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 (EPRI) (3), and ^{19}F 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 T_2 (5,6), there have been several recent studies using hyperoxia primarily to decrease T_1 with dissolved molecular oxygen in order to study tissue oxygen delivery to normal tissue and tumors (7,8). Studies using hyperoxic R_1 enhancement have shown large heterogeneities between tissue types in the ability of oxygen to increase R_1 (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 R_1 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 R_1 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 R_1 relaxation enhancement *in vivo*. Our central premise is that dissolved oxygen R_1 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 R_2, CBF and $CMRO_2$ based on the expected changes in dHb concentration and CBV. In a similar manner, we developed a quantitative model relating R_1 changes during oxygen inhalation to CBF and $CMRO_2$ based on the expected change in oxyhemoglobin concentration (HbO_2) and CBV, 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:
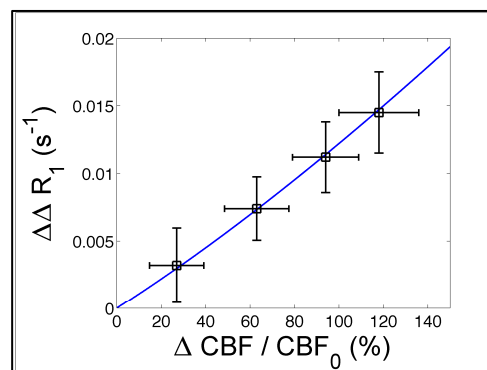

FIG.1. The change in hyperoxic longitudinal relaxation enhancement ($\Delta\Delta R_1$) versus relative change in the CBF (% increase from baseline). $\Delta\Delta R_1$ data appears to increase monotonically with CBF, and shows close agreement the proposed biophysical model.the ten minute hypercapnia challenge, and with a BOLD signal was approximately at baseline level.

$$\Delta\Delta R_1 = E \cdot \left(\left(\frac{CMRO_{2,0}}{CMRO_2} \right) \left(\frac{CBF}{CBF_0} \right)^{\alpha+1} - 1 \right) \left(\frac{PaO_2}{PaO_{2,0}} - 1 \right)$$

where $\Delta\Delta R_1$ is the change (different physiological states) in the change (same physiological state) in R_1 due to a hyperoxic challenge, $CMRO_2$ is the cerebral metabolic rate of oxygen, CBF is the cerebral blood flow, PaO_2 is the arterial partial pressure of oxygen, α 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 T_1 accurately describes the contrast *in vivo*, we set out to measure the effect of an isometabolic increase in CBF using hypercapnia on the measured R_1 contrast. If our model is correct, we expect to see an approximately linear change in $\Delta\Delta R_1$ versus CBF. To generate an isometabolic increase in $CMRO_2$, 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% CO_2 to generate four increased isometabolic levels of perfusion. During each of these steady state levels of hypercapnia, two oxygen challenges from FiO_2=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 R_1 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 T_1 recovery curve in Matlab.

Results

Hypercapnia increased CBF by 27 ± 12 %, 63 ± 14 %, 94 ± 15 %, and 118 ± 17 %, for 5%, 10%, 15%, and 20% CO_2 inhalations, respectively. The ΔR_1 of hyperoxia was determined to be $10.2 \pm 2.1 \times 10^{-3}$, $14.4 \pm 1.5 \times 10^{-3}$, $18.2 \pm 1.9 \times 10^{-3}$, and $21.5 \pm 2.4 \times 10^{-3}$ s^{-1} for 5%, 10%, 15%, and 20% CO_2 inhalations, respectively. The trace of $\Delta\Delta R_1$ 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 $CMRO_2$ to the hyperoxic R_1 enhancement. Measurements made during an isometabolic increase in $CMRO_2$ 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 CO_2 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 R_1 contrast is the opposite of hyperoxic R_2 (BOLD) contrast. As $CMRO_2$ 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 $CMRO_2$, we expect to see BOLD contrast sensitivity increase, since that will also increase deoxyhemoglobin concentration. In this way, in relation to physiological conditions, R_1 provides contrast that is complementary in sensitivity to BOLD.

References

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