Hyperoxic Calibrated Quantitative fMRI for the Measurement of Regional Cerebral Metabolic Rate of Oxygen in a Hypermetabolic Swine Model

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Introduction

Significant work has been done developing quantitative approaches to measure relative changes in cerebral oxygen metabolism ($CMRO_2$) in animals and humans using simultaneous blood oxygenation level-dependent (BOLD) and arterial spin labeling (ASL) data calibrated with inspired gas mixtures. Our group has recently developed a method to measure absolute $CMRO_2$ in a large animal model using $^{17}O_2$ inhalation (1). In this study, we set out to determine the feasibility of measuring $CMRO_2$ in a hypermetabolic swine model (1) using simultaneous BOLD and ASL acquisitions calibrated with isometabolic dHb dilution using hyperoxia (2) and hypercapnia (3). The goal of this study was twofold: (i) to cross-validate the results of the change in $CMRO_2$ with the same protocol measured with $^{17}O_2$ inhalation (1) and (ii) to compare the results of the hyperoxic and hypercapnic calibration methods.

Materials and Methods

All imaging experiments were performed using a whole-body clinical 1.5T MRI scanner (Siemens Sonata; Siemens Healthcare, Erlangen, Germany) and an actively decoupled custom-built 80 mm receive-only surface coil. The experimental protocol was approved by our Institutional Animal Care and Use Committee. Yorkshire pigs (n=8; 23-30 kg) were anesthetized with ketamine and mechanically ventilated through an endotracheal tube using a custom-built breathing circuit (4). Arterial oxygen saturation, heart rate, and end-tidal CO_2 were continuously monitored. The swine were given a single, ten minute hyperoxia (FiO_2 = 1.0) and hypercapnia (6% CO_2 in air) challenge in a baseline – stimulation – rest paradigm (5 min baseline, 10 min challenge, 10 min rest). A hypermetabolic state was induced using the proton ionophore 2,4-dinitrophenol (DNP), using the same protocol as our prior ^{17}O inhalation study (1). After all gas calibrations were performed, 9 mg/kg of DNP were administered to the animal by IV infusion. Arterial blood gases drawn during normoxia, hyperoxia, hypercapnia, and 30 min after DNP infusion. An interleaved BOLD/ASL sequence with a single-shot fast spin echo (FSE) readout and a pseudocontinuous arterial spin labeling (PCASL) preparation (5). Imaging parameters were: TE/TR=118/4000 ms, FOV=180x180 mm^2, matrix=64x64, slice thickness=8 mm, labeling duration=1500 ms, and post-label delay=1000 ms. Images were analyzed using manually-drawn whole-brain ROIs. Relative $CMRO_2$ changes were calculated with hyperoxia (2) and hypercapnia (3) as described previously, where a value of the constant M is calculated relating the BOLD and ASL signal changes while assuming isometabolism. It was assumed that the resting oxygen extraction fraction (OEF) was 0.3 (2).

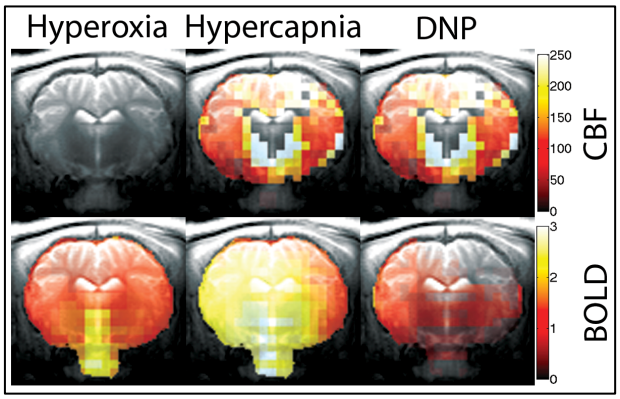

FIG.1. Baseline-normalized changes in BOLD and CBF for each experimental condition., with color scales representing percent signal change from baseline. Hyperoxia showed a slight reduction in CBF, and an increase in the BOLD, which was lower than that measured during hypercapnia. Hypercapnia yielded an approximate two-fold increase in CBF. Measurements taken thirty minutes after DNP infusion show a CBF increase approximately equivalent to that after the ten minute hypercapnia challenge, and with a BOLD signal was approximately at baseline level.

Results

Arterial blood gases were (baseline, hyperoxia, hypercapnia, DNP): pH (7,48, 7.49, 7.31*, 7.22*), pO_2 (102, 524*, 101, 108 mmHg), pCO_2 (38.1, 42.2, 62.3*, 81.7* mmHg), and SaO_2 (98.1, 100*, 96.2, 96.6%), where * indicates $P<0.05$ from baseline. Figure 1 shows the relative changes in BOLD and CBF for the gas calibrations and post-DNP infusion. For hyperoxia and hyperoxia, M was calculated to be 3.24 ± 0.37 and 2.35 ± 0.36, respectively. The average value of M calculated with hyperoxia was determined to be significantly lower ($P<0.001$) than that calculated during hyperoxia. Percent increase in $CMRO_2$ thirty minutes after DNP infusion was determined to be 147 ± 28 and 139 ± 22 for the hyperoxic and hypercapnic calibrations, respectively.

Discussion

In this study, the relative $CMRO_2$ changes in a hypermetabolic swine model were measured using simultaneous BOLD and ASL data, calibrated with isometabolic dHb dilution using inhaled oxygen and carbon dioxide. Using this method, we observed rapid and steady increases in $CMRO_2$ after administering DNP. While the $CMRO_2$ increase at thirty minutes was found to be slightly less than that from a prior study using $^{17}O_2$ inhalation, both methods showed an approximate 150% increase in $CMRO_2$ after thirty minutes of 9 mg/kg DNP. A superior experiment for cross-validation would be simultaneous use both methods in the same animals. However, due to the need to first determine the feasibility of relative $CMRO_2$ measurements using calibrated BOLD/ASL data in this context, as well as the expense of $^{17}O_2$ gas, this was not done for these initial studies. Given that we have shown the feasibility of this approach, this will be the goal of future work. Although we found that hyperoxic and hypercapnic approaches to calibration produced very similar final $CMRO_2$ estimations, the calculated M values were significantly different between the methods. M values calculated here were lower for hyperoxia than for hypercapnia, which is same trend seen in prior studies (6). This difference may be due to inaccurate estimates of OEF (2) or of the Grubb relationship coefficient alpha. Although it produces similar results to hypercapnia, there are several distinct advantages to the use of hyperoxia, including: (i) oxygen exhibits faster wash-in and wash-out times, (ii) there is less uncertainty concerning the cerebral isometabolism of hyperoxia (7,8), and (iii) there is less sensitivity to flow estimation errors when using hyperoxia. In conclusion, we have shown that it is feasible to measure $CMRO_2$ changes with simultaneous BOLD/ASL data calibrated with hyperoxia or hypercapnia in a hypermetabolic swine model, and that these methods show calculated increases in metabolism very similar to those measured with $^{17}O_2$ inhalation.

References

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