Separation and Quantitative Assessment of Mobile Lipid and Lactate Level by Diffusion Weighted Magnetic Resonance Spectroscopy (DW-MRS)

Anna M. WANG[1,2], Karrie Mei-Yee Kiang[3], GK Leung[3], Adrian Tsang[1,2], Victor B. Xie[1,2], Hua Guo[4], and Ed X. Wu[1,2]

[1]Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Hong Kong, Hong Kong, [2]Department of Electrical and Electronic Engineering, The University of Hong Kong, Hong Kong, Hong Kong, [3]Department of Surgery, The University of Hong Kong, Hong Kong, Hong Kong, [4]Center for Biomedical Imaging Research, School of Medicine, Tsinghua University, China

INTRODUCTION: Both lactate and lipid levels have high diagnostic value as lactate could reveal the presence of hypoxia, which induces resistance to both radiotherapy and chemotherapy and lipid indicate the presence of necrotic cell death or apoptosis (1). Lactate is a valuable biomarker in ^{1}H-MRS or spectroscopic imaging for cancer management (2). Patient lactate detection is in a pressing need for its diagnosis and the evaluation of response to therapy. However, the presence of mobile lipid, which has a strong signal resonant at 1.2-1.4 ppm would overlap with lactate peak at 1.3 ppm. Conventionally they were resolved at TE=144ms when the lactate doublet at 1.3ppm reverses and points to the negative direction (2,3). Yet this method is SNR inefficient and often compromised by the chemical shift displacement artifact (4). Here we hypothesize that diffusion weighted magnetic resonance spectroscopy (DW-MRS) can efficiently separate the overlapped lactate and lipid signal at 1.3ppm as lactate is a small metabolite which had relatively high diffusivity compare with lipid. The large discrepancy of lipid and lactate diffusivity allows the robust bi-exponential fitting and computation of the lipid and lactate content.

MATERIALS AND METHODS: A total of 6 SD rats (body weight around 260g) were injected with 10^6 C6 glioma cells into the right striatum using a stereotactic device. The MR experiments were conducted on the18th day after injection. All MR experiments were performed on a 7T Bruker animal scanner. For each rat, the tumor part of varied volume (80-250μL) was selected for localized spectroscopy. For DW-MRS, a stimulated-echo (STEAM) based single-voxel MRS sequence was implemented by adding a pair of unipolar diffusion gradients in two TE/2 intervals and diffusion gradient was applied along the interaural line, i.e. along x axis. Diffusion weighted spectra were acquired with TR/TE = 1300/50ms, δ/ Δ =18/60ms, 6 b-values (0 and 50000 s/mm^2). On resonance frequency was shifted on 1.3ppm. Phantom experiment was performed on a double layer cylinder that contained 400mM lactate solution in the outer layer and olive oil inside the central tube. The experimental reproducibility was checked by repeating the experiments 3 times on 2 rats. Spectral analysis was performed using JMRUI and TOPSPIN software packages. The overlapped lipid and lactate signals at 1.3ppm were quantified by fitting the spectrum to a Lorentzian line shape using the AMARES algorithm. The diffusion weighted signals at 1.3ppm were fitted to a bi-exponential decay model. The ADC value and content of lactate and lipid were calculated for each rat from the fit. The relative lipid and lactate concentration were normalized by noise and voxel size.

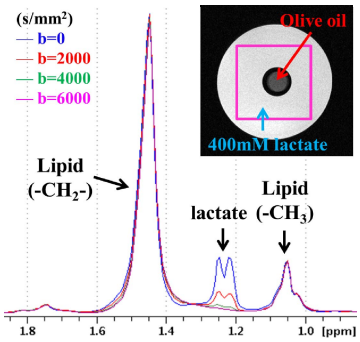

Fig.1 The lactate signal suppressed by diffusion weighting. T1-weighted image of the lipid/lactate phantom is given on the upper right. Lipid resonance was shifted to 1.45ppm due to the bulk susceptibility effect.

RESULTS: Fig. 1 shows the lactate signal can be efficiently suppressed by diffusion weighting without largely reduce the lipid signal. In this phantom experiment, the cylinder was placed along the main magnetic field and the DW-MRS voxel (Fig. 1, pink square) contains both olive oil and lactate solution. Under this condition, the lipid signal was shifted to 1.45ppm due to the bulk susceptibility effect and resolved with the lactate signal (5). The lactate signal decayed to undetectable level with b=6000s/mm^2 while the lipid signal had not much decreased, showing the large discrepancy of the diffusivity, i.e. the ADC value of lactate and lipid. For the in vivo C6 glioma rat model, the tumor size varied a lot among these 6 rats. Fig.2a gives the medium tumor size and corresponding DW-MRS voxel in the T2-weighted image. The presence of mobile lipid was confirmed by the Oil Red O staining. Note that the lipid was accumulated in the form of lipid droplet inside the C6 tumor cells (Fig 2b). Typical diffusion weighted spectra are showed in Fig. 2c, the strong lipid signal had dominated the spectra and the reduced creatine and NAA signal is the sign of massive neuronal cell death. The bi-exponential fit of the peak at 1.3ppm is shown at the upper left part in Fig. 2c. The signal is well fitted using the bi-exponential model to compute the content and ADC of lipid and lactate. The lipid and lactate concentration (per μL) of these 6 rats are given in Fig.3 along with the ADC values. Our result shows the lactate ADC in C6 glioma is 2.9(±0.9)×10^{-4} mm^2/s and the lipid ADC is 3.3(±1.3)×10^{-4} mm^2/s.

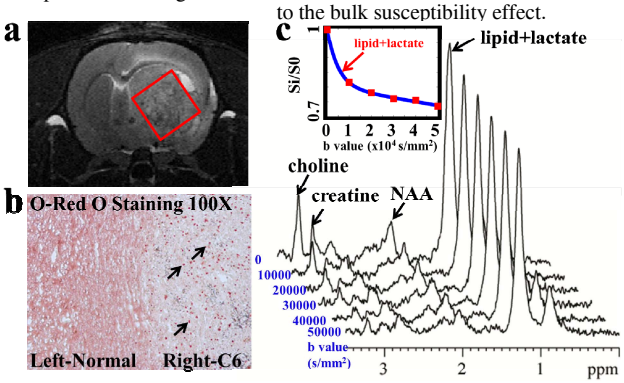

Fig.2 (a) T2-weighted image for the localization of DW-MRS voxel (red rectangle). (b) Oil Red O staining of the normal brain and tumor tissue. The red dots pointed out by the arrow are the mobile lipid accumulated in the form of lipid droplets. (c) Separation of lipid and lactate by DW-MRS, corresponding fitting of the lipid and lactate signal is shown in the upper left figure.

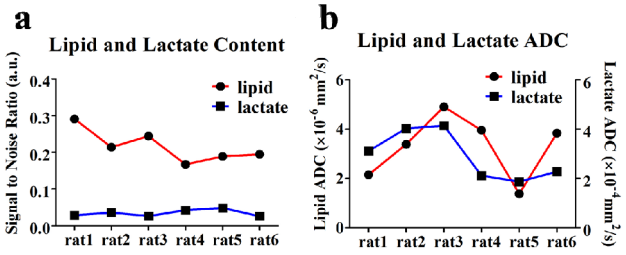

Fig.3 The individual plot of the lipid and lactate content (per μL) (a) and ADC value (b).

DISCUSSIONS AND CONCLUSION: Lactate plays a pivotal role in many brain pathologies such as tumors, stroke, hypoxia, and several mitochondrial disorders(4). The presence of mobile lipid in brain may be the sign of both necrotic cell death and apoptosis (1,6). The highly necrotic nature of tumor tissue would cause large amount of lipid accumulated which make the lactate measurement difficult. Previous NMR studies had measured the mobile lipid ADC value in the rat glioma model and suggested the fast diffusion component at 1.3ppm to be lactate (7). The diffusion coefficient of lactate from previous human brain tumor study was 2.3×10^{-4} mm^2/s (8), which is comparable to our results. In our results, the lactate and lipid ADC shared the similar inter-animal fluctuation pattern (Fig. 3b), implying that these ADC value could be affected by the highly necrotic and inhomogeneous structure in the tumor center. The reproducibility of the content and ADC measurement was checked by repeat the whole experiment for 3 times on 2 rats. The inter-experimental variations for content measurement are 1.9% (lipid) and 6.4% (lactate) while for the ADC measurements are 6.7% (lipid) and 9.2% (lactate). The reproducibility for lactate measurement are lower than lipid because the concentration of lactate is much lower than lipid in this experimental glioma model which had the lipid concentration almost 10 times higher than the lactate (Fig 3a). Our data suggested that DW-MRS can be a useful tool for the separation and measurement of mobile lipid and lactate signal for not only the tumor but also other brain disorders. The clinical application of this method might be possible by using a minimum of 3 b-values to calculate the lactate and lipid signal yet it could still be challenging due to the low gradient strength on the clinical MR system.

REFERENCES: 1. Delikatny EJ, et al.. Nmr Biomed 2011;24(6):592-611. **2.** Kobus T, et al.. Magnet Reson Med 2013. **3.** Yamasaki F, et al. Neurosurgical review 2005;28(4):267-277. **4.** Lange T, et al., Am J Neuroradiol 2006;27(4):895-901. **5.** Szczepaniak LS, et al. Magnet Reson Med 2002;47(3):607-610. **6.** Blankenberg FG, et al.. Blood 1996;87(5):1951-1956. **7.** Lahrech H, et al.. Magn Reson Med 2001;45(3):409-414. **8.** Sotak CH. Nmr Biomed 1991;4(2):70-72.