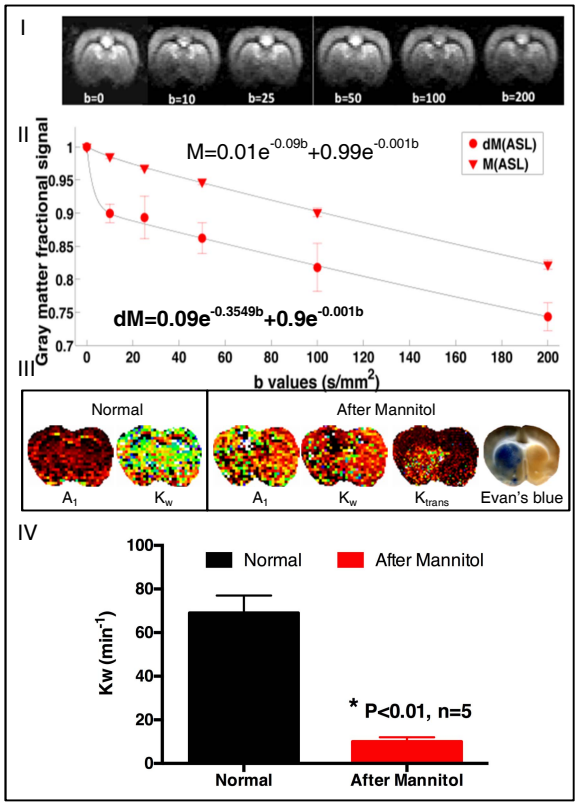
Measuring blood-brain-barrier permeability using Diffusion-Weighted Arterial Spin Labeling (DW-ASL): Corroboration with Ktrans and Evan's blue measurements

Yash Vardhan Tiwari[1,2], Qiang Shen[1], Zhao Jiang[1], Wei Li[1], Justin Long[1,2], Chenling Fang[1,2], and Timothy Duong[1]

[1]*Research Imaging Institute, UT Health Science Center, San Antonio, Texas, United States,* [2]*Biomedical Engineering, UT, San Antonio, Texas, United States*

Target Audience: Researchers interested in blood brain barrier permeability.

Purpose: Blood-brain-barrier (BBB) dysfunction has been implicated in a number of neurological disorders, such as multiple sclerosis, stroke and cancer. BBB integrity can be assessed by measuring the water exchange rate across the BBB (K_w) – defined as PS/V_c where PS is permeability surface area product and V_c is capillary distribution volume of water. Diffusion-weighted arterial spin labeling (DW-ASL) was recently proposed to measure K_w without using an exogenous contrast agent in humans[1]. However, this approach has not been validated. The goal of this study was to compare K_w measurements (DW-ASL) with K_{trans} (DCE MRI) and histological staining (Evan's blue) in the same rats. Measurements were also made before and after mannitol administration to break the BBB.



Methods: Rats were ventilated with 1.5% isoflurane and physiological parameters were maintained in normal range. DW-ASL was implemented on a 7T Bruker scanner.

Study#1 (n=8): Multi-b DW-ASL scans with b values=0, 10, 25, 50, 100, 200 s /mm^2 (at post labeling delay > tissue transit time, τ_a) were acquired and fitted to the bi-exponential model $\Delta M(b)/\Delta M(0) = A_1 e^{-bD1} + A_2 e^{-bD2}$, where ΔM is the mean ASL perfusion image, A_1 and A_2 are fractions of the fast (vascular) and slow (tissue) components, D_1 and D_2 are the pseudo-ADCs. K_w was estimated from A_1 and A_2 using single pass approximation model (K_w 0:200 min^{-1} with T_{1blood} =2.212 s, $T_{1tissue}$= 1.8 s, τ_a=350ms, PLD=500 ms, LD=2.33 s). In addition, A_1, A_2 and K_w were also calculated from the simplified two-b experiments (b=0, 50 s/mm^2).

Study#2 (n=5): Two-b DW-ASL experiments were performed before and 15 mins after mannitol injection (25%, 5g/kg, retrograde via external carotid artery[2]). This was followed immediately by K_{trans} measurement using Gadolinium (0.2 ml/kg Omniscan)[3]. After MRI experiments, 4% Evan's blue (1ml) was administered I.V. and brain slices were obtained for histochemical analysis.

MRI methods: Four 3 mm thick slices were acquired. DW-ASL used spin-echo EPI with matrix=64x64, TR=3000ms TE=28 ms, LD=2.33s, PLD=500ms, $\delta_{diffusion}$=1.6 ms, $\Delta_{diffusion}$=7.08 ms. ASL was measured using the two-coil continuous ASL technique. K_{trans} used FLASH with TE=2.4 ms, FA=30^0, TR=200 and 3000ms, matrix=128x128, FOV=25.6x25.6 mm^4.

Results: Arterial transit time (ATT) was estimated to be 250 ms from ΔM signal curve using multiple post labeling delays (n=4). Transit time to capillary-tissue compartment (τ_a) was assumed to be 350 ms (arterial transit time+100 ms).

ΔM and M (non-labeled ASL) signals from multi-b data fitted well to the bi-exponential model (n=8, R^2= 0.997, 0.998 respectively) (**Figure I-II**). Using the full model, A_1 and K_w were estimated to be 0.094 (95% Confidence bounds: 0.053, 0.14) and 70 min^{-1} (95% Confidence bounds: 59 min^{-1}, 86 min'$^{-1}$) respectively. Using the simplified two-b model, A_1 and K_w were estimated to be 0.14±0.02 and 58±6 min^{-1} respectively.

Figure III shows the A_1 and K_w map before and after mannitol, along with the K_{trans} map and Evan's blue brain slice. K_w measured before mannitol was similar to study#1 (69±8 min^{-1}, n=5). Mannitol caused BBB disruption laregely to one hemisphere. K_w in the affected hemisphere decreased to 10±2 min^{-1} after mannitol (P<0.01, n=5) (**Figure IV**). K_{trans} and Evan's blue staining showed similar patterns of BBB disruption.

Discussion and Conclusions: Our K_w estimate under normal conditions is similar to previously reported values (PS~138-319 ml/100g/min [5-6], V_c~1.5-2 ml/100g [7]: K_w~69-160 min^{-1}) using microtransillumination and radiotracer techniques. Mannitol mediated BBB disruption resulted in changes in K_w and K_{trans}. Extravasation of Evan's blue further confirmed mannitol-mediated BBB leakage. Quantitative comparison of K_w, K_{trans} and Evan's blue stains is challenging as these methods measure different aspects of BBB permeability. These measurements were also made at slightly different time points after mannitol injection. As a result, the amount of tracers and time allowed for tracer accumulation also differed.

An advantage of K_w measurement by DW-ASL is that no external contrast agent is required. As a result, serial measurements can be performed for monitoring longitudinal changes in BBB. However, inherent low SNR of ASL technique is a potential limitation. Future studies will incorporate K_w measurements in ischemic stroke and TBI.

In conclusion, we successfully implemented the DW-ASL measurement to obtain the water exchange rate K_w in the rat brain without using a contrast agent. Mannitol modulated K_w which was corroborated by K_{trans} measurements and Evan's blue extravasation. This approach could have potential applications in many neurological diseases.

References: (1) St Lawrence MRM 2012. (2) Duong MRM 2000. (3) Ewing MRM 2003.(4) Li PlosOne 2014. (5) Pardridge JCBFM 1985. (6) Ginsberg Brain Res 1985. (7) Pawlik Brain Res 1981.