Multi-compartment analysis on water dynamics in rat brain by heavy water perfusion

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Introduction: Heavy water (D_2O) has been used as a freely diffusible tracer for MR perfusion imaging since early days. A multi-compartmental analysis of the tracer dynamics were utilized in a few pioneering reports. [1, 2] In a recent study, a new strategy for detecting heavy water tracer by monitoring the attenuation of ^1H signal has been suggested for its advantage of good SNR. [3] In this study, by using this new strategy for rodent brain imaging, we further re-investigate the heavy water dynamics with a multi-compartmental analysis method, and explored the spatial distribution of fast and slow compartments of heavy water flow. This study on free diffusible tracer may shed new light on the *in vivo* water dynamics between blood and tissues.

Material and methods: A two-compartment model was used by modeling the tissue concentration-time curve as a result of convolution AIF with a combination of two exponential residue functions: $C_t(t)=AIF(t)\otimes(F_1\exp(-k_1t)+F_2\exp(-k_2t))$, where F_i, k_i is the flow and efflux constant of *i*th compartment, respectively. Adult male Sprague-Dawley rats (weight=290~350g, N=6) were scanned under 1.5% isoflurane anesthesia at a 7T Bruker Clinscan MRI scanner. For each rat, isotonic D_2O saline was steadily infused with a dose of 2ml /100g in two minutes through tail vein with a syringe pump. 80 dynamic scans were acquired with following parameters: turbo spin-echo with TR/TE=2000/14ms, matrix size=256*128, FOV=35mm, turbo factor=8, slice=8, slice thickness=1.5mm, distance factor=40%, sampling interval=34s. Heavy water infusion was started after 20 baseline measurements. Relative concentration-time curve was estimated by calculating signal change from baseline level. The AIF was extracted by averaging 3-6 selected pixels in the area of middle cerebral artery. Then the wash-in phase was reconstructed by linear function and wash-out bi-exponential function as used in DCE-MRI studies.

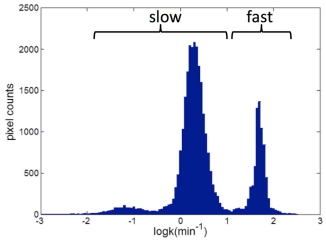

Fig. 1 The histogram of efflux constant k. Two major peaks were observed in all rats.

Results: Fig.1 shows a histogram of pixel count according to the $\log_{10}$ of efflux constant k in one rat brain. Two major peaks were observed in all 6 rats, while the minor peak at -1 was unobvious in several cases. The corresponding flows were categorized into slow and fast k compartments according to the k constant. Fig. 2 shows the flow maps of slow and fast compartment. Note that the slow flow in Fig. 2b covers almost whole brain with nice contrast of white matter. On the contrary, the fast flow is observed in some specific areas (Fig. 2c), including the ventricles (e. g. white arrow). Fig. 3 depicted typical concentration-time curves of single pixel. It is noted that the curve in Fig. 3a is a combination of fast and slow compartment, and the curve in Fig. 3b is dominated by slow compartment.

Discussion and Conclusion: In DCE-MRI with Gd-based contrast agent, the tracer is perfused into the limited extracellular-extravascular space. However, using heavy water as a free diffusible tracer, the observed tracer kinetics is quite different, and may be used to reveal the water dynamics *in vivo*. Taking advantage of good resolution and SNR by using the new imaging strategy, we demonstrated the feasibility of multi-compartmental analysis with temporal and spatial information. Some observations of fast and slow compartment may be inconsistent with the early report by Detre JA et al., and need to be further investigated. The slow flow map contains a nice contrast of brain tissues and covers almost whole brain. Therefore, the slow flow is anticipated as cerebral blood flow. The concentration-time curve of the fast k compartment shows a significant peak of rapid wash-in and wash-out, and the spatial distribution is limited in specific regions. It is speculated that there are high vessel densities in these specific regions. It is interesting to see the regions with CSF are included in the fast compartment. A possible explanation of this phenomenon may be due to the active secretion of CSF or a more diffusible blood-CSF-barrier than the BBB.

Reference:[1] Kim SG and Ackerman JJH, *Magn Reson Med*, 8:410-426, 1988.[2] Detre JA et al., *Magn Reson Med*, 14:389-395, 1990.[3] Wang FN et.al. *NMR Biomed*, 26:692-8, 2013. [4] CE Johanson –Neuroscience in Medicine, 2008

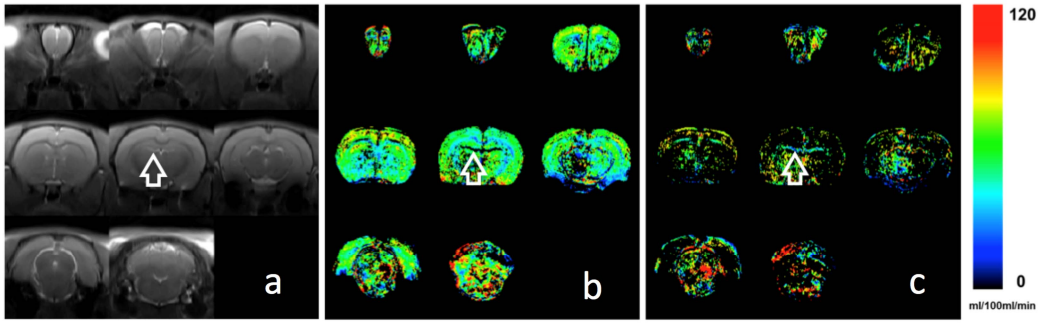

Fig. 2 (a) Anatomic TSE images. (b) Slow flow maps. Note the wide coverage of slow compartment and nice white matter contrast. (c) Fast flow maps. Note the ventricles are included in the fast map (e.g. white arrows)

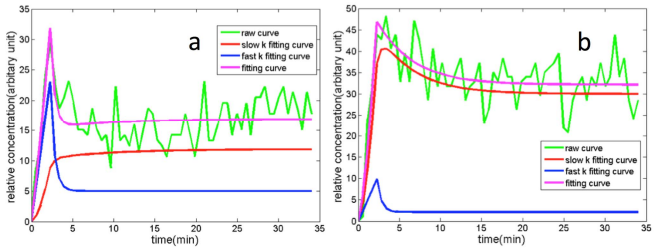

Fig. 3 The concentration time curves fitted by slow (red line) and fast (blue line) compartments in single pixels. (a) A curve consists of fast and slow compartments. (b) A curve dominated by the slow compartment. Rapid wash-in and wash-out was observed in the curve of fast compartment.