Gadolinium Based Steady-state Technique for Longitudinal Fractional Cerebral Blood Volume Mapping

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Introduction Cerebrovascular abnormalities have been shown to be indicative in the conversion from mild cognitive impairment to Alzheimer Disease (1), supporting the notion of a vascular role in AD pathogenesis (2). Hypometabolism in AD can be measured indirectly through metabolic coupling to perfusion by measuring cerebral blood volume (CBV) and cerebral blood flow. In a transgenic mouse model of AD, it was reported that regional CBV is lower in hippocampus, cerebral cortex, and thalamus (3) in 4 months old APP (V717F, K670N/M671L) mice compared to age-matched normal. To investigate whether CBV is a predictive biomarker in transgenic APP mouse model, longitudinal studies of CBV require non-invasive techniques and procedures. Currently, dynamic contrast imaging and steady state imaging are two main techniques to measure CBV. However, they both require intravenous injection of contrast agent while the animal is inside the scanner, necessitating surgical cannulation of the vein. The procedure is invasive and is not feasible for longitudinal studies.

Recently, intraperitoneal injection of high-dose Gd-DTPA has also proven useful for generating strong changes in the transverse relaxation rates of mouse brain in vivo at 9.4T (4). The current study has the following aims: 1) to validate the method at 4.7 T using a similar contrast dose; 2) study the change in transverse relaxation rate versus contrast concentration in large blood vessels following intraperitoneal injection of Gd-DTPA; and 3) evaluate the feasibility of its use as a normalization parameter to enable longitudinal studies of fractional blood volume in animals with intact blood brain barriers.

Materials and Method The imaging experiments were performed on a 4.7T horizontal bore system interfaced with a Bruker console. C57BL/6 mice (n=4) were anesthetized at 1.5% isofluorane with 95% oxygen to minimize the magnetic susceptibility introduced by deoxyhemoglobin in blood. Magnevist^{Tm} Gd-DTPA was injected intraperitoneally at 8 mmol/kg through a 1m IP catheter. After 6 minutes post injection delay when the T1 enhancement in large veins has been surpassed by T2 shortening, low resolution T2-weighted coronal MR images were acquired with a 2D FSE sequence at TR/TE_{eff}/ETL=2000ms/9.5ms/2 to capture the blood signal at superficial temporal vein and sagittal sinus at 2 mins temporal resolution followed by a high resolution T2-weighted 2D FSE sequence to cover the mouse brain. Scan parameters of the high resolution protocol were TR/TE_{eff}/ETL=2000ms/72ms/8 at 1mm slice thickness and an in-plane resolution of 78µmx150µm with a temporal resolution of 12 mins. The low resolution scan and high resolution scan were repeated 6-7 times to capture all contrast changes in large veins and concurrent transverse relaxivity changes in brain tissue. The change in transverse relaxivity, ΔR_2, at steady-state was computed by:

$$\Delta R_2 = 1/TE_{eff} * \log (S_{pre}/S_{post}) \quad \text{(Eq. 1)}$$

where S_{pre} and S_{post} are the pre-contrast and post-contrast image intensity respectively.

From the low resolution protocol, ΔR_2 in a large vein was computed and fitted to a 3nd order polynomial (R^2>0.99 for all cases) to estimate the ΔR_2 in the blood during the acquisition of the high resolution protocol. To understand the concentration change intravenously, consider a two compartment model of peritoneal cavity transport (5) where C_{pc} is the Gadolinium concentration in peritoneal cavity and C_{blood} is the Gadolinium concentration in blood:

$$V_{pc}\, dC_{pc}/dt = MTC\, (C_{blood}-C_{pc}) \quad \text{(Eq. 2)}$$

where MTC is the mass transfer coefficient, V_{pc} is the volume in the peritoneal cavity. At t=0, $C_{blood}(0)=0$, $C_{pc}=C_{pc}(0)$, the asymptotic limit is computed as:

$$dC_{pc}/dt = -MTC/V_{pc}C_{pc}(0)$$

For small C_{blood}, a concurrently linear increase of C_{blood} over time is expected given blood flow is not a limiting factor:

$$C_{blood}=k_{12}C_{pc}t \quad \text{(Eq. 3)}$$

At later time when C_{blood} and C_{pc} are equal, the transfer process stop and C_{blood} would be driven by extravasations and ultrafiltration mechanisms.

Fractional blood volume, fBV, can be computed by Eq. 4 as defined in (6):

$$\Delta R_{2,tissue}=k\, fBV\, (C_{blood}B_0)^{2/3} \quad \text{(Eq. 4)}$$

$$\Delta R_{2,blood}=f(C_{blood}(t)) \quad \text{(Eq. 5)}$$

where f is a characteristic function relating ΔR_2 in the blood and the contrast concentration within. If f is a constant,

$$fBV = \xi \Delta R_{2,tissue}/(\Delta R_{2,blood})^{2/3} \quad \text{(Eq. 6)}$$

where $\xi=(f/B_0)^{2/3}/k$. ξ for a group of animals can be determined from fBV ranges in the literature. To confirm the assumption that f is constant, $\Delta R_{2,tissue}$ of different brain regions would be least square fitted to the $(\Delta R_{2,blood})^{2/3}$ multiplied by a scalar to confirm the assumption of f over a large concentration range .

Results Fig. 1 showed a representative example of ΔR_2 of blood, which increased linearly in the superficial temporal vein for the first 30-45 minutes. According to our models at Eq. 3 and Eq. 5, the characteristic function f can be reasonably assumed to be a constant for linear region of $\Delta R_{2,blood}$ under the experimental conditions in this study. ΔR_2 in different brain regions were found to consistently correlate to $(\Delta R_{2,blood})^{2/3}$ of both superficial temporal vein and sagittal sinus, but superficial temporal vein are much larger to identify and usually gives a better fit to ΔR_2 of different brain tissues. The $\Delta R_{2,tissue}$ all fits well to $(\Delta R_{2,blood})^{2/3}$ (R^2=0.95 to 0.99) as in Fig. 2 and also in 2 other cases (R^2=0.88 to 0.99) and one case with motion (R^2=0.81 to 0.98). The summarized fBV from all four cases were plotted as mean fBV ± 1SD in Fig. 3 where the fBV ranges from 2% to 4% which matches well to known physiological range with low fBV in hippocampus and hypothalamus and high fBV in superior colliculus, thalamus, and midbrain (3). The scaling parameters, ξ, common to all four cases were found to be 0.3.

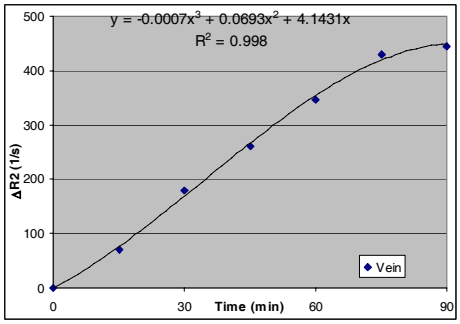

Fig. 1 ΔR_2 in large blood vessel after IP injection.

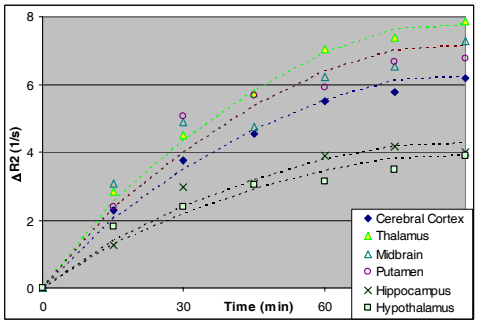

Fig. 2 ΔR_2 at different brain regions after IP injection

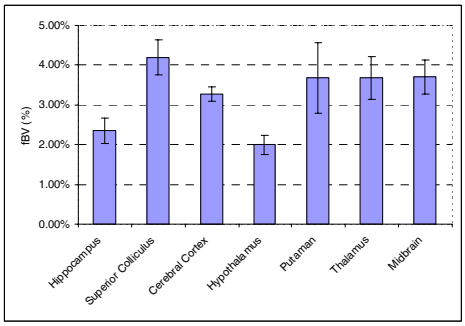

Fig. 3 Fitted fBV at different brain regions (n=4)

Discussion We used a simplified model of peritoneal transport and used it to validate our assumption of proportional increase of blood ΔR_2 with the gadolinium contrast concentration in the blood. The assumption seems valid as it fits well over a large contrast concentration range with the tissue ΔR_2, suggesting a good experimental agreement of the relationship between $\Delta R_{2,tissue}$ and C_{blood}. Fractional blood volume can be mapped with IP injection of gadolinium at 4.7T using large blood vessel as a normalization parameter. The determined fractional blood volume in different brain regions is consistent with known physiological range.

References

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