Estimation of the regional cerebral metabolic rate of oxygen consumption with MRI during the first 60 seconds of $^{17}O_2$ inhalation in swine

E. A. Mellon[1], R. S. Beesam[1], J. E. Baumgardner[2], A. Borthakur[1], W. R. Witschey[1], and R. Reddy[1]

[1]MMRRCC -- Department of Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]Department of Anesthesia, University of Pennsylvania, Philadelphia, PA, United States

Objective

Our objective is to measure the cerebral metabolic rate of oxygen consumption ($CMRO_2$) by MRI in a large animal model by the conversion of $^{17}O_2$ to $H_2{}^{17}O$ during the first minute of $^{17}O_2$ inhalation on clinical MR scanners with the goal of future studies with humans.

Background

Differences in $CMRO_2$ are noted both in normal and pathologic physiology. Despite the importance of measuring $CMRO_2$, there are no routinely used clinical techniques that directly assess changes in oxygen metabolism due to drawbacks in existing technologies. Detection of $H_2{}^{17}O$ can be performed by direct imaging at the ^{17}O Larmor frequency or by the indirect method based on J-coupling of ^{17}O to detected bound ^1H (1). Indirect images pre-encoded with low amplitude spin lock pulses provide measurable $H_2{}^{17}O$ based contrast greater than that achievable with direct ^{17}O measurements and without artifacts related to long TE T_2 measurements (2). Meanwhile, $^{17}O_2$ is invisible to MR, so its delivery kinetics must be modeled. In large animals it has been hypothesized that there is a time delay between the start of $H_2{}^{17}O$ generation in parenchyma and the start of incoming metabolically generated water recirculated from other tissues after $^{17}O_2$ delivery. During this delay,^{15}O PET studies have estimated $CMRO_2$ in normal subjects (3). While an analogous recirculation delay for ^{17}O is expected and has been suggested (4), no group has combined $^{17}O_2$ delivery in a large animal model with fast MRI techniques to further investigate the possibility of measuring $CMRO_2$ from the pre-recirculation time. We propose that in large animals it is possible for $CMRO_2$ to be estimated by watching the formation of $H_2{}^{17}O$ in brain during this recirculation delay. In this study, we correlate indirect imaging using 20-40kg swine in a 1.5T clinical MR scanner with arterial sampling and 3T direct ^{17}O spectroscopy to measure $CMRO_2$ with the long-term goal of human studies.

Methods

All experiments were approved by the Institutional Animal Care and Use Committee. Direct imaging was performed with a broadband-enabled 3T Siemens Trio scanner. After T_1-weighted images were taken with the body coil, one ^{17}O image was taken in each plane with a 9cm surface coil placed over the pig's head. A series of pulse acquire spectra were taken with the same hard pulse over 15 minutes during which time $^{17}O_2$ was given as 1.2 breaths of 80% N_2/20% ^{17}O enriched $^{17}O_2$. Pulse acquire parameters were: TR 100ms, 256 points, two step phase cycling, 40kHz bandwidth. Indirect imaging was performed on separate occasions with a 1.5T Siemens Sonata scanner. Images were taken with a 15cm vendor supplied surface coil placed on the head of the pig. Serial images during room air and $^{17}O_2$ delivery were taken with a $T_{1\rho}$-prepared single-shot, high flip angle, centrically encoded, fully-balanced sequence reported previously (5). Parameters were: TR/TE 9.7/4.7ms, ST 6mm, FoV 200mm^2, 128x128 matrix, BW 130Hz/Px, α=180°, spin locking amplitude 100Hz, spin locking time 75 or 200ms, fat saturation on, time per image 1.6 seconds, 2 second delay for T_1 recovery. During some indirect imaging sessions, arterial blood sampling was performed. An arterial catheter was placed under ultrasound guidance into the femoral artery. Approximately 2cc of blood was collected over 3-5 seconds into each serum separator tube at a rate of one sample each 10 seconds for the first 12 samples and then 60 seconds each for six more samples. Four control samples were taken before the experiment began. An 11.7T Bruker DMX400 Avance Spectrometer equipped with a 1H/X nucleus decoupler probe tuned to ^{17}O was used to measure 1mL of each sample serum loaded into 5mm NMR tubes just before analysis. Integrals of each ^{17}O Fourier transformed spectra from pulse acquire data were normalized by integrals of the water ^1H spectrum to control for shim and loading volume. The parameters for ^{17}O spectroscopy were: TR 41ms, 4096 points, bandwidth 50kHz, 4000 averages, flip angle 90°. The parameters for ^1H spectroscopy were: TR 1.34s, 8192 points, bandwidth 12kHz, 8 averages, 4 dummy scans, flip angle 45°. A precision breathing delivery circuit was used to deliver gas that provides near step-changes in $^{17}O_2$ concentration at the mouth as described previously (6). Each breath is modeled according to a step-wise equation accounting for incoming breathing of $^{17}O_2$, its mixing with $^{17}O_2$ in the lungs, and physiologic oxygen uptake to provide an average ^{17}O atomic fraction during the first minute of inhalation. Data analysis was performed by taking regional signal change over 50 seconds after a 10 second delay after the start of $^{17}O_2$ inhalation and fitting that to a linear function. The $CMRO_2$ was calculated according to $\ln(S/S_0)*f_i/(TSL*R_{1\rho}*f*2)$ where S is the fitted signal change over 1 minute according to the linear fit, $R_{1\rho}$ is $5.96*10^{-6}$ mM^{-1} ms^{-1} (7), fi is g water/g tissue for brain .77, and f is 63.58% of the atomic fraction delivered $^{17}O_2$ (mean of 10-59 sec in Fig. 1). A factor of 2 is required as 2 $H_2{}^{17}O$ are generated per $^{17}O_2$.

Results

Figure 1 shows the results of a simulation of ^{17}O atomic fraction metabolized by cells in the first minute of 70% $^{17}O_2$ delivery. The shaded area is the area over which $CMRO_2$ is computed. To validate the delay before recirculation hypothesis, blood sampling was performed during scanning on two separate occasions. Figure 2 shows the delay between the start of $^{17}O_2$ delivery and the start of wash-in to be 60-80 seconds by arterial blood ^{17}O NMR. Figure 3 shows metabolic water generation in arterial blood (triangles/dashed line) correlated with simultaneous indirect imaging (thin line) and also metabolic water generation by direct imaging (thick line) at a separate session. Figure 4 shows signal drops from the whole brains of 4 pigs (a) with their linear fits and a metabolic map of one pig brain (c). The average $CMRO_2$ from 8 pig brain hemispheres is calculated as 1.23 ± 0.24µmol/g/min and $CMRO_2$ from the direct session shown in Figure 3 as 1.10 ± 0.43 µmol/g/min, in agreement with existing values measured by microspheres in similarly sized pigs (8).

Figure 1

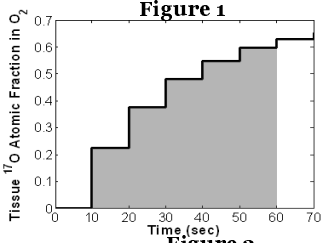


Figure 2

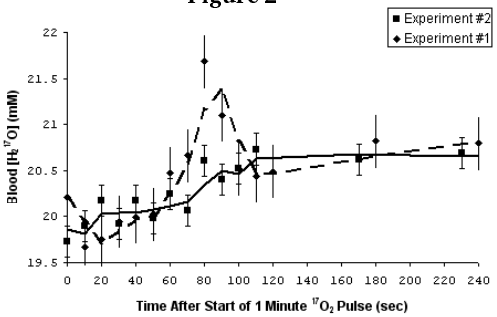


Figure 3

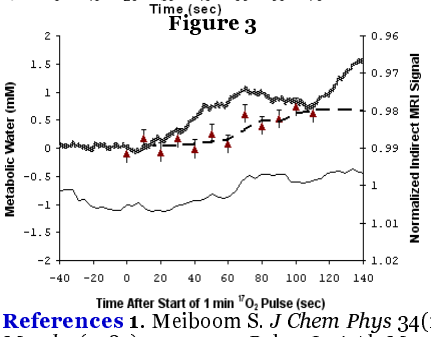
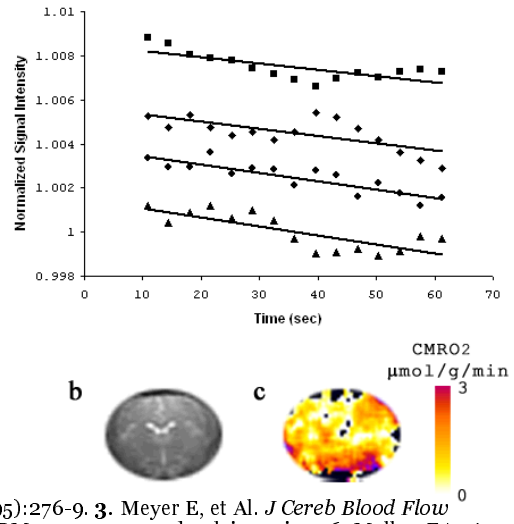


Figure 4



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