Chapter 30
Physiological Mechanism of Increase in Deoxyhemoglobin Concentration During Neuronal Activation in Patients with Cerebral Ischemia: A Simulation Study with the Balloon Model

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Abstract Patients with cerebral ischemia or brain tumor have been reported to exhibit an increase of deoxygenated hemoglobin (deoxy-Hb) together with an increase of oxygenated hemoglobin (oxy-Hb). However, the physiological mechanisms underlying this hemodynamic response pattern are unclear. In this study, we performed a simulation using the balloon model (Buxton et al., Magn Reson Med 39:855–864, 1998). We hypothesized that the oxygen extraction rate during the rest period (E_0) in the patients is larger than in normal subjects, because the cerebral blood flow and the speed at which the blood passes through the brain tissues are lower in the patients. The simulation result showed an increase of deoxy-Hb as well as oxy-Hb, especially when E_0 is extremely high. Thus, the results of our simulation suggest that the increase of deoxy-Hb during activation in patients with ischemia or brain tumor is caused by an increased oxygen extraction rate at rest, compared with that of healthy adults.

Keywords Cerebral blood oxygenation • Ischemia • Near-infrared spectroscopy • Balloon model

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1 Introduction

In general, neuronal activation induces a regional increase of oxygenated hemoglobin (oxy-Hb), accompanied with a decrease of deoxygenated hemoglobin (deoxy-Hb). However, in some patients with cerebral ischemia or brain tumor, deoxy-Hb increases, as well as oxy-Hb, during neuronal activation [1–3].

The balloon model [4] is one of the physiological models used to study cerebral hemodynamics and oxygen dynamics. The model assumes that the BOLD signal or the optical signal measured by fMRI or NIRS reflects the change of venous oxy- and deoxy-Hb concentrations around the site of neuronal activation. When oxygen is metabolized in the region around a capillary vessel, blood flows into an expandable compartment in the vein. Since the increase rate of the regional cerebral blood flow (rCBF) is larger than the increase rate of oxygen metabolism, blood with high oxy-Hb concentration flows into the vein compartment and "washes out" the blood with high deoxy-Hb concentration. Consequently, the concentration of oxy-Hb in the vein increases, while the concentration of deoxy-Hb decreases. However, cerebral blood flow in patients with ischemia is smaller than normal, and consequently the oxygen extraction fraction (OEF) becomes larger [5].

In the present study, we conducted simulations with the balloon model in order to examine whether this model can reproduce the increase of deoxy-Hb concentration in ischemia patients, on the assumption that the OEF during the resting state is higher in patients with ischemia than that in healthy subjects.

2 Methods

First, the balloon model for the simulation of dynamic changes in rCBF and OEF is described. Then, the manipulation of the model for the simulation of ischemia is explained.

2.1 The Balloon Model

The balloon model [4] is a mathematical model that describes the temporal change of rCBF, rCBV and OEF. Under the assumption that all of the oxygen that leaves the capillary is metabolized and that blood flow increases are accomplished by increased capillary blood velocity rather than capillary recruitment. Increased blood flow leads to reduced oxygen extraction.

Designating rCBF that enters the vein compartment and rCBF that leaves it at time t as $f_{\text{in}}(t)$ and $f_{\text{out}}(t)$, and the OEF at time t and at rest as $E(t)$ and E_0, we can write

the temporal expansion of the deoxy-Hb content $q(t)$ and the cerebral blood volume (rCBV) in the compartment $v(t)$ as follows:

$$\frac{dq(t)}{dt} = \frac{1}{\tau_0}\left[f_{in}(t)\frac{E(t)}{E_0} - f_{out}(v)\frac{q(t)}{v(t)} \right], \tag{30.1}$$

$$\frac{dv(t)}{dt} = \frac{1}{\tau_0}\left[f_{in}(t) - f_{out}(v) \right]. \tag{30.2}$$

Note that τ_0 is the time constant, and $f_{\text{in}}(t), f_{\text{out}}(t)$, $q(t)$, $v(t)$ are relative values such that the value at the rest period is 1. $E(t)$ decreases as the blood flow increases, and is given by:

$$E(t) = E\left(f_{in}(t)\right) = 1 - \left(1 - E_0\right)^{\frac{1}{f_{in}(t)}}. \tag{30.3}$$

rCBF that leaves the compartment is dependent to the blood volume in the compartment.

$$f_{out}(v) = f_{out}\left(v(t)\right) = v(t)^{1/\alpha}. \tag{30.4}$$

Here, α is a coefficient to describe the relationship between flow and volume. The hysteresis of the flow [6, 7] is not considered here, because it is outside the scope of the present study.

2.2 Simulation of Ischemia

The parameter α is set to 0.4, following the original model [4]. The time constant is set to 2. When neuronal activation occurs, the rCBF that enters the vein compartment $f_{\text{in}}(t)$ is assumed to increase to the maximum blood flow f_a. In the present simulation, the rest duration is 10 s, task (activation) duration is 35 s, and rest duration after the task is 35 s. When the task starts, $f_{\text{in}}(t)$ increases linearly to f_a in 5 s. After the task period, $f_{\text{in}}(t)$ decreases linearly to the rest value (=1.0) in 5 s. These temporal changes of $f_{\text{in}}(t)$ are shown in Fig. 30.1a. These transient times (5 s) are chosen to ensure the convergence of the observed values (rCBV, $CMRO_2$, and deoxy-Hb) during the simulation. The time step to drive the temporal differential (30.1)–(30.4) is 0.01 s.

We conducted two simulations. First, we used a static maximum blood flow (f_{a}=0.7), following the original model [4]. Then, we simulated six cases where the OEFs at rest are as follows:

$$E_0 = \left[0.4, 0.5, 0.6, 0.7, 0.8, 0.9\right].$$

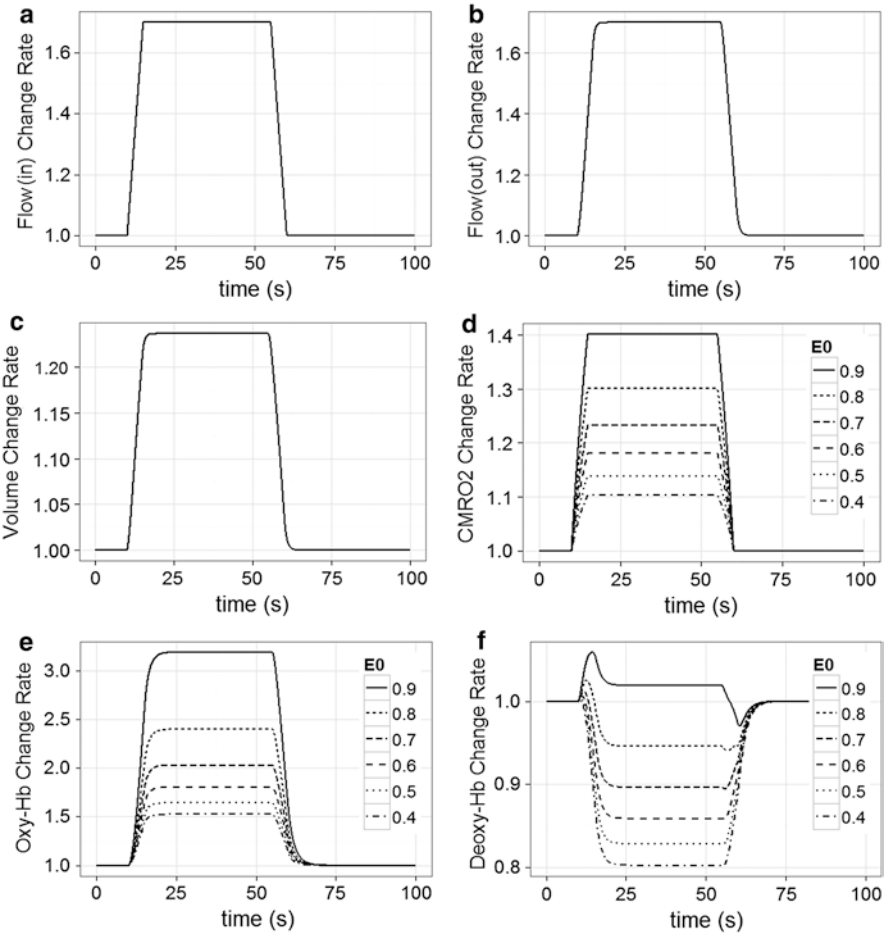

Fig. 30.1 Simulation results for the case of static maximum flow. **a**: rCBF (in-flow) change rate. **b**: rCBF (out-flow) change rate. **c**: rCBV change rate. **d**: $CMRO_2$ change rate. **e**: oxy-Hb change rate. **f**: deoxy-Hb change rate. *Dotted lines* denote the cases of larger E_0

For the second simulation, we introduced the hypothesis that, in ischemic patients, the cerebral blood vessel at the rest period is already dilated in order to compensate for the low perfusion [5], and therefore, the maximum blood flow during the neuronal activation is smaller than that in healthy subjects. We used the following six pairs of OEF at rest and maximum blood flow:

$(E_0, f_a) = [(0.4, 0.7), (0.5, 0.6), (0.6, 0.5), (0.7, 0.4), (0.8, 0.3), (0.9, 0.2)]$.

The combination of E_0 and f_a values are determined only by increasing f_a values by 0.1 against the increase of E_0 values by 0.1 in order to how the concurrent change of these values result in the change of the rCBO. The temporal flow into the compartment in the second simulation is shown in Fig. 30.2a.

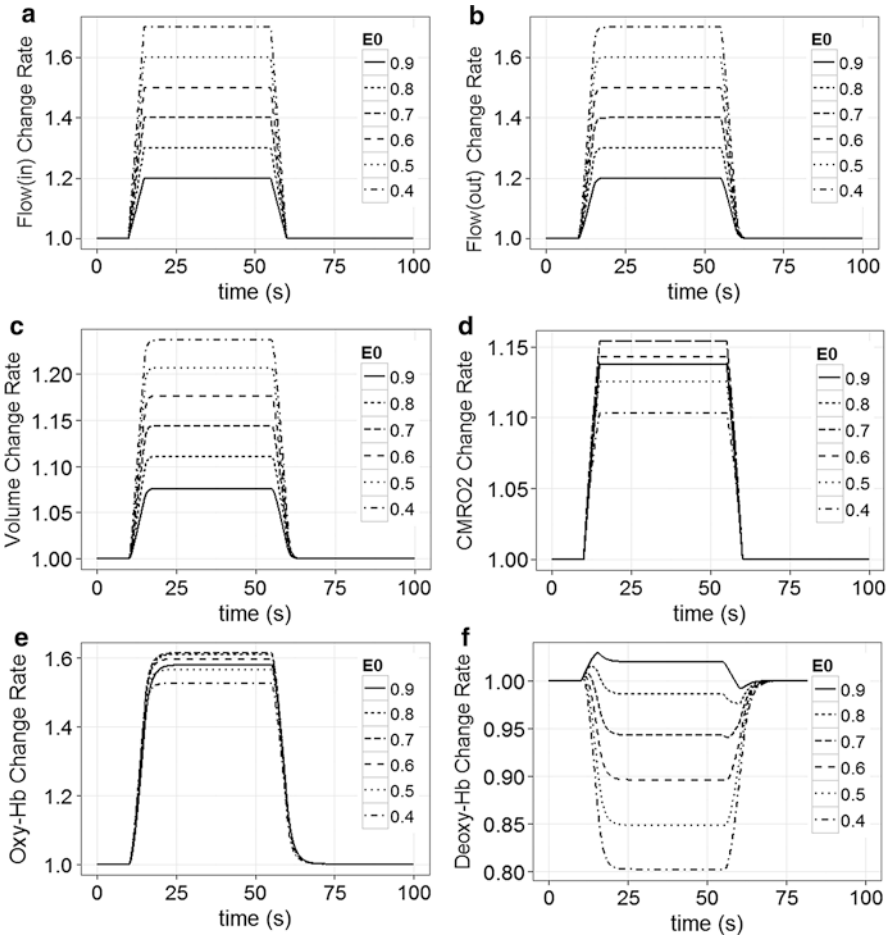

Fig. 30.2 Simulation results for the case of variable maximum flow. **a**: rCBF (in-flow) change rate. **b**: rCBF (out-flow) change rate. **c**: rCBV change rate. **d**: $CMRO_2$ change rate. **e**: oxy-Hb change rate. **f**: deoxy-Hb change rate. *Dotted lines* denote the cases of larger OEF at rest and smaller maximum flow

3 Results

The results of the first simulation are shown in Fig. 30.1. As the OEF (E_0) at rest increases, the cerebral metabolic rate of oxygen ($CMRO_2$) and the oxy-Hb during activation both increase more (Fig. 30.1c, f), and the deoxy-Hb decreases less (Fig. 30.1e). In the case of the largest E_0 (= 0.9), the deoxy-Hb even increases during activation (Fig. 30.1e). Note that the $CMRO_2$ change rate is calculated as follows:

$$CMRO_2(t) = f_{in}(t)E(t)/E_0.$$

The results of the second simulation are shown in Fig. 30.2. As the OEF (E_0) at rest increases and rCBF change rate during activation decreases (Fig. 30.2a, b), the rCBV increases less (Fig. 30.2d) and the deoxy-Hb decreases less (Fig. 30.2e). Again, in the case of large E_0 (= 0.8 or 0.9), deoxy-Hb even increases during activation (Fig. 30.2e). In this simulation, $CMRO_2$ and oxy-Hb in the case of ischemia are similar to these in healthy subjects (Fig. 30.2c, f).

4 Discussion

The simulation results reproduced the quantitative features of cerebral blood oxygenation (CBO), i.e., that the deoxy-Hb concentration increases during neuronal activation in patients with cerebral ischemia (E_0=0.9 in the simulation), while it decreases in healthy subjects. In simulation 1, the assumption that the OEF at rest is large for ischemic patients resulted in increases of $CMRO_2$ and oxy-Hb concentration. In simulation 2, on the other hand, the assumption that the OEF at rest is large and the rCBF increase rate during activation is small for ischemic patients resulted in relatively similar $CMRO_2$ and oxy-Hb concentration to those of healthy subjects.

At present, it is impossible to discuss the plausibility of these two simulations, because physiological observations of the absolute values of the CBO during activation are lacking. In general, NIRS can only measure the product of the change of the CBO and the light path length, and therefore, the absolute values of these parameters are not measurable. On the other hand, the results of the present simulation can only show the change rate of these parameters, which makes it impossible to compare the physiological measurement and the simulation result. One essential development of the present study will be to conduct simulations with absolute values of the blood flow and the blood volume. It makes it possible to compare the absolute values of the cerebral blood variables in the physiological experiments and these in the simulation. And by determining the blood flow and the blood volume, the time constant τ can also be determined, and the comparison of characteristics of the temporal development of the variables can be made.

Previous observations [2, 3], suggest that the higher the level of ischemia is, the less oxy-Hb increases during activation. The reason for this result might be either differences of the light path length between patients, or differences in the change of absolute value of the parameter. In order to investigate these possibilities, it will be necessary to measure the CBO independently of the light path length by using time-resolved near-infrared spectroscopy (TRS), and to conduct simulation using a model with absolute values of rCBF, rCBV, during resting state and activation, not relative values, of parameters. These variables are available in the literature from PET and SPECT studies. However, it is not possible to obtain these measurements simultaneously with the measurement of the CBO. Even so, we can conduct simulations based on the speculation that the characteristics of these CBF and CBV variables are preserved during the measurement of the CBO.

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References

1. Fujiwara N, Sakatani K, Katayama Y, Murata Y, Hoshino T, Fukaya C, Yamamoto T (2004) Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors. Neuroimage 21:1464–1471
2. Murata Y, Sakatani K, Hoshino T, Fujiwara N, Kano T, Nakamura S, Katayama Y (2006) Effects of cerebral ischemia on evoked cerebral blood oxygenation responses and BOLD contrast functional MRI in stroke patients. Stroke 37:2514–2520
3. Sakatani K, Murata Y, Fujiwara N, Hoshino T, Nakamura S, Kano T (2007) Comparison of blood-oxygen-level-dependent functional magnetic resonance imaging and near-infrared spectroscopy recording during functional brain activation in patients with stroke and brain tumors. J Biomed Optics 12:062110
4. Buxton RB, Wong EC, Frank LR (1998) Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn Reson Med 39:855–864
5. Powers WJ, Grubb R Jr, Raichle ME (1984) Physiological responses to focal cerebral ischemia in humans. Ann Neurol 16:546–552
6. Buxton RB, Uludag K, Dubowitz DJ, Liu TT (2004) Modeling the hemodynamic response to brain activation. Neuroimage 23(Suppl 1):S220–S233
7. Tang L, Avison MJ, Gore JC (2009) Nonlinear blood oxygen level-dependent responses for transient activations and deactivations in V1 – insights into the hemodynamic response function with the balloon model. Magn Reson Imaging 27:449–459