High temporal resolution measurements of metabolic water production from 17-Oxygen bolus gas delivery in a large animal

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Objective

To investigate signal changes generated by metabolically produced 17-oxygen labeled water ($H_2{}^{17}O$) *in vivo* after 17-oxygen gas ($^{17}O_2$) delivery as a bolus by a precision breathing circuit in a large animal brain.

Background

Differences in the cerebral metabolic rate of oxygen consumption ($CMRO_2$) within the central nervous system *in vivo* are noted both in normal and pathologic physiology. Despite the importance of measuring $CMRO_2$, there are currently no routinely used clinical techniques that directly assess changes in oxygen metabolism due to drawbacks in existing technologies. We propose that a non-radioactive, naturally occurring, NMR active isotope of oxygen, ^{17}O, can be used to provide MRI contrast for the *in vivo*, non-invasive, non-toxic, and widely employable quantification of tissue metabolism in humans and animals. Detection of ^{17}O by the indirect method is based on scalar coupling to bound protons. In $T_{1\rho}$-dispersion imaging, high amplitude SL pulse sequences provide effective ^1H-^{17}O decoupling without violating SAR limits. Repeated low amplitude SL pulse sequences provide measurable ^{17}O based contrast greater than that achievable with direct ^{17}O measurements and without artifacts related to long TE T_2 measurements[1]. Because the custom precision delivery breathing circuit allows for precise measurement of delivery kinetics, the concentration of blood $^{17}O_2$ gas can be accurately modeled[2]. As the concentration of $H_2{}^{17}O$ is measured as shown here, the rate of $^{17}O_2$ conversion to $H_2{}^{17}O$, i.e. $CMRO_2$, can be calculated. In this feasibility study, we demonstrate $T_{1\rho}$-weighted ^{17}O imaging with a precision breathing circuit (Fig. 1) on a 1.5 Tesla clinical scanner using pigs. The pulse sequence used is a 2D centrically sampled $T_{1\rho}$ prepared bSSFP sequence known as Spin Locked Imaging with Precession in the Steady-State (SLIPS). Only low power SL pulses are used here, giving relative $H_2{}^{17}O$ concentrations.

Methods

The Institutional Animal Care and Use Committee of the University of Pennsylvania approved all animal experiments. The head of a live, anesthetized pig (30-50kg) was placed in a GE T/R head coil in a 1.5T Siemens Sonata MR scanner. Once placed inside, an oral intubation tube was connected to the breathing circuit by tubing run through a small wall port to the inhalation and exhalation pumps. A standard T1-weighted localizer sequence was run to find a suitable coronal image and a T1-weighted IR-prepared GRE image obtained. Comfortable breathing and stable imaging were confirmed by five minutes of room air breathing provided by the breathing circuit during serial $T_{1\rho}$ weighted images. Two pigs were imaged with a protocol of 5 minutes of 100% $^{16}O_2$, 2 breaths (1200-1400mL over 20sec) of 40/60% $^{17}O_2/^{16}O_2$, followed immediately by five minutes 100% $^{16}O_2$ and then room air. The third pig was imaged with 2 breaths of 20/80% $^{16}O_2/N_2$, 5 minutes of room air, 2 breaths of 14/6/80% $^{17}O_2/^{16}O_2/N_2$, and then room air. The normalized signal trace from the third experiment is very similar and it has been pooled with the first two experiments. SLIPS parameters: TR/TE 9.7/4.8ms, ST 5-10mm, FoV 200mm^2, 128x128 matrix, BW 130Hz/Px, FA 90°, spin lock amplitude 100Hz, duration of spin lock (TSL) 200ms, fat sat. on, 1.6sec sequence time, 2sec delay between acquisitions (to minimize T1 saturation effects).

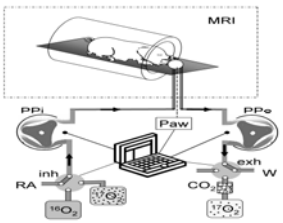

Figure 1. (Left) The system for mechanical ventilation in the current study displayed schematically. Gases are pumped to and from the pig by two large peristaltic pumps, one for assisting or controlling inhalation (PPi), and one for assisting or controlling exhalation (PPe). The pumps outside of the MRI scanner are connected to the animal inside the scanner by 25 feet of 0.25 inch ID tubing. Pressure at the animal's airway is transmitted by 0.125 inch ID nylon tubing to a pressure transducer (Paw). Information on airway pressure is transmitted to a computer which uses feedback control to adjust the pump speeds for both pumps during assisted spontaneous ventilation or for the exhalation pump during volume-controlled mechanical ventilation. Inhaled gases can be chosen via a computer controlled stream select valve to select air, regular 100% O_2, or oxygen with enriched $^{17}O_2$. Exhaled air can be directed to either waste or recovery of the partially enriched $^{17}O_2$. A carbon dioxide absorbent removes CO_2 from the recovered, exhaled gas.

Results

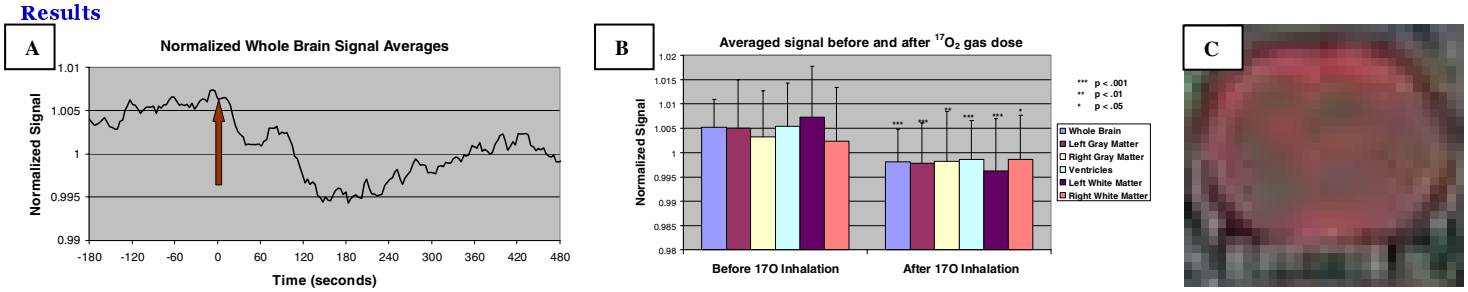

Figure 2. Three experiments were performed with the SLIPS sequence, though other experiments were conducted using $T_{1\rho}$ prepared multiple shot FSE, single shot FSE, and SE-EPI and these show the same general effect. **(A)** A moving average trace of the averaged, normalized signal from the three experiments described in the methods. The red arrow points to the start of the 20 second bolus delivery of $^{17}O_2$. Signal decreases as $H_2{}^{17}O$ is produced locally, and then decreases further as $H_2{}^{17}O$ is washed in from other areas of the body. Eventually, a steady state signal is reached. **(B)** Region of interest analyses show the signal in all areas analyzed decreased significantly after $^{17}O_2$ inhalation (62 images each set, 3.6sec/image, $p<.05$). **(C)** A red difference map was computed from the images used in B and overlaid on the grayscale anatomical image. Brighter red indicates larger decreases in intensity, and thus larger increases in $H_2{}^{17}O$. As expected, the areas with the greatest $H_2{}^{17}O$ changes are identified as cortex, ventricles, and brainstem.

This data presents two major advances towards the clinical application of this technology in humans. First, in 20 seconds (2 breaths) only about 1L of the expensive $^{17}O_2$ gas is used per experiment in a nearly human-sized animal, representing the shortest time of delivery and smallest per weight delivery yet reported. It should be mentioned here that in all previous reports continuous inhalation of $^{17}O_2$ gas was used for at least several minutes. The pulse sequence applied to these experiments is the fastest $T_{1\rho}$ sequence yet applied to the detection of ^{17}O with measurements of 3.6sec/image. In the long-term, we hope that oxidative metabolism in humans may be imaged using this approach. We hope that better results will be achieved in humans by better filling the standard human head coils we are using in these experiments and by using more $^{17}O_2$ as necessary.

References 1. Reddy, et al. J Magn Reson B 1995;108:276-9 2. Tailor DR, et al. Neuroimage 2004;22(2):611-618.

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