NUMERICAL SIMULATION OF OXYGEN TRANSPORT BASED ON MICROVASCULAR NETWORKS IN RAT CEREBRAL CORTEX: EFFECTS OF CEREBRAL BLOOD FLOW REDISTRIBUTION ON TISSUE OXYGENATION

Tomoko Negishi[1], Kazuto Masamoto[1], Tetsuro Omura[1],
Naosada Takizawa[2], Hirosuke Kobayashi[3],
Kazuo Tanishita[4]

1 Department of Science and Technology，Keio University，Yokohama, Japan
2 Center of Information Science, Kitasato University, Sagamihara, Japan
3 Department of Medicine, Kitasato University School of Medicine, Sagamihara, Japan
4 Department of System Design Engineering, Keio University, Yokohama, Japan

INTRODUCTION

Brain activity consumes large quantity of oxygen. On the other hand brain is very vulnerable to lack of oxygen. Then adequate supply of oxygen by cerebral blood flow is needed for the maintenance of brain function. Additionally, cerebral blood flow is regulated locally to meet oxygen demand at the activated area , because brain activity takes place in micro region which is called column, 200-650 micron diameter [1].Therefore Po2 is determined on the local spot by the balance between cerebral metabolic rate of oxygen ($CMRO_2$) and supply oxygen from micro blood vessels tied related to rCBF. So, understanding the mechanisms of these regulations are very important to avoid the disturbance in brain function for hypoxia.

Nowadays various measuring instruments are developing - fMRI , NIRS, PET, and excessive increases in rCBF of 30-50 % have been demonstrated beyond increases in $CMRO_2$ of 5% in human visual cortex [2]. However, the physiological reasons of these mismatchings are still obscure. Additionally CBF is known to increase rapidly when Po2 in arteriole is below 50 mmHg [3]. Actually, hypoxia raised rCBF by 69 +/- 7 % in rat cortex [4].

So far the main site of oxygen supply to tissue is believed in capillaries with higher density, but recently there are many researches which discussed precapillary oxygen loss [5]. Then arteriole may play an important part in oxygen supply to tissues as well as capillaries. It means that that microvascular arrangement including arterioles and capillary networks affects Po2 distribution in tissue largely.

In this study, we mathematically analyzed O_2 delivery from micro vessels to tissue based on microvascular networks in rat cortex. The aim of this study is follows.

(1) Examine how $CMRO_2$ and rCBF effect on tissue oxygenation.
(2) Estimate the role of redistribution of rCBF to recover the hypoxic region after hypoxia.

METHODS

model geometry

At first, we got the CT images of arterioles in rat cortex. (SKYSCAN1072, TOYO TECHNICHA), then reconstructed 3d image (3D-Doctor, Able Software Corp). And we validated the intervals between arterioles. Next we observed geometry of microvessels and capillary density in each cortex layers by confocal laser scanning microscopy （Oz, Noran . We constructed simulation model (300 × 400 × 300 $micron^3$) based on these data. The following are the geometrical parameters of upper layers model (I-Ⅲ layer) .

arteriolar diameter : 38 micron
capillary diameter : 5 micron
capillary length density (mm / mm^3_tissue)
0-100 micro-m (I layer) : 250 , 100-300 micro-m (Ⅱ-Ⅲ layer) : 600

Now there is no anastomoses between capillaries and arteriole in the upper layer model , because most of precapillaries' brunches occurred from middle layer according to confocal laser microscopy images.

Then we meshed each 5 micron position in arteriole and tissue, each 2 micron position in capillary by meshing soft (GAMBIT, Fluent Inc).

OXYGEN TRANSPORT

The transport equations are represented as follows.

In blood

$$\frac{\partial Po_2}{\partial t}+u\frac{\partial Po_2}{\partial x}+v\frac{\partial Po_2}{\partial y}+w\frac{\partial Po_2}{\partial z}=\mathrm{Deff}\,\alpha_b\left(\frac{\partial^2 Po_2}{\partial x^2}+\frac{\partial^2 Po_2}{\partial y^2}+\frac{\partial^2 Po_2}{\partial z^2}\right) \quad (1)$$

In tissue

$$\frac{\partial Po_2}{\partial t}=D_t\alpha_t\left(\frac{\partial^2 Po_2}{\partial x^2}+\frac{\partial^2 Po_2}{\partial y^2}+\frac{\partial^2 Po_2}{\partial z^2}\right)-M \quad (2)$$

Basic parameters

Deff = 6.47e-05 cm^2/s | maximal value at Po_2 20mmHg
| effective O_2 diffusion coefficient in blood reflecting oxyhemoglobin dissociation curve |

D_t = 1.5e-05 cm^2/s
| O_2 diffusion coefficient in tissue |

α_t , α_b = 3e-05 cm^3_O_2/ml/mmHg
| O_2 solubility coefficient in tissue and in blood |

M = 2.1 〜 4.8 cm^3_O_2/100g_tissue/ min | $CMRO_2$|

Boundary conditions and model assumptions

1. Oxygen flux matches at interface between vessels and tissue.
2. Oxygen is consumed only in the simulation model.
   It means Po_2 gradient is 0 at the end of the tissue.
3. Oxygen consumption in cortex surface (0 〜 100 micron deep) is 0.
4. There is no capillary recruitment when acute hypoxia .
   Thus oxygen delivery is only increased by increasing velocity of microvessel perfusion.
5. Po_2 is 100 mmHg at arteriolar inflow and 50 mmHg at capillary inflow under normal condition, and 45 mmHg, 30 mmHg during hypoxia respectively.

Result and discussions

Po2 contours

We showed the Po2 contours at the center of upper layer model in physiological condition (Fig.1). Po2 declined gradually in the direction of depth and near the end of tissue. These indicates that the distance from arteriole dominates the general distribution of Po_2, and Po_2 continues to reduce until the area with high capillary density. Our previous research [6] found that Po2 falls steadily from cortex surface to middle of layer Ⅲ (350 micron).

Estimate of changes in CBF necessary to increase $CMRO_2$

(1) Normal condition

The relative changes of total supply of oxygen from microvessels (JO_2(cm^3 / s)) related to $CMRO_2$ and CBF were shown in Fig.2. Though JO_2 increased slightly as upgrade of $CMRO_2$ without change of CBF, the increase of JO_2 couldn't meet with the increase of $CMRO_2$. This suggests the importance of redistribution of CBF. Here CBF in arteriole increased (30 % in total CBF), and JO_2 increased 13 % on the average at each CMRO2. Subsequently CBF in capillary networks increased (100% in capillary networks, 2% in total CBF), then JO_2 increased 23 % on the average. In this case, the increase of $CMRO_2$ up to 40% was supported by redistribution of arteriole and capillary networks. These imply that an increase in capillary CBF is very available for upper layers. Presumably much oxygen in arteriole must be transported to the middle layers with higher neuron activity and $CMRO_2$. So upper layer needs the redistribution of capillary networks which come from adjacent columns or return to surface from middle layer.

(2) During hypoxia

The change of JO_2 (cm^3/s) during hypoxia was showed in Fig.3. It shows relative change from standard value in Fig.2. Here, large drop of JO_2 during hypoxia was found. It was only 20〜56% of standard point. And low Po_2 area (< 5mmHg) appeared at CMRO2 ratio >2. JO2 also increased as CBF increased, but with smaller rate than normal condition. These results indicate that quick recovery of erythrocyte concentration is essential. If it is impossible because of critical condition, reducing $CMRO_2$ should be considered as a mean to improve tissue oxygenation.

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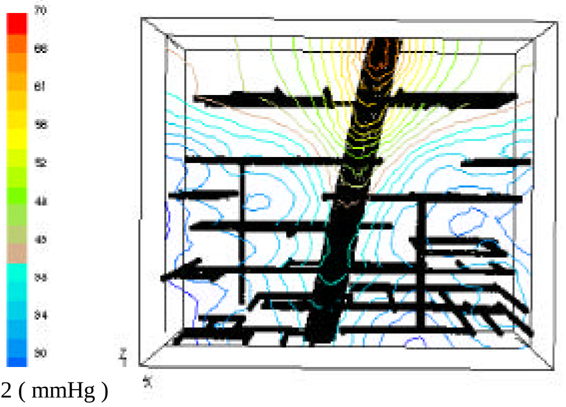

Figure 1. Counter of Po_2

$CMRO_2$: 2.1 cm^3 /100g/min,
CBF : 12.1 cm^3 /cm^3 _tissue/ min in arteriole
: 0.317 cm^3 /cm^3 _tissue/ min in capillary networks

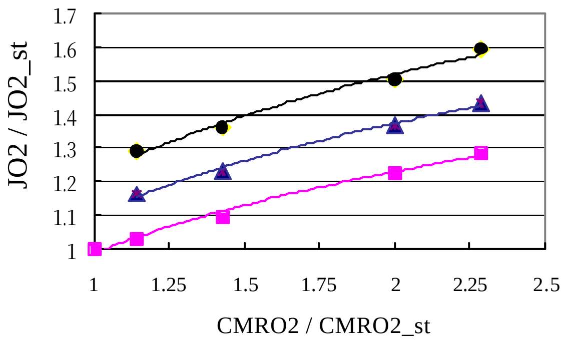

Figure 2. Relative change of $CMRO_2$ and JO_2

JO_2_st, $CMRO_2$_st : standard value at $CMRO_2$ and CBF control point

■ : CBF control , ▲ : CBF in arteriole 30%up, ● :CBF in capillary networks 100%up (2% up totally , so 32 % up together with arteriolar increase)

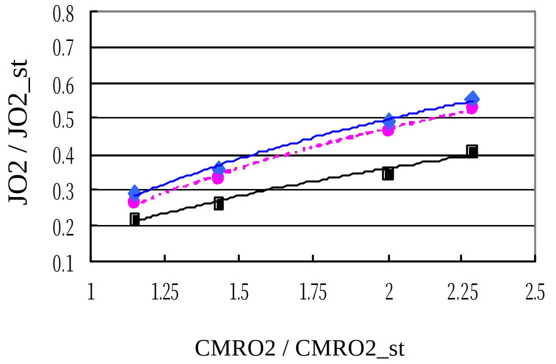

Figure 3. Relative change of $CMRO_2$ and JO_2 during hypoxia

■ : CBF control, ● : CBF in arteriole 30%up and 100%up in capillary network , ◆ : CBF in arteriole 50%up and 167%up in capillary network