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Evaluation of Cardiac Oxygen Consumption under Hypoxia with Tissue Model integrating Microcirculation Model and Cell Model

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Abstract— **Analyzing the microscopic energy balance of cardiac tissue is very important for understanding heart diseases. However, such analysis is difficult with animal experiments. Therefore, the accurate simulation model is expected to be an important tool for such research. We propose a cardiac tissue model which can reproduce accurate distribution of oxygen consumption under hypoxia. The model includes blood tissue exchange model of capillary and oxygen consumption model of cells. The capillary model is based on the model proposed by Dash et al. 2006, and the cell model is based on the model proposed by Kuzumoto et al. 2007. By analyzing the oxygen consumption of the proposed model, the relation between the oxygen consumption and the arterial oxygen concentration was found to be largely different from that of single cell model. This implies that the animal experimental data should be carefully used for constructing a biological simulation model, depending on whether the experiment is performed within a cell or a tissue.**

I. Introduction

Since the major factor of many heart diseases is considered to be the lack of the balance between the energy (ATP) production and consumption, the evaluation of energetics of heart is important for understanding the heart diseases. For example, revealing the local energy balance of the cardiac tissue under the hypoxic or anoxic condition will accelerate the development of new clinical treatment methods. However, it is difficult to measure the local tissue energetics accurately so that the computer simulations of accurate heart models are expected to be powerful tools for such research.

Myocardial cell model was first introduced by Noble et al. at 1962, followed by many improved models. One of the most accurate myocardial cell models is the model proposed by Kuzumoto et al. (Kyoto Model 2007) [1] which is based on the model proposed by Noma et al. [2]. There are many parameters in the model whose values are basically determined from experiments on cells. However, there are several parameters whose values are difficult to measure by the cell experiments. Therefore, the values are determined by estimation. One of such parameter in Kyoto Model 2007 is K_{mO} which affects the oxygen consumption under hypoxic condition. However, the oxygen consumption of a cardiac cell is difficult to measure, thus there are no reliable reports about them. In Kyoto Model 2007, the value of this parameter is determined from the organ (whole heart) animal experiment under the assumption that the oxygen consumption of the organ under the hypoxic condition is not so different from that of the single cell.

In this research, we focus on the difference between the oxygen consumption of a single cell model and a tissue model under various hypoxic conditions. We propose a cardiac tissue model which includes microcirculation model which represents substrate transport, permeation and diffusion of capillary, and multiple cell models which represent electrophysiological phenomena, excitation contraction coupling, oxygen consumption and ATP production.

II. Background

A. Cardiac Cell Model: Kyoto Model

In this research, we used Kyoto Model 2007 for the cardiac cell model which is an accurate ventricular cell model of small mammals. See [1] for the model details. The model includes accurate model of ion channels, transporters, contraction mechanism, SR, volume regulation, β stimulation system and mitochondrial oxidative phosphorylation model. By using this model, we can reproduce various physiological activities such as membrane potential, ion channel and transporter currents, excitation contraction coupling, ATP production and consumption which includes parallel activation mechanism [3].

The oxidative phosphorylation model of Kyoto Model 2007 is based on the model proposed by Korzeniewski et al. [4] which includes Complex I, III, IV, ATP synthase, ATP/ADP exchanger and proton inorganic phosphate cotransporter. The ATP production is calculated by the mitochondrial membrane potential and proton gradient generated by the activities of Complex I, III and IV.

The oxygen consumption rate V_{C_4} at Complex IV is calculated by equation (1). Note that k_{C_4} represents a rate constant, $[Cyta^{2+}]$ represents reduced cytochrome a concentration, $[Cytc^{2+}]$ represents reduced cytochrome c concentration, $[O_2]$ represents oxygen concentration of cytosol and K_{mO} is a parameter related to oxygen consumption.

$$V_{C_4} = k_{C_4}[Cyta^{2+}][Cytc^{2+}]\frac{1}{1+\frac{K_{mO}}{[O_2]}} \quad (1)$$

The oxygen consumption of Kyoto Model 2007 is calculated by multiplying the coefficient α with equation (1). This is because the mitochondrial model used in Kyoto Model 2007 is basically a model of skeletal muscle whose mitochondrial concentration is small in comparison to the cardiac muscle. The value of α is determined by which the relative NADH

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concentration fits the animal experiments reported by Jo et al. [5].

B. Microcirculation Model

In this research, we used the microcirculation (blood tissue exchange) model proposed by Dash et al. (Dash Model 2006). See [6] for the model details.

Dash Model 2006 is a model which calculates blood flow transportation, diffusion, permeation of oxygen (O_2), carbon dioxide (CO_2), H^+, HCO_3^- of red blood cell, plasma, interstitial fluid and parenchymal cell. The capillary length is 0.1[cm] and the position of x=0[cm] corresponds to the arterial side and the position of x=0.1[cm] corresponds to the venous side.

The effect of blood flow is modeled for the red blood cell and plasma in the model as follows.

$$\begin{aligned} F_{rbc} &= HctF_{bl} \\ F_{pl} &= (1-Hct)F_{bl} \end{aligned}$$

Note that F_{rbc}, F_{pl} and F_{bl} represent the volumetric flow rates of red blood cell, plasma and capillary, respectively. Hct represents hematocrit. Since hematocrit represents the volume ratio between red blood cell and the blood, F_{bl} becomes sum of F_{rbc} and F_{pl}.

The effect of diffusion of O_2, CO_2, HCO_3^- and H^+ in red blood cell, plasma, interstitial fluid and parenchymal cell are modeled. The diffusion coefficients at red blood cell, plasma, interstitial fluid and parenchymal cell are represented by D_{rbc}, D_{pl}, D_{isf} and D_{pc}, respectively. Note that the identical value is used for the diffusion coefficients for four substrates in this model.

The effect of permeation of O_2, CO_2, HCO_3^- and H^+ between the red blood cell and plasma, plasma and interstitial fluid, interstitial fluid and parenchymal cell are modeled. The permeability of each border are represented by PS_{rbc}, PS_{cap} and PS_{pc}, respectively. Note that the identical value is used for the permeability for four substrates in this model.

By binding with hemoglobin (Hb), O_2 is transported as HbO_2, since red blood cell is transported by blood flow (F_{rbc}). CO_2 produced in parenchymal cell is also transported as $HbCO_2$ by binding with Hb in red blood cell. There are detailed model of oxyhemoglobin saturation and oxygen hemoglobin dissociation in Dash Model 2006. There is also myoglobin (Mb) in parenchymal cell which buffers O_2 as MbO_2.

C. Oxygen Consumption

By consuming O_2, parenchymal cells produce CO_2. In Dash Model 2006, the simplified equation is adopted for this oxygen consumption model.

In the model, oxygen concentration change at parenchymal cell is calculated by equation (2).

$$\begin{aligned} \frac{\partial({}^oC_{pc} + C_{MbO_2})}{\partial t} &= \frac{{}^oPS_{pc}}{V'_{pc}}({}^oC_{isf} - {}^oC_{pc}) \\ &- \frac{{}^oG_{pc}}{V'_{pc}}{}^oC_{pc} + {}^oD_{pc}\frac{\partial^2({}^oC_{pc} + C_{MbO_2})}{\partial x^2} \end{aligned} \quad (2)$$

The first term in rhs is the permeation between interstitial fluid and parenchymal cell, the second term is the oxygen consumption by parenchymal cell, and the third term is the diffusion at parenchymal cell. Note that ${}^oC_{pc}$ represents oxygen concentration at parenchymal cell, C_{MbO_2} represents oxymyoglobin concentration at parenchymal cell, ${}^oC_{isf}$ represents oxygen concentration at interstitial fluid, V'_{pc} represents the conversion coefficient from the dry weight to the wet weight, x represents the position along the capillary.

The oxygen consumption of the parenchymal cell is calculated by the following equation.

$${}^oG_{pc}{}^oC_{pc} = \frac{V_{max}{}^oC_{pc}}{K_m + {}^oC_{pc}} \quad (3)$$

Here we refer to K_m of ${}^oG_{pc}$ (equ.(3)) as the oxygen consumption parameter in Dash Model 2006. The value of the parameter is 7.00×10^{-7}.

This oxygen consumption model is very simple so that the detailed analysis of the relation between the oxygen consumption and the other physiological substrates cannot be performed. To investigate further mechanism of the oxygen consumption of the cardiac tissue, the equation is replaced by the oxygen consumption equation of Kyoto Model 2007.

III. Combined Model

Here we propose a "Combined Model" which combines Dash Model 2006 and Kyoto Model 2007. These models are integrated by determining the correspondences or conversion between the variables of both models.

A. Dash Model 2006

To reproduce the oxygen consumption under hypoxic condition, we modified the oxygen consumption parameter, permeability of each border and the diffusion coefficients. The accuracy of these parameter values was considered to be not very high since sufficient experimental evidence were not provided in the paper. We used the experimental results of sheep coronary flow under hypoxia [7]. They reported that, under 70% decrease in the inspired oxygen concentration, the modest increase of the coronary flow was observed, however the myocardial oxygen consumption did not change.

We assumed that under 70% decrease in oxygen concentration, some of the myocardial cells become ischemic state with baseline F_{bl}, and by increasing F_{bl} to the 1.5 times the baseline value, every cell along the capillary became normal. By searching the parameter values exhaustively, we used $K_m = 1.00 \times 10^{-8}$ [M] for the oxygen consumption parameter, 1/2 of the original value for each permeability parameter and the diffusion coefficients were not changed.

All the other elements of Dash Model 2006 were used as in the published model for the combined model.

B. Kyoto Model 2007

All the elements described in Kyoto Model 2007 [1] was used in the cell model of the combined model. Since Kyoto Model 2007 is already validated for the hypoxic condition, only the oxygen consumption parameter K_{mO} was changed

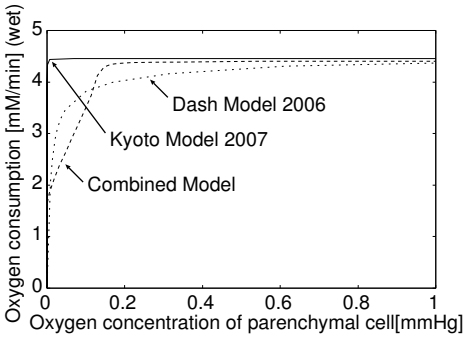

Fig. 1. Oxygen consumption of the proposed combined model, Kyoto Model 2007 and Dash Model 2006.

to 1.00×10^{-8} [M] according to the above adjustment. 51 cell models were used to calculate the oxygen consumption of each calculation point along the capillary.

C. Parameter Correspondances

The oxygen consumption of Dash Model 2006 is large in comparison to Kyoto Model 2007. Therefore, we first assumed that the external force of the myocardial cell is at around the maximum where oxygen consumption becomes near maximum. We used 60 [mN/mm^2] for the external force of Kyoto Model 2007 which is the maximum force used in the published paper. There is still a difference between the oxygen consumption of these models, thus, we applied conversion coefficient which equalizes the maximum oxygen consumption of these two models.

For Dash Model 2006, oxygen consumption becomes 4.46[mM/min] (wet) under the condition where $K_m = 1.00\times 10^{-8}$[M] and ${}^oC_{pc}$ =100[mmHg]. For Kyoto Model 2007, oxygen consumption becomes 2.30[mM/min] (wet) under the condition where $K_{mO} = 1.00 \times 10^{-8}$[M], $[O_2] = 100$[mmHg] and $forceExt$ =60[mN/mm^2].

We replaced the oxygen consumption equation in Dash Model 2006 by equation (1) in Kyoto Model 2007 with α multiplied by 4.46/2.30(=1.94).

H^+ of mitochondria plasma and cytosol are both modeled in Korzeniewski model, however, H^+ concentration of parenchymal cell is handled as constant in our model. This is one of the limitations of our model. This is because H^+ and HCO_3^- concentrations of parenchymal cell are not modeled in Kyoto Model 2007. The handling of cytosol H^+ in Kyoto Model is currently under development.

All the other variables in both models are considered in the combined model.

The simulation condition of the proposed combined model is shown in Table I.

We used simBio package [8] to calculate Kyoto Model 2007 and DynaBioS [9] to calculate Dash Model 2006. DynaBioS was also used as the distributed computation platform. All the programs were written in Java. The computation time was about 45 minutes with PC.

TABLE I

SIMULATION CONDITION OF THE COMBINED MODEL AT STEADY STATE HYPOXIA.

x=0[cm] oxygen concentration [mmHg]	red blood cell	25.0
	plasma	25.0
	interstitial fluid	10.0
	parenchymal cell	10.0
x=0[cm] carbon dioxide concentration [mmHg]	red blood cell	32.14
	plasma	32.14
	interstitial fluid	34.0
	parenchymal cell	34.0
x=0[cm] HCO_3^- concentration [mM]	red blood cell !!	19.11
	plasma	27.70
	interstitial fluid	18.02
	parenchymal cell	14.31
x=0[cm] pH	red blood cell	7.39
	plasma	7.55
	interstitial fluid	7.34
	parenchymal cell	7.24
blood flow F_{bl}[ml/min/g]		1.5
external force of Kyoto Model 2007 $forceExt$[mN/mm^2]		60.0
oxygen consumption parameter of Kyoto Model 2007 K_{mO}[M]		1.00 $\times 10^{-8}$
permeability of Dash Model 2006 [ml/min/g]		PS_{region}/2
Simulation Time (Duration)[ms]		40000
Time Step (dt)[ms]		0.1
capillary length x[cm]		0.1
Number of calculation points		51

IV. SIMULATION RESULTS

The oxygen consumption of the proposed combined model to the oxygen concentration of parenchymal cell at arterial side is shown in Fig.1. The oxygen consumption of Kyoto Model 2007 and Dash Model 2006 is also shown in the figure. The simulation condition of three models is the same as in Table I.

The oxygen consumption of the combined model is calculated by averaging the oxygen consumption of 51 cells along the capillary, and the oxygen concentration of this model is indicated by the arterial (x=0) oxygen concentration.

From the results, we can find that the oxygen consumption is largely different between the single cell model and the tissue model. Note that the oxygen consumption of combined model is similar with that of Dash Model 2006. If we measure the Michaelis-Menten constant from the simulation results, it becomes 2.22×10^{-2}[mmHg] for the combined model while it becomes 1.00×10^{-5}[mmHg] for Kyoto Model 2007.

Oxygen is consumed by the identical cell model in both combined model and Kyoto Model 2007. However, the resulting oxygen consumption curve becomes different. This implies that we have to be careful in using the published animal experimental results whether the experiment is performed with a single cell or a tissue or an organ.

The oxygen concentration and the oxygen consumption of parenchymal cell along the capillary with three different arterial oxygen concentrations (${}^oC_{rbc}$ = 11.25, 11.50, 11.75[mmHg]) are shown in Fig.2 and Fig.3, respectively. The oxygen consumption at arterial side is almost constant with the value of 4.35[mM/min] (wet). This is because the

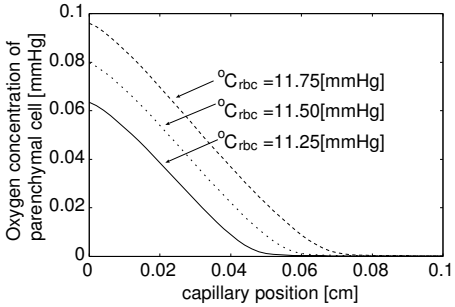

Fig. 2. The distribution of the oxygen concentration along the capillary under three arterial oxygen concentration.

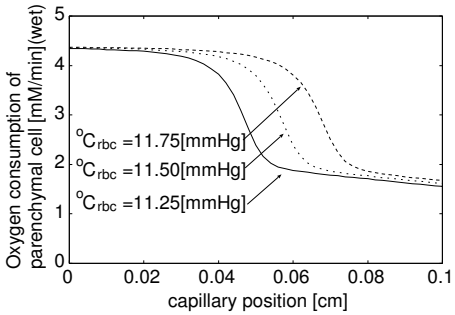

Fig. 3. The distribution of the oxygen consumption along the capillary under three arterial oxygen concentration.

oxygen is produced by Hb in the arterial side. The value decrease to a almost constant value of 1.6[mM/min] (wet) at venous side. This is because the cell cannot use oxygen if the concentration falls under this threshold.

In Fig.2, the arterial (x=0) oxygen concentration was 0.0635, 0.0797, 0.0961[mmHg] for ${}^oC_{rbc}$=11.25, 11.50, 11.75[mmHg] whose intervals are almost the same. Here, the oxygen consumption of the combined model is same to the area under the oxygen consumption curve in Fig.2. The area difference between the oxygen consumption curve for ${}^oC_{rbc}$=11.25[mmHg] and ${}^oC_{rbc}$=11.50[mmHg] is very close to that of ${}^oC_{rbc}$=11.50[mmHg] and ${}^oC_{rbc}$=11.75[mmHg]. This is the reason why the curve of oxygen consumption of the combined model to the oxygen concentration in Fig.1 is close to a linear line.

V. Conclusions

We proposed a cardiac tissue model which includes blood tissue exchange model of capillary and cardiac cell model. The blood tissue exchange model is based on the model proposed by Dash et al. at 2006 which includes transportation, diffusion and permeation of O_2, CO_2, HCO_3^- and H^+ at red blood cell, plasma, interstitial fluid and parenchymal cells. The original oxygen consumption equation was replaced by the accurate equation of cardiac cell model proposed by Kuzumoto et al. at 2007.

The results show that the oxygen consumption under different arterial oxygen concentration is largely different for the tissue model and the single cell model. This implies that we have to be careful in using the published animal experimental data whether the experiment is performed with a single cell or a tissue or an organ.

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