Characterization of Vascular Response in White Matter to Hypercapnia and Hyperoxia

Binu P Thomas[1], Virendra Mishra[1], Shin-Lei Peng[1], Hao Huang[1], and Hanzhang Lu[1]
[1]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States*

TARGET AUDIENCE: Researcher's interested in studying vascular physiology in the WM will benefit from this work.

PURPOSE: White matter (WM) dysfunction is typically studied using structural imaging techniques such as DTI, magnetization transfer and T2weighted-MRI. Unfortunately, no physiological information is provided by these methods. We recently reported that vascular response time to CO_2 gas was significantly delayed in the WM after response was measured in the GM.[1] WM in this study was composed of only the innermost core of the WM. A thorough study on this aspect of delay in vascular response in all other sub-regions of WM is further warranted. WM vascular response delay to O_2 gas is also not known. The goal of this work is to perform a thorough classification of WM into WM fiber tracts and into multiple layers in WM, with increasing depth from the cortical surface and to examine vascular response in these regions to O_2 and CO_2 gas. Results showed that most WM regions have significantly long delay in vascular response, to both O_2 and CO_2 compared to GM. One of the striking findings was that with increase in depth in WM, longer delay in vascular response to O_2 and CO_2 was seen, which suggests that blood volume and reactivity of blood vessels, decreased in deeper WM compared to WM layers closer to the cortex. We also found differences in delay to O_2 and CO_2 between different fiber tracts, which suggest that fiber tracts have differences in blood supply and reactivity.

METHODS: EXPERIMENT: 9 young (age: 30±1.4 years, gender: 4M/5F) subjects participated in the study. BOLD and DTI scans were performed on a 3T Philips system. BOLD data were acquired simultaneously with gas inhalation, in two sessions: once with O_2 inhalation and in another session with CO_2 inhalation. Each subject's End-tidal (ET)-O_2 and ET-CO_2 was continuously recorded during the scan. Both scans used standard imaging parameters and same in-plane resolution was used for better coregistration. Voxel size for the BOLD scan was 2.5 × 2.5 × 5.0 mm^3. For the DTI scan diffusion was encoded along 30 directions, with b value of 1000 sec/mm^2, and slice thickness of 2.5 mm. DATA ANALYSIS: Only ROI analysis was performed, as it is more sensitive compared to voxel-wise analysis. BOLD images were realigned, coregistered to the B0 image. DTI scans were realigned and corrected for eddy current distortion and the tensor was fit in DTI studio. 10 major WM fibers were then tracked using protocol by Wakana et al.[2] Given that arteries originate on the cortical surface, perfuse GM and then perfuse WM, it is possible that vascular response in WM is dependent on its depth from the cortical surface. So, we estimated a layer index for each voxel within WM using a step-wise erosion process that involved peeling off a single layer of WM at a time and assigning all voxels in that layer a layer index. This step was repeated to peel off multiple layers. A region with minimal partial volume effects (PVE) from GM was obtained after peeling off 7 WM layers; this ROI was called the WM core. To compare data from all WM ROIs, a GM ROI was also identified, which included GM from all slices above the lateral ventricles. To further eliminate PVE, only voxels containing 95% or higher probability of same tissue type were included. BOLD time course was then extracted from all ROIs, and delay and magnitude of response calculated. The procedure to obtain delay and magnitude was published previously.[1] Briefly, multiple-regression analyses were performed between the (ET) time course and BOLD time course for a range of delays and identifying the delay and magnitude that corresponds to the best fit.

RESULTS AND DISCUSSION: A map of vascular response to the O_2 gas (Fig. 1a) and CO_2 gas (Fig. 1b) for a representative subject is shown; a good contrast is seen between GM and WM. The delay between Et-O_2 and vascular response in GM was 11.5 ± 0.8 seconds; this delay represents the time taken by the O_2 gas to travel from the lungs to the brain and be detected in GM. In comparison the delay from Et-O_2 to the core of the WM was 32.8 ± 1.4 seconds. It takes around 21 seconds to measure vascular response in WM after response was measured in GM. This delay cannot be explained by transit delay, because bolus tracking studies show that it takes only 600ms for blood to transit from GM to WM.[3] This data suggests that the delayed response in WM is primarily due to the time taken for partial pressure of O_2 to increase and reach steady state in extravascular (tissue) space in WM and then increase in the venous blood vessels where it is detected by the BOLD scan. Vascular response delay in GM and WM to CO_2 gas was similar to that reported previously.[1] Both GM and WM ROIs take around 4 seconds more to obtain vascular response to CO_2 compared to O_2, which is attributed to the time it takes for blood vessels to dilate in response to extravascular CO_2. The core of the WM is comprised of WM layers: 7, 8, 9 and 10; we are also interested in measuring delay for individual layers 6 to layer 1 (closest to the cortical surface). Delay and magnitude of response for each layer are shown for O_2 gas (Fig. 2a) and for CO_2 gas (Fig. 2b), the delay (blue color) increases monotonically for each layer from layer 1 to 7 and then it plateaus in layers 8, 9 and 10 for both O_2 and CO_2 gas. Response to O_2 is an indicator of blood volume. This data seems to suggest that blood volume and reactivity of blood vessels in WM seems to decrease with increase in depth from the cortical surface. This theory also explains the magnitude of vascular response (red color in Fig. 2a, 2b) data, which is highest in layer1 as expected, since PVE from GM is highest in layer 1, and decreases from layer 1 to layer 7. WM was also classified into 10 major fiber tracts as shown in Fig. 3; 5 fibers: CGC, CGH, ATR, Fmajor and Fminor are shown in Fig. 3a and 5 fibers: CST, ILF, IFO, SLFt and UNC are shown in Fig 3b, displayed separately for clarity. Delay in each fiber tract to O_2 and CO_2 gas are shown in Fig. 2c, and for comparison purposes delay from the GM and core of the WM are also shown. All fibers show delays longer than the GM, but less than that for the core of the WM. Delay in response in the fiber tracts can be dependent on two factors: 1) blood supply to the fiber tract and 2) the layer in which the fiber tract is located. To obtain a fiber tract's delay due to blood supply, we factored out the layer index for each fiber tract from the analysis and obtained the delay. Significant ($p<0.001$) differences in delay between fiber tracts were measured for both O_2 and CO_2, which suggests that WM fibers show differences in blood supply and reactivity. A strong relationship was also seen between the delays measured due to O_2 and that measured due to CO_2 for the WM layers (Fig. 4a) and the fibers (Fig. 4b), which suggests that WM regions with a long delay to O_2 also show long delay to CO_2. Fig. 4 also shows that delays to CO_2 are longer than delays to O_2 in most WM regions and are attributed to the mechanism of action of these gases.

CONCLUSIONS: In summary, WM fiber tracts show differences in blood supply and reactivity in blood vessels. These data need to be further studied and compared with delays measured from patients. With increase in depth of WM from the cortical surface, both blood volume and vascular reactivity decrease. Vascular response time in WM to O_2 gas was shorter compared to that for CO_2 gas, and were found to be strongly correlated.

REFERENCES: 1) Thomas et al. JCBFM, 34: 242 (2013). 2) Wakana et al. Neuroimage 36: 630 (2007). 3) Liu et al. NMR Biomed, 25: 779 (2012).

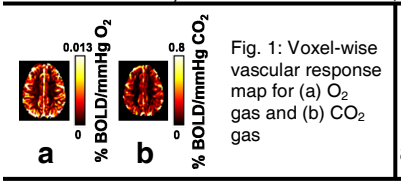

Fig. 1: Voxel-wise vascular response map for (a) O_2 gas and (b) CO_2 gas

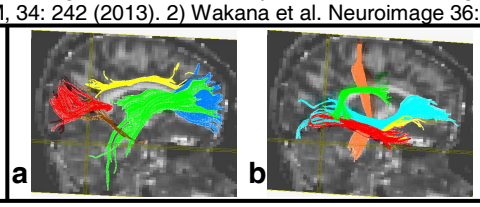

Fig. 3: 10 major WM fiber tracts (a) shows CGC, CGH, ATR, Fmajor, and Fminor, (b) shows CST, ILF, IFO, SLFt, and UNC.

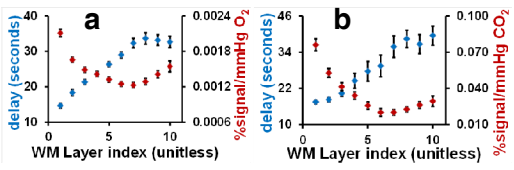

Fig. 2: Results: Delay and magnitude of response in WM layers for (a) O_2, and (b) CO_2; delay is shown in blue color and magnitude in red; (c) Delay in 10 major fibers; blue color represents O_2 delay and red CO_2 delay; error bars are std. error

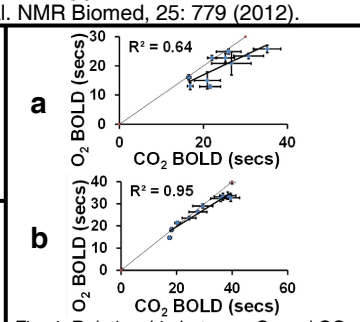

Fig. 4: Relationship between O_2 and CO_2 delay; for (a) WM layers, (b) 10 WM fibers; error bars are standard error