Dependence of Cerebral Blood Flow and Oxygen Consumption on Hyperoxia-Induced Changes in the Longitudinal Relaxation Time

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Introduction

Tumor oxygenation and the methods to improve it are important in clinical oncology, because tumor hypoxia modulates radiation responsiveness (1). Hyperoxic contrast is an attractive method of studying tumor oxygenation because other methods capable of imaging oxygen, such as PET (2), electron paramagnetic resonance imaging (EPR) (3), and ¹³C compounds (4), are much more difficult to use, particularly in humans. While most studies of tissue lesions, including ischemic stroke and tumors, have focused on the ability of oxygen to dilute dHb and increase T₁, there have been several recent studies using hyperoxia primarily to decrease T₁ with dissolved molecular oxygen in order to study tissue oxygen delivery to normal tissue and tumors (7,8). Studies using hyperoxic R₁ enhancement have shown large heterogeneities between tissue types in the ability of oxygen to increase R₁ (7,9). Although qualitative means to explain these differences have been proposed, such as differences in blood flow rate and/or blood volume (8), no attempts have been made to develop a quantitative understanding of the relationship between hyperoxic R₁ enhancement and major physiologic parameters including blood flow, blood volume, and oxygen consumption. An understanding of these relationships is crucial to a more rigorous interpretation of hyperoxic R₁ enhancement and a more rational approach to its clinical use. In this study, we set out to take the initial steps toward developing a detailed quantitative biophysical model of R₁ relaxation enhancement in vivo. Our central premise is that dissolved oxygen R₁ contrast within a volume of tissue is dependent solely on the increase in plasma and tissue concentration of oxygen, which in turn will depend primarily on the volume of blood and its concentration of oxygenated hemoglobin.

Theory

The biophysical model first developed by Hoge, et al. (10) establishes a relationship between R₁, CBF and CMRO₂ based on the expected changes in dHb concentration and CBF. In a similar manner, we developed a quantitative model relating R₁ changes during oxygen inhalation to CBF and CMRO₂ based on the expected change in oxygen concentration (HBO₂) and CBF, which in turn determines the amount and distribution of molecular oxygen in tissues. A reproduction of our derivation of this model is beyond the scope of the text here, but the final relationship is:

\[ \Delta R_1 = E \left( \left( \frac{\text{CMRO}_2}{\text{CMRO}_2} \right) \left( \frac{\text{CBF}}{\text{CBF}_0} \right)^{\alpha_1} \right) \left( \frac{\text{PaO}_2}{\text{PaO}_2} - 1 \right) \]

where \( \Delta R_1 \) is the change (different physiological states) in the value (same physiological state) in R₁ due to a hyperoxic challenge, CMRO₂ is the cerebral metabolic rate of oxygen, CBF is the cerebral blood flow, PaO₂ is the arterial partial pressure of oxygen, \( \alpha \) is a constant equal to 0.38, and E is a constant depending on tissue parameters (0° denotes the initial state).

Materials and Methods

Since the main purpose of this study was to determine if our model of hyperoxia-induced changes in T₁ accurately describes the contrast in vivo, we set out to measure the effect of an isometabolic increase in CBF using hypercapnia on the measured R₁ contrast. If our model is correct, we expect to see an approximately linear change in \( \Delta R_1 \) versus CBF. To generate an isometabolic increase in CMRO₂, we performed experiments on isoflurane anesthetized SD rats (N=6), where the animals were ventilated in a steady-state manner with increasing levels of hypercapnia. Starting at with normoxia, animals were ventilated with 5%, 10%, 15%, and 20% CO₂ to generate four increased isometabolic levels of perfusion. Challenges from FiO₂=0.3 to 0.8 were delivered in a baseline (5 min) – stimulation (10 min) – rest paradigm. In this way, we sought to increase the arterial partial pressure of oxygen by approximately the same amount for each hypercapnic epoch. All imaging experiments were performed using a whole-body clinical 3T MRI scanner (Siemens Trio; Siemens Healthcare, Erlangen, Germany) and a passively decoupled custom-built 20 mm receive-only surface coil. CBF was determined using a pulsed ASL method and R₁ was determined using an inversion-prepared fast gradient echo Look-Locker readout. All images were analyzed using whole brain ROIs and nonlinear-least squares fits to the T₁ recovery curve in Matlab.

Results

Hypercapnia increased CBF by 27 ± 12 %, 63 ± 14 %, 94 ± 15 %, and 118 ± 17 %, for 5%, 10%, 15%, and 20% CO₂ inhalations, respectively. The AR₁ of hyperoxia was determined to be 10.2 ± 2.1 × 10⁻¹, 14.4 ± 1.5 × 10⁻¹, 18.2 ± 1.9 × 10⁻¹, and 21.5 ± 2.4 × 10⁻¹ s⁻¹ for 5%, 10%, 15%, and 20% CO₂ inhalations, respectively. The trace of \( \Delta R_1 \) versus the percent change in CBF is shown in Fig. 1. A fit to the model showed very close agreement to the experimental data.

Discussion

In this work, we have developed a biophysical model relating CBF, CBV, and CMRO₂ to the hyperoxic R₁ enhancement. Measurements made during an isometabolic increase in CMRO₂ were in close agreement to our model. Furthermore, we can conclude from this study that increasing the blood flow does increase the amount of excess oxygen delivered to tissues. This is an important finding since the relationship between tissue flow and oxygenation enhancement with hyperoxia is still somewhat controversial (8). Although this does not recommend the use of CO₂ for all tumors, as it does not vasodilate in all types of cancerous tissue, it highlights the importance of increasing blood flow to maximize tumor oxygenation. It is important to note that the behavior of hyperoxic R₁ contrast is the opposite of hyperoxic R₂ (BOLD) contrast. As CMRO₂ increases at the same CBF, we expect the sensitivity of BOLD contrast to increase because the deoxyhemoglobin concentration increases. Also, as CBF decreases at the same CMRO₂, we expect to see BOLD contrast sensitivity increase, since that will also increase deoxyhemoglobin concentration. In this way, in relation to physiological conditions, R₁ provides contrast that is complementary in sensitivity to BOLD.

References


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