Comparison of transvascular water exchange between Mannitol and CO_2 challenges

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Introduction: Previous studies have shown that trans-vascular water movement (i.e.,intra-/extra-vascular water exchange rate: WER) and cerebral blood volume (CBV) can be quantified using a widely available 3D spoiled gradient echo sequence and a long-circulating intravascular contrast agent (Gd-PGC).[1,2,3] In this study, we used two distinctive physiological challenges: (1) intravenous administration of Mannitol and (2) CO_2 inhalation, to describe and compare independent changes in CBV and WER. Although a number of reports suggest that both CBV and cerebrovascular permeability are perturbed in response to these challenges[4], the vascular parameters have never been either fully assessed or compared using proper quantification strategies. In this regard, we demonstrated the relationships between CBV and WER and investigated possible mechanistic differences between two challenges.

Materials and Method: Ten C57BL mice were used in this study. A 3D SPGR (spoiled gradient echo) pulse sequence was used for MRI data acquisition at a 9.4T scanner (Bruker Biospin). Before and after intravenous administration of Gd-PGC, 3D volume images (Matrix: 64 x 64 x 128, FOV: 1.5 x 1.5 x 2.5 cm) were collected with TR/TE = 30/3 ms with varying flip angle = 30 and 90° degrees. Additional 3D-SPGR scans with TR/TE = 30/5, 7 ms at fixed flip angle of 30° were also performed to calculate changes in T_2^* due to Gd-PGC. After baseline data collection, 7 mice were given three Mannitol bolus (20%, 100ul) everything 30 minutes in addition to a low dose infusion of Mannitol (20%, 100ul/hr). Other three mice received 10% and 15% CO_2 challenge. ROI analysis was performed in cerebral cortex. The apparent blood volume was calculated based on: $V_{app}^{\alpha} = \dfrac{SI_{postGd-PGC}^{tisue} - SI_{preGd-PGC}^{tisue}}{SI_{postGd-PGC}^{blood} - SI_{preGd-PGC}^{blood}}$, where SI is the signal intensity and α is the flip angle. The water exchange index (WEI) is defined as shown in the following equation: $WEI = \dfrac{V_{app}^{30}}{V_{app}^{90}}$. While, the absolute CBV was estimated using V measured using $\alpha = 90°$.

Results and Discussion: In general, there was a steady and significant increase of CBV after each Mannitol bolus (Fig 1A). The WEI also increased significantly after the initial Mannitol administration (Fig 1B). However, the measured WEI after the first Mannitol bolus was not affected significantly by the repeated Mannitol administrations and the associated CBV changes (Fig 1B). On the other hand, the CBV increased by ~ 50% due to the increase of CO_2 (i.e., 10 and 15 %) in the gas mixture (Fig 2A). The average WEI value increased in response to the CO_2 challenge, suggesting small but appreciable increases of the BBB water permeability (Fig 2B); however, this increase was not statistically significant. In addition, the increased average WEI was correlative with the CBV changes (Fig 3A). These results agree with the previous observations, in which hypercapnia increases the BBB permeability to protein and surgar[4]. Interestingly, the slope of the WEI vs. CBV curve due to repeated Mannitol injections (excluding the baseline) was similar to that obtained during CO_2 challenge (Fig 3), implying that the WEI increases due to the 2nd and 3rd Mannitol injections are probably caused by the same mechanism that is also responsible for the WEI increase during CO_2 inhalation (i.e., CBV increase). On the other hand, the dramatic increase in WEI due to the 1st Mannitol bolus is more likely induced by the sudden change in osmotic pressure across the BBB. In summary, we demonstrate that the proposed MRI technique is independently sensitive to changes in CBV and altered BBB integrity. Using Mannitol and CO_2 challenges, this study revealed that the WEI increase is associated with the CBV change and that the current technique provides means to describe the altered cerebrovascular function.

References: 1. Kim, YR, MRM 2002. 2. Bogdanov, AA, Radiology, 1993, 3. Kim, YR, MRM 2008, 4. Evans, C. A., J. Physiol, 1976,

Acknowledgement: MIND and NCRR

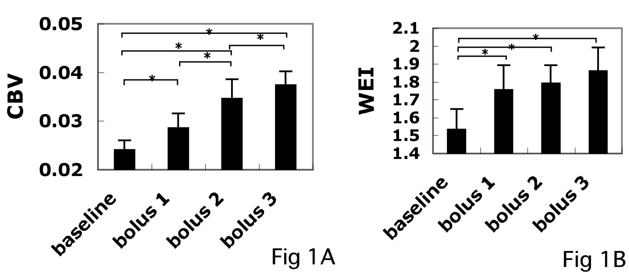

Figure 1: CBV and WEI changes due to Mannitol.

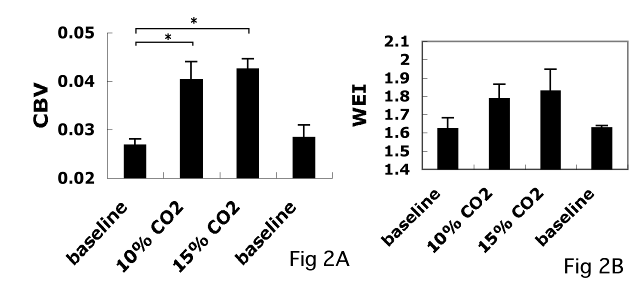

Figure 2: CBV and WEI changes due to CO_2 challenge.

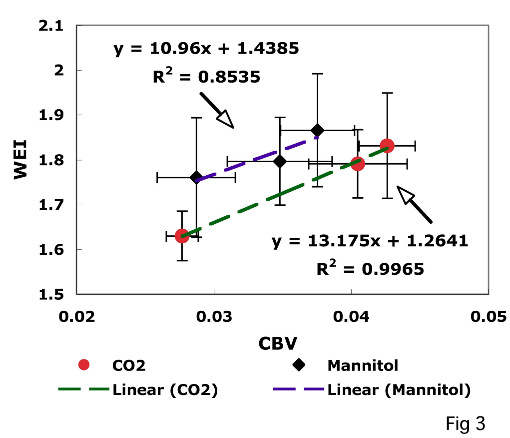

Figure 3: WEI vs. CBV curve for Mannitol and CO_2