Quantification of Blood Volume and Transvascular Water Exchange using Gd-DTPA in Mouse Brain

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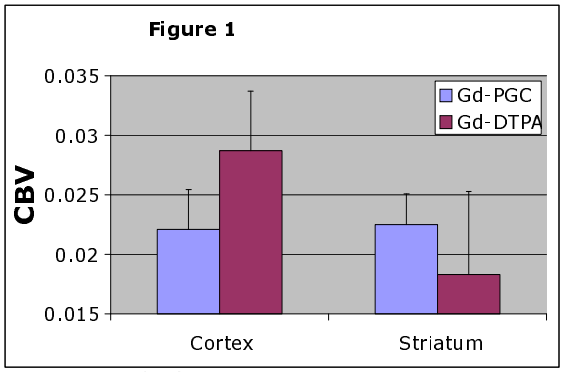
INTRODUCTION Previously, the water exchange rate (WER) through a semi-permeable membrane has been quantified using MRI and T_1 changes due to compartment-occupying (e.g., intravascular, extra-cellular) MR contrast agents. In order to successfully execute such measurements, (1) the contrast agent should not leak into the other compartment across membrane, and (2) the contrast agent concentration should be invariant over the MR imaging time. To meet these conditions, continuous infusion of contrast agent (compensating for the decaying concentration over time) and the use of long circulating macromolecular agents (e.g., Gd-PGC) have been employed for calculating the WER across cytolemmal membrane and the blood-brain barrier (BBB), respectively.[1,2] In the current study, we have developed a novel MRI scheme with corrections for T_2*-weighted signals for quantifying relative WER across non-leaky cerebrovascular membrane (i.e., BBB) and absolute cerebral blood volume (CBV), irrespective of the time-dependence of systemic contrast agent (e.g., Gd-DTPA: MW ~500 Da) concentration. Using normal wild type mouse models, we compared regional WER and CBV (cortex vs. striatum) determined by the typical macromolecular approach (Gd-PGC: MW ~500,000 Da) with the results acquired with the proposed method using the widely available Gd-DTPA. Despite the severe time dependence of the blood Gd-DTPA concentration, the measured CBV and WER were similar to those quantified by the traditional macromolecular method.

MATERIALS AND METHODS Six normal healthy C57BL/6 mice (~25g) were used for used for (1) Gd-PGC (n=4) and (2) Gd-DTPA experiments (n=2). A modified-3D SPGR (spoiled gradient echo) pulse sequence was used for MRI data acquisition at 9.4T. Each phase encoding was interleaved with three different TE in order to obtain the averaged signal over varying systemic contrast agent concentration (e.g., Gd-DTPA). Multi-TE acquisitions were designed in order to correct for the time-dependent T_2*-weighted signal contribution. For *in vivo* MRI experiments, before and after intravenous administration of Gd-PGC, a set of 3D volume images (Matrix = 64 x 64 x 128 and FOV = 1.5 x 1.5 x 3 cm^3) were collected using TR/TE = 30/[3, 5, 8] ms for each flip angle (40 and 80°). For the different set of mice, the same MRI acquisition was performed except the Gd-PGC was replaced by Gd-DTPA. ROI analysis was performed in the cerebral cortex and striatum. The apparent blood volume V_{app}^{α} was calculated using $V_{app}^{\alpha} = \frac{SI_{postGd}^{tisue} - SI_{preGd}^{tisue}}{SI_{postGd}^{blood} - SI_{preGd}^{blood}}$, where *SI* is the MRI signal intensity and α is the flip angle. Water exchange index (WEI) is defined as V^{40}/V^{80} while the absolute CBV was estimated using V measured using $\alpha = 80°$.[1] For each flip angle, exponential fitting was performed to calculate changes in T_2* due to Gd-PGC and Gd-DTPA.

RESULTS AND DISCUSSION For the Gd-PGC technique, the absolute CBV fraction was similar between cortex and striatum. However, the CBV estimated using Gd-DTPA was regionally differentiable, in which the cortical CBV was consistently greater than that measured in the striatum (Fig 1). As shown in Fig 2, for both Gd-PGC and Gd-DTPA techniques, greater WEI values were observed for the cortex than the striatum, probably due to a large population of capillaries in the cortex. Different WEI values (magnitude) were expected between two techniques due to unmatched contrast agent concentrations and corresponding differences in blood T_1. However, the WEI ratio (striatum/cortex) was also inconsistent between two contrast agents. We speculate that incomplete correction of region-dependent T_2* contribution and a small number of animals (n=2) may have resulted in such a discrepancy. Although still preliminary, our findings demonstrate the important feasibility of using a widely available contrast agent for determining both CBV and WER without complicated algorithms. In particular, the availability of Gd-DTPA for human use extends the application of this current technique to assess regional BBB water exchange differences in clinical populations. However, the inconsistencies noted in the current results warrant additional signal simulations for determining the measurement accuracy and sensitivity.



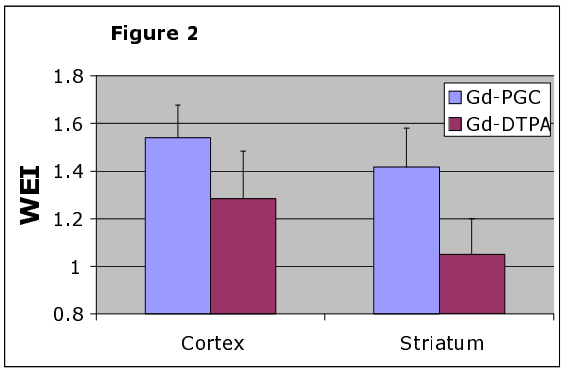


Figure 1 and 2. Measured CBV (Fig. 1) and WEI (Fig. 2) based on ROI analysis (cortex and striatum) using Gd-PGC and Gd-DTPA.

REFERENCES

1. Kim et al., *Magn Reson Med* 60(4): 813-21. 2. Landis et al., *Magn Reson Med* 44(4): 563-74.