Tracking tissue oxygenation status and response using Diffusion-Weighted functional MRI

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Target audience: Researchers and clinicians with interest in tissue oxygenation using non-invasive MRI.

Purpose: Non-invasive oxygen-enhanced MRI (OE-MRI, such as BOLD (blood oxygen level dependant) and TOLD (tissue oxygen level dependant) and diffusion MRI provide new insights into tumor oxygenation and tumor microenvironment. Specifically, DWI MRI provides an endogenous image contrast at a cellular level based on the Brownian motion of water molecules. Intravoxel incoherent motion (IVIM) theory states that tissue diffusion was affected by capillary perfusion at low b-values[1]. Such effect may be eliminated, or at least minimized using higher b-value diffusion gradients (b > 200s/mm^2). Under the condition of oxygen challenge, the diffusion-sensitized fMRI (DfMRI) has the potential to provide noninvasive measurements of tissue oxygenation using oxygen as an endogenous paramagnetic contrast agent, the DfMRI signal changes in a voxel appear as a more complex function of the changes of tissue ADC (ΔADC), a residual relaxivity component $\Delta R'_{2t}$, intravascular deoxyHb content and a relaxivity component induced by dissolved O_2 ($\Delta R'_{2,O2} \sim \gamma \varepsilon B_0 \Delta pO_2$). To test this hypothesis, we aimed in this study to: 1) compare DfMRI response with BOLD, TOLD responses to gas breathing challenge under different baseline pO_2 level; 2) evaluate the feasibility of DfMRI for tracking tissue oxygenation status.

Methods: The well-characterized Dunning R3327 H rat prostate cancer subline was chosen (N=7). MRI was performed when tumors reached approximately 1-3 cm in diameter. Rats were examined while breathing medical air (21% O_2) and 100% O_2 at 2L/min in the order of: (1) air; (2) oxygen; and (3) return to air (Figure 1). Anesthesia was induced with isoflurane (5%) and maintained as an isoflurane/gas mixture (1.5% isoflurane at 2 L/min) delivered by a face mask. The tumors were placed inside a 35 mm home-built solenoid volume coil. MRI experiments were performed on a horizontal bore, 4.7T MRI scanner. After anatomical images were acquired, multi-parametric ^{1}H MRI-based *OXygen* Imaging (*MOXI*)[2] was performed to measure baseline oxygen tension (pO_2) during air inhalation followed by oxygen-enhanced imaging. MOXI strategy includes a series of quantitative R_1, R_2 and IVIM measurements. Briefly, quantitative R_1 measurement was performed using an inversion recovery (IR) turbo Fast Low-Angle SHot (FLASH) pulse sequence with magnitude reconstruction (TR = 2700 ms, TE 5 ms, flip angle = 10°, 5 TIs = 50, 200, 500, 1100, 2300 ms); Quantitative R_2 measurement was performed using a multiple spin-echo CPMG sequence (TR =2000 ms, 12 TEs ranged from 10 to 120ms with echo spacing 10 ms); IVIM measurement used a fast spin echo based DWI sequence (TR = 2000ms, effective TE = 56ms, diffusion gradients were applied in three orthogonal directions with 10 b-values of 0, 25, 50, 100, 150, 200, 300, 500, 1000 and 1500 s/mm^2). Oxygen-enhanced MRI includes: 1) Interleaved BOLD and TOLD acquisition. BOLD MRI data were acquired by using a T_2*-weighted FLASH sequence: TR = 200ms, 16 echoes ranging from 4ms to 64 ms with echo spacing 4ms, flip angle = 30°, TOLD MRI with a T_1-weighted FLASH sequence: TR = 30ms, TE = 3ms, flip angle = 45°. 2) DfMRI acquisition. DfMRI images were acquired using a diffusion-sensitized FSE sequence, TR = 2000 ms, Echo train Length =4, echo spacing = 10.33ms, effective TE= 51ms. Diffusion gradients applied at 3 orthogonal directions with amplitude 16.8mT/m, duration time 3ms and separation time 12ms, b value = 600 s/mm^2. A total of 40 sequential scans were acquired during medical air and 100% O_2-breathing, total acquisition time was about 20 min. A 30min interval between interleaved BOLD and TOLD and DfMRI was setup to avoid residual effect from previous oxygen challenge. All oxygen-enhanced images were co-registered and resized to same FOV (40×40mm) and same acquisition matrix (64 × 64). Activation maps showing the localized oxygen-induced signal changes, were calculated using the statistical approach (t-test) based on baseline air and oxygen challenge (air replacement period was not included). BOLD, TOLD and DfMRI time-series images were analyzed using a program written in MATLAB (MathWorks). Based on MOXI pO_2 maps ROIs were selected with different baseline pO_2's, and the averaged signal values calculated. Percent changes in the BOLD, TOLD, or DfMRI signals were calculated as % changes in signal intensity:

$$= \left(\frac{Average\ signals\ within\ ROI\ during\ oxygen\ challenge}{Average\ signals\ within\ ROI\ during\ baseline} - 1 \right) \times 100.$$

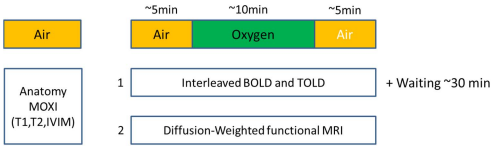

Figure1: Oxygen challenge scheme for BOLD, TOLD and DfMRI. The anatomical images and MOXI were acquired before oxygen-enhanced MRI. The OE-MRI was performed with about 5min air, followed by 10min O2, and switched to air for about 5min.

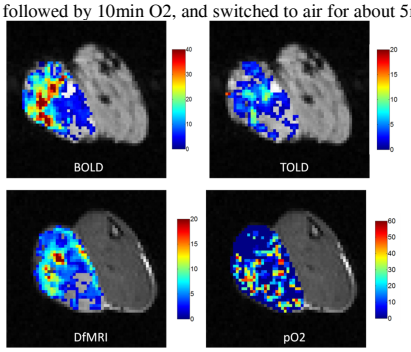

Figure 2: The activation maps of BOLD, TOLD and DfMRI responses which were overlaid on the corresponding anatomical images. The MOXI baseline pO2 maps were also generated.

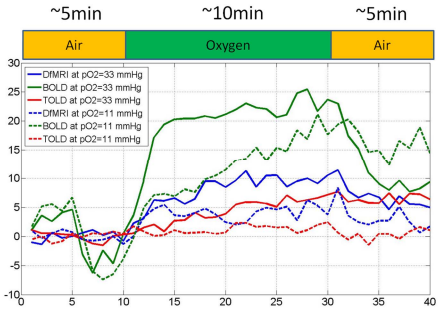

Figure 3: A typical time course of BOLD, TOLD and DfMRI responses with gas breathing challenge under 1.5% anesthesia.

Results: Representative activation maps of BOLD, TOLD and DfMRI responses together with baseline pO_2 maps are shown in Figure2. The spatially heterogeneous responses of DfMRI reflect inhomogeneous tissue (tumor) oxygenation status. Under oxygen challenge, the DfMRI signal change was 2-10 times smaller than those of the BOLD, but about 2-3 times larger than TOLD responses. In a typical case (shown in Figure 3) with higher pO_2 = 33mmHg, the average BOLD, TOLD and DfMRI responses were 19.9%, 3.6% and 8.4%, respectively. In comparison, at lower pO_2 = 11mm Hg, the average BOLD, TOLD and DfMRI responses are 14.3%, 1.4% and 3.1%, respectively. Higher baseline pO_2 exhibited larger signal changes.

Discussion: In this study, we showed that DfMRI response contents a component which is closely linked to the tissue oxygenation response. BOLD appears an overestimation of oxygenation response while TOLD gives an underestimated response. DfMRI is a powerful tool to tracking tissue oxygenation status and it can also provide the extent of response when combining baseline pO_2 measurement. Further studies should be allowed to evaluate the relationship between the baseline pO_2 and the signal changes rate (slope) which could reflects the blood flow and/or oxygen consumption in tissues.

References:

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