

## Preliminary studies to assess CMRO<sub>2</sub> with integrated T1 rho MRI and hybrid DRS/DCS optical approach in clinical scanners

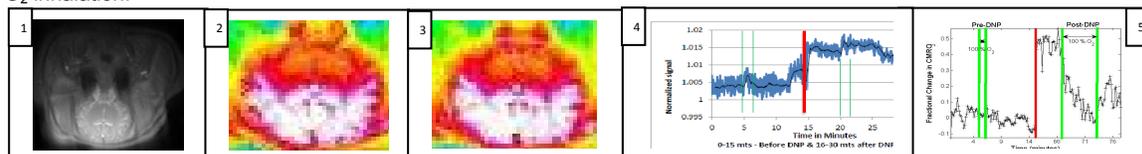
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**Objective:** To assess cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>) by two independent methods - (i). T1ρ MRI based indirect detection and (ii) the hybrid diffuse reflectance spectroscopy (DRS) and diffuse correlation spectroscopy (DCS) optical approach. This preliminary study was designed to optimize the protocol in large animal model on clinical MR scanner for simultaneous T1ρ MRI and optical measurements.

**Background:** Quantitative estimates of CMRO<sub>2</sub> measurements are important both in normal and pathologic physiology of humans. But there are no routinely used clinical techniques that directly measure changes in oxygen metabolism due to technological drawbacks. Detection of metabolically produced H<sub>2</sub><sup>17</sup>O can be performed by direct imaging at the <sup>17</sup>O Larmor frequency or by the indirect method based on J-coupling of <sup>17</sup>O to detected water 1H<sup>(1)</sup>. Indirect images obtained with a pulse sequence pre-encoded with low amplitude spin lock pulses provide measurable H<sub>2</sub><sup>17</sup>O based contrast greater than that is achievable with direct <sup>17</sup>O measurements and without artifacts related to long TE and T2 measurements<sup>(2)</sup>. Of late, we have been working on T1ρ based indirect detection of CMRO<sub>2</sub> on swine, a large animal model with a lung capacity that is comparable to humans<sup>(3)</sup>. A closed respiratory system has been designed and validated to use with adult swine of 25-40 kg weight. In the present study, a combined MRI-optical experiment has been designed to measure CMRO<sub>2</sub> simultaneously in young adult swine using two independent methods - the hybrid DRS/DCS approach<sup>(4)</sup> and T1ρ MRI based indirect detection of metabolic H<sub>2</sub><sup>17</sup>O. The T1ρ MRI method uses metabolically produced H<sub>2</sub><sup>17</sup>O in parenchyma as well as the metabolically generated water re-circulated from other tissues after <sup>17</sup>O<sub>2</sub> delivery. On the other hand, DRS/DCS hybrid method uses a compartmental approach of oxygen exchange to estimate changes in CMRO<sub>2</sub> from global changes in blood flow and blood oxygenation in the brain<sup>(5)</sup>. Though the recirculation delay for <sup>17</sup>O is known and has been suggested<sup>(6)</sup> no group has worked on <sup>17</sup>O<sub>2</sub> delivery in a large animal model with fast MRI techniques and combined MRI and optical techniques to investigate the possibility of measuring CMRO<sub>2</sub> from the pre-recirculation time simultaneously. We use a swine model to demonstrate the feasibility of measuring CMRO<sub>2</sub> simultaneously with two independent and different techniques as a way of validating the accuracy of these techniques.

**Methods:** All animal experiments were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. The T1ρ and T1-weighted measurements were carried out on 1.5 T Siemens Sonata Clinical MRI scanner with vendor's 15 cm spine array surface coil keeping the swine in supine-head first position. A hybrid instrument combining both the DRS and DCS techniques was used for monitoring oxygenation and flow. For DRS measurements, a commercial heterodyne instrument (ISS Imagent, Urbana-Champaign, Illinois) was employed with a self-calibrating probe<sup>(7)</sup>. For DCS measurements, we used a custom instrument consisting of two coherent 785 nm lasers (CrystalLaser Inc., Reno, NV) coupled to 1 mm fibers and eight avalanche photodiodes (PerkinElmer, Canada) coupled to single mode fibers to inject and detect light at different locations in the brain. Two 4-channel autocorrelator boards (Correlator.com, Bridgewater, NJ) were used to compute the intensity temporal correlation function for an integration time of three seconds, from which changes in blood flow were determined. Swine of 20-25 kg were selected for the study and anesthetized during the study<sup>(9)</sup>. A standard T1-weighted localizer sequence was run to find a suitable coronal image to position optical probes at middle of the brain. We have chosen administration of 2, 4-dinitrophenol (DNP) to stimulate metabolism. Three swine were imaged with a protocol of 5 minutes of room air and then with 100% <sup>16</sup>O<sub>2</sub> for 60sec followed immediately by 10 minutes of room air and the same was repeated after DNP injection. The normalized signal trace from the three experiments is similar and pooled together. Serial images were collected during room air and 100% oxygen with a T1ρ-prepared single-shot fully balanced sequence<sup>(8-9)</sup> before (300 images) and after (300 images) DNP injection. From the 600 T1ρ images 600 ROIs are taken from the whole brain and computed for signal change. T1ρ signal change is evident after DNP injection and also during 1 minute of 100% O<sub>2</sub> inhalation.



**Results:** Figure 1 is T1ρ weighted swine brain image. Figure 2 is T1ρ weighted image before DNP and Figure 3 is after DNP with signal elevation. Figure 4 shows T1ρ MRI signal change before and after DNP injection. Figure 5 shows Optical data of metabolic changes before and after DNP injection.

**Summary:** We demonstrated the feasibility of simultaneous measurement of T1ρ MRI and optical data on swine brain in the same sessions. The fractional change in CMRO<sub>2</sub> computed from optical data before and after DNP injection is ~ 47%. The T1ρ signal elevation was evident after DNP injection and also during 1 minute of 100% O<sub>2</sub> inhalation. Further studies using this optimized integrated protocol with <sup>17</sup>O<sub>2</sub> gas on swine are in progress.

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**References:** (1). Meiboom S. J Chem. Phys **34**, 375 (1961), (2). Reddy R, et al. J Magn. Reson. B **108**, 276-9 (1995), (3). Mellon E, et al. PNAS **107**, 11787-11792 (2010), (4). Durduran T, et al. Opt. Lett. **29**, 1766-68 (2004), (5). Culver JP, et al. J. Cereb. Blood Flow Metab. **23**, 911-24 (2003), (6). Pekar J, et al. Magn. Reson. Med. **21**, 313-9 (1991), (7). Yu G, et al. J Biomed. Opt. **10**, 024027-1-12 (2005), (8). Mellon E. et al. Adv.Exp.Med.Biol **645**, 270-86 (2009), (9). Mellon E, et al. J. Neuroscien Methods **179**, 29-39 (2009).