right) (4)$$

$$\mathbf{J}_{in} = -\sigma_{in} \nabla \Phi_{in} (5)$$

B. Myocardial Cell Model

1) Culture of the Myocardial Sheet

The cultured myocardial sheet was used as an experimental model. Ventricles were separately dissected from mice fetuses of ages between 14 and 15 days old (ICR strain). The fetal ventricles were dispersed by 0.25% trypsin. The digestion step was repeated two or three times. After centrifugation at 1,000 rpm for 5 min., the cells were re-suspended in culture medium 199, supplemented with 10% fetal bovine serum, and the pre-plated for one hour to minimize non-myocyte contamination. The remaining, un-adhered cells (mostly myocytes) were collected and seeded (approximately 3.0×10^6 cells/dish) into collagen-coated-glass-placed dishes (diameter: 30 mm). The cells were then incubated at 37°C in medium 199 supplemented with 10% fetal bovine serum under an atmosphere of 5% CO_2 and 95% air. Within three days, a monolayer sheet of spontaneously beating cells was formed [4], [5].

Spontaneous beats of cultured myocardial cells were observed approximately one day later, and a sheet was formed approximately three days after the culture was started. The extra-cellular potential and the distribution of extra-cellular potential on the myocardial sheet were measured using the measurement system described below.

A research system was developed to measure real-time electrical phenomena on myocardial sheets. This research system was composed of a printed circuit board for measurement and stimulation, a multi-channel electrical potential measurement device, and a cross-field stimulation device.

IV. Results an discussion

A. Computer Simulation Model

1) Spiral Wave Reentry Simulation

Figure 2 illustrates the generation process of a spiral wave. The figure on the right shows the action potential of one cell, and the figure on the left shows the propagation of the action potential with a gray-scaled color map, in which black indicates the state of depolarization. The magnitude of the potential in given in simulation units that can only be used in the computer simulation (not a real dimension). For the FHN model simulation under two-dimensional uniform media, the generated spiral wave was stable and continued to spin under sufficient media size. The cycle of one term was approximately T = 13. The spiral wave disappeared when the defibrillation stimulation was applied at the time indicated by "Def." in Fig. 2.

Figure 3 shows the potential propagation during fibrillation induced by additional stimulation over the entire region where the spiral wave was generated. In the model of a two-dimensional uniform media, there were no irregular disorganized patterns of fibrillation that showed chaotic extra-systole. In the wave patterns of all fibrillations, the disappearance of excitation waves was confirmed after the

defibrillation stimulation. In addition, partial disappearance of excitation waves was observed at the point of the collision between waves.

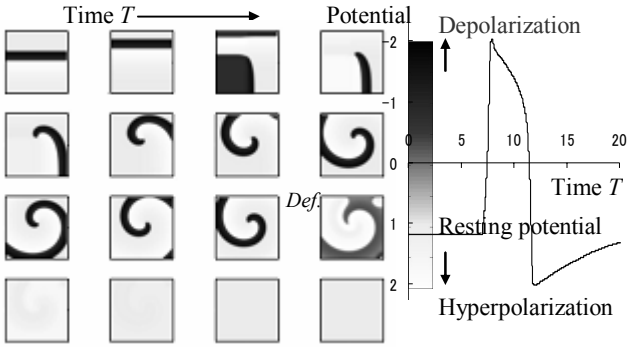
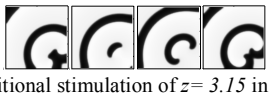
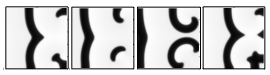


Fig. 2. Spiral wave generation and disappearance process.



(a) Additional stimulation of *z= 3.15* in *T= 58*

(b) Additional stimulation of *z= 3.0* in *T= 60*

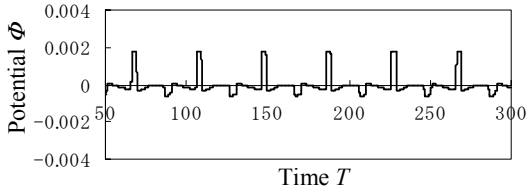


(c) Additional stimulation of *z= 3.1* in *T= 71*

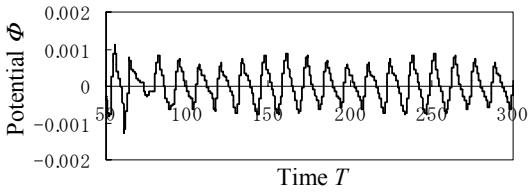
Fig. 3. Potential propagation during fibrillation for each parameter.

2) Calculation of ECG during Fibrillation

ECGs were obtained by an electrode E2-E4 placed above the myocardial sheet. ECGs are shown in Fig. 4, for a spiral wave and under normal conditions, respectively.



(a) ECG under normal conditions



(b) ECG of a spiral wave

Fig. 4. ECGs obtained through computer simulation.

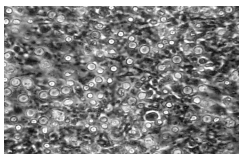


Fig. 5. Cultured myocardial sheet.

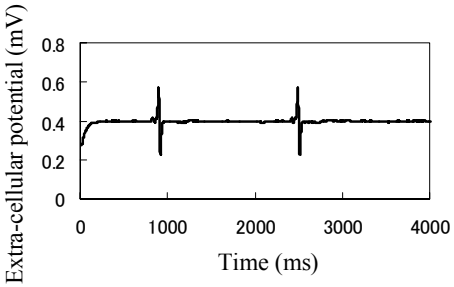


Fig. 6. Example of extra-cellular potential of myocardial cells in a channel.

B. Experimental Model

Figure 5 shows a photograph of the cultured myocardial sheet observed by a microscope with a magnification power of 400. Autonomic beats of cultured myocardial cells were observed approximately one day later, and a sheet was formed approximately three days after the culture was started. In order to eliminate inhibited muscle contraction, 2,3-butanedione monoxime (15 mM) was added one day before measurement. Figure 6 shows the measurement results of the time-dependent extra-cellular potential of one channel with moving average processing.

The extra-cellular potential propagations before and after cross-field stimulation are shown in Fig. 7. In the normal condition before cross-field stimulation, potential propagation in one direction from the initiation area of excitement was observed. There is a large difference in potential distribution after the cross-field stimulation. Due to the observation of a chaotic potential distribution, fibrillation is confirmed to have occurred on the myocardial sheet, although a spiral wave, which indicates the process of the shift to fibrillation, was not observed.

10 (ms) interval

(a) Excitement propagation in the normal state

10 (ms) interval

(b) Excitement propagation during fibrillation

Fig. 7. Example of extra-cellular excitement propagation.

C. Estimation of the Low-energy Defibrillation Method

A spiral wave was not observed after cross-field stimulation using the experimental model. Since the experimental model did not provide a sufficient result, the method was examined by computer simulation in a more detailed analysis. The plotted curve of the defibrillation threshold z for the time in the occurring spiral wave is shown in Fig.8. The upper figure shows action potential propagation

at the time when the defibrillation shock was applied. The defibrillation threshold was calculated for every time step, and the change in the threshold was confirmed periodically during fibrillation. The defibrillation shock was applied with the top-down direction. The change in the defibrillation threshold is indicated in the difference of the stimulation timing. As a result of defibrillation shock, the magnitude of the defibrillation threshold, which is the minimum energy required for successful defibrillation, undergoes a definite cycle of changes with specific time intervals. The defibrillation threshold has a cycle, which corresponds with that of the spiral wave and fibrillation. Providing a defibrillation shock to cardiac muscle at the point in time showing the minimum energy was effective.

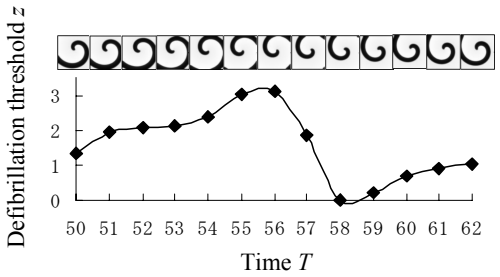


Fig. 8. Plotted curve of the defibrillation threshold for each time.

In order to determine the stimulation timing for successful defibrillation by low-energy shock, we analyzed ECGs calculated from the potential propagation of the FHN model. Two ECGs were calculated at the same time using two paired electrodes placed in the lengthwise (E2-E4) and crosswise (E1-E3) directions of the myocardium sheet, respectively, as illustrated in Fig. 1. Vectors in both directions were obtained using these electrodes, and the vector sum was defined as an excitation vector for the entire myocardium sheet. The value *n* was defined as the horizontal component subtracted from the intensity of the excitation vector. When *n* was approximately zero, the component of the electrical potential in the crosswise direction of the excitation vector was relatively large. In other words, the electrical potential component in the lengthwise direction was small and the excitation vector comes to be in the crosswise direction.

Figure 9 shows the relationship among *n*, the electrical potential component in the crosswise direction *m* (scaled on the left-hand axis), and the defibrillation threshold *Th_z* (scaled on right-hand axis) in the state of fibrillation. When *m* and *n* are small, defibrillation threshold *z* tends to be small. This suggests that the low threshold occurred when the excitation vector changed to the crosswise direction and the vector length was small. Low-energy defibrillation might be achieved by applying a defibrillation shock at the proper time, although several exceptions have been confirmed.

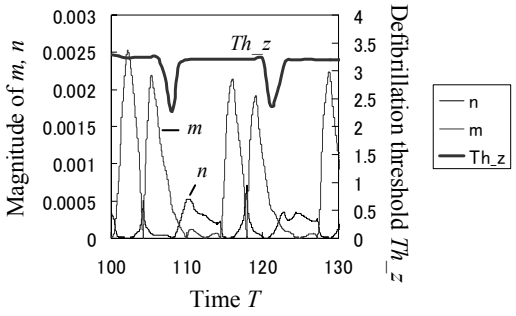


Fig. 9. ECG analysis. The Th_z curve indicates the threshold, and n and m are the magnitudes of the vertical and horizontal vectors, respectively.

V. Conclusion

A spiral wave was not observed after cross-field stimulation in the experimental model. Therefore, the cross-field stimulation method was found to require re-examination in order to determine how the stimulation interval changed. The differences in behavior between the computer simulation and the experimental models were observed during fibrillation. In the normal state, repeated pulsations of potential propagation were obtained by computer simulation and experimental models, whereas in the state of fibrillation, it was necessary to derive a more detailed correspondence in both models. However, experimental results of potential mapping were used to confirm that both models were useful in the investigation of defibrillation. According to results obtained by computer simulation, the stimulation timing for low-energy defibrillation was indicated by the calculation results of ECG. The defibrillation threshold might be replaced by the difference in stimulation timing. It is thought that the consideration of stimulation timing is one important factor in low-energy defibrillation. In addition, the three-dimensional FHN model, which has a laminated structure, must be used for further quantitative analysis.

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