Diffusion Tensor Imaging reviles the evolution of Neuronal Cell Membrane Damage in Stroke Patients: A Simulation Study

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INTRODUCTION: At acute ischemic stroke, a reduction of the apparent diffusion coefficient (ADC) has been attributed to the following reasons; migration of water from extracellular space into intracellular space [1, 2], decreasing membrane permeability cased by collapse of transmembrane ion gradients [3], decreasing in energy-dependent cytoplasmic circulation or increasing in water viscosity [4, 5, 6], and cell swelling [6, 7]. The eigen values ($\lambda1>\lambda2>\lambda3$) of diffusion tensor matrix, which are obtained from the diffusion tensor magnetic resonance imaging (DT-MRI) represents a condition of water molecule diffusion in a voxel. We postulated that the eigen values in patients with acute brain infarctions will reflect specific condition/environment of the water molecule's in pathologic condition. Especially, we supposed that the transverse eigen values ($\lambda2$, $\lambda3$) will decrease due to failure in membrane transportation. Accordingly, we constructed a numerical diffusion model of a normal brain tissue and acute brain infarct at tightly packed white matter bundle, and simulated water molecule diffusion in the simple tube model by using random walk algorithm [8].

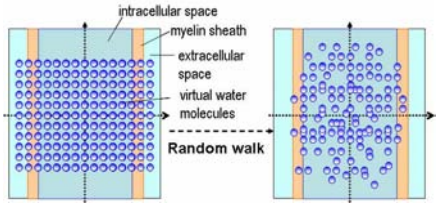

Figure 1. The simple tube model and random walk of virtual water molecules

METHODS: We propose a two pools tube model as a simulation model based on Szafer et al [8]. Figure 1 shows the proposed model. In our model, water molecules exist in two pools, namely the intracellular space and extracellular space. We choose the system parameters for our proposal model as follows: a; inner diameter of intracellular space [μm], l; size of extracellular space [μm] for one axon, θ; random walk angle. The length of axon was unlimited. Since myelin sheath is a hydrophobic membrane, we controlled the water molecular thoroughfare by its velocity and the position of the pores. The pore's positions were assumed by permeability parameter p_{ie}, p_{ei}, and p_{ex}. The p_{ie} and p_{ei} indicate that virtual water molecule permeable percentage toward intra- to extra-cellular spaces and extra- to intra-cellular spaces, respectively. The p_{ex} indicates permeable percentage among cellular space. At the onset, inner diameter of intracellular a will be increased to a' by swelling (Figure 2). The virtual water molecules were regularly and discretely set in the two pools model initially. Then the molecules move along the θ at each time step. We assumed that the thickness of myelin sheath does not change before and after onset. The extracellular space is decreased by cell swelling and the migration of water molecules are limited by decreasing membrane permeability.

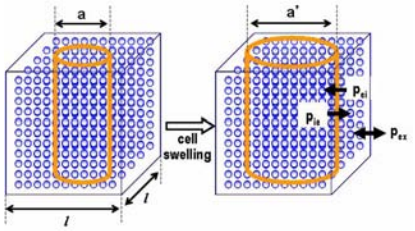

Figure 2. Inner diameter changes by cell swelling after onset

We calculated diffusivity of virtual water molecules by averaged displacement of direction to parallel ($\lambda1$) and to perpendicular ($\lambda2$, $\lambda3$) to the axon. We also calculated ADC, fractional anisotropy (FA) by using formally mentioned $\lambda1$, $\lambda2$ and $\lambda3$ as eigen values of the diffusion tensor. In our proposal model, we used the random walk parameters as follows [8, 9]: δt; one time step 5.0 [μm], vi; diffusion speed in intracellular space 1.0 [μm/μsec], ve; diffusion speed in extracellular space 2.50 [μm/μsec], p; permeability parameter 20.0 [%].

Table 1. Results of simulation

Status quo	diameter	FA	ADC	$\lambda1$	$\lambda2$	$\lambda3$
normal	6	0.45	1.17	1.83	0.84	0.84
onset	12	0.62	1.00	1.83	0.59	0.59

RESULTS AND DISCUSSION: Table 1 shows the results of cell swelling (a=6 [μm] , a'=12 [μm]) and decline in membrane permeability. We limited the permeability for myelin sheath only after the onset of ischemia. We set $p_{ie} = p_{ex} = p_{ei} = 20$ [%] at the normal case and $p_{ie} = p_{ex} = 0$ [%], and $p_{ei} = 20$ [%] at the onset case. From this Table, we can see the decrease in $\lambda2$, $\lambda3$, and ADC. The $\lambda1$ on the other hand remained as a same value. As a result, the FA was slightly increased. This result is in accordance with the data of Green et al [10] (FA value increases in an acute stroke (<27 hours old)). The ADC reduction can be easily understood from as the reduction in the $\lambda2$ and $\lambda3$ due to the restriction on membrane permeability.

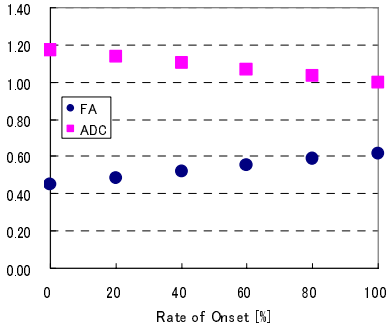

Figure 3. Results of permeability failure evolution

Figure 3 shows the simulation results of the evolution in number of axons with membrane failure. The results of this figure were obtained from interpolation between the normal condition (number of abnormal fibers = 0%) and complete infarct (number of abnormal fibers = 100%).Benveniste et al. have reported that the shift of water from extra- to intra-cellular space occurs within 2 minutes when there is breakdown of the Na^+, K^+-ATPase pump [11]. This report suggests that the evolution of FA and ADC are not caused by gradual change in the cellular diameter (swelling) of all axons within a voxel over several hours, but rather it is the change in ratio of axons that degenerate over time. Thus, we assumed that abnormal cell ratio within a voxel will directly affect the evolution of FA and ADC.

CONCLUSION: We used the following three elements for our simulation model: 1) membrane permeability, 2) cell swelling, and 3) evolution of 1) and 2). We simulated the virtual water molecule diffusion in a stroke by using the two pools simple tube model. From our simulation study, we can understand that one of the reasons for ADC reduction and slightly increase of FA at the acute stage of brain infarction occurs by change in membrane permeability and population of the axons that are affected.

In this paper, we have tried to estimate the situation using limited set of parameters and events. As future works, we are planning to investigate more parameters including the edema and viscosity of the lesion.

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