Diffusion measurement of Mobile Lipids using co-resonant coupled metabolite dephasing

G. Melkus[1], P. Mörchel[1], M. Flentje[2], and P. M. Jakob[1,3]

[1]Experimental Physics 5, University of Würzburg, Würzburg, Germany, [2]Radiation Oncology, University of Würzburg, Würzburg, Germany, [3]Research Center for Magnetic Resonance Bavaria (MRB), Würzburg, Germany

Introduction: The ^{1}H spectra of certain tumor cells, *in vivo* tumors and biopsies, show an intense resonance in the 1.26-1.30 ppm area that has been usually assigned to NMR visible mobile lipids (MLs) [1,2]. The presence of large ML signal seems to correlate with necrotic areas in the tumors [3] and the non-invasive detection of necrosis would suggest a high grade of malignancy in untreated tumors or could be used to monitor the response to tumor therapy [4,5]. The MLs remain visible at long echo times (TE = 136 ms) and were investigated in different studies using diffusion weighted NMR spectroscopy [2,6]. The altered glycolysis in many tumors results in a lactate (Lac) accumulation and an increased Lac CH_3 signal at 1.31 ppm, which is overlapping with MLs and complicates its analysis. In this study a single scan selective spin-echo sequence for the MLs is presented, where an additional selective pulse on the Lac CH pulse minimizes Lac CH_3 contribution to the ML signal.

Material and Methods: The pulse sequence is shown in Fig. 1: A basic frequency selective spin-echo method for the 0.5-2.5 ppm area was extended with an additional frequency selective pulse (red pulse in Fig.1) applied at 3.0-4.5 ppm. The first selective 90° pulse excites the MLs and the Lac CH_3 resonance. Lac evolves under J-coupling and after $\tau = 1/(2J) \approx 70$ ms the second selective 90° pulse excites the Lac CH group (4.11 ppm), creating a mixture of zero quantum coherences (ZQC) and double quantum coherences (DQC) for Lac CH_3, while the MLs remain in their single quantum coherences (SQC). The dephasing effect of the first spoiling gradient (Sp1) is twice as strong for the DQC as for the SQC and has no effect on the ZQC. The selective 180° refocusing pulse interchanges the ZQC and DQC and the second spoiler gradient Sp2 (= Sp1) rephases the SQC while the DQC→ZQC and the ZQC→DQC pathways remain dephased. Pulsed field gradients (DW) were applied for ML diffusion weighting.
Phantom experiments were carried out at 17.6 T with and without the second 90° pulse on a four compartment phantom containing 100 mM lactate / alanine (Ala), sunflower-oil, machine-oil and water (Fig. 2). Localization was achieved by replacing the first pulse with a slice selective pulse without noticeable degradation of the dephasing efficiency, and phase encoding in the remaining spatial dimensions. The *in vivo* experiments were carried out on a FaDu tumor located on the lower leg of a mouse. Sequence parameters: pulse shapes = hermite, pulse durations: first 90° pulse = 1 ms, second 90° pulse = 7 ms, 180° pulse = 4 ms. Phantom: voxel size = (1.3x1.3x2) mm^3, TR = 1 s, NS = 1000, hanning weighted. *In vivo*: voxel size = (2x2x6) mm^3, TR = 1 s, NS = 200, hanning weighted, four different b-values (Fig. 4, Δ = 80 ms, δ = 3 ms).

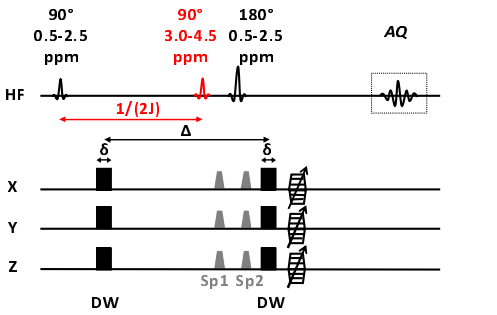

Fig. 1. Sequence for single scan mobile lipid (ML) detection

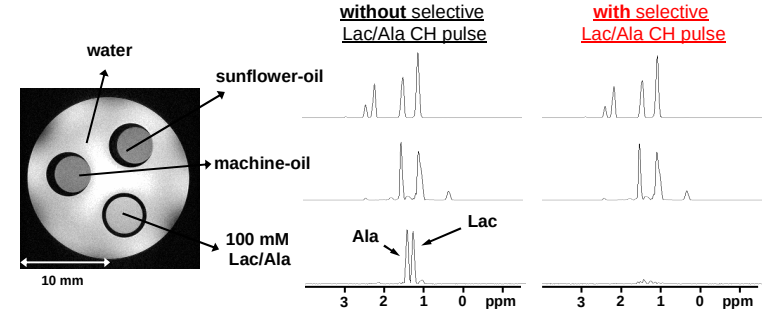

Fig. 2. Phantom experiment. Selective spin-echo applied **with** and **without** selective pulse on 3.0-4.5 ppm

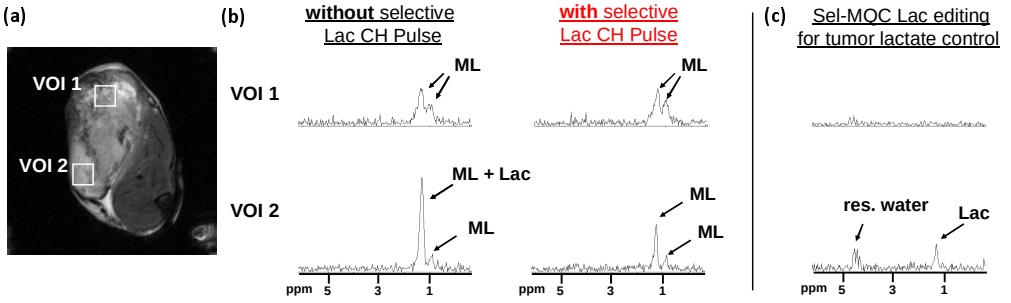

Fig. 3 (**a**) Tumor with two indicated voxels (**b**) Spectra from voxels applied **with** / **without** the Lac CH pulse (**c**) Lac Sel-MQC

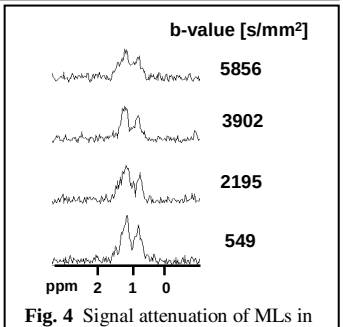

Fig. 4 Signal attenuation of MLs in VOI 1 at different b-values

Results: Fig. 2 shows the spectra acquired from the phantom: When the second 90° pulse is applied at the Lac/Ala CH (Ala has a similar spin system and J-coupling constant as Lac) the Lac/Ala CH_3 signal gets dephased. There is no effect on the oil resonances. In Fig. 3b spectra from two different voxels located in the tumor (Fig. 3a) are shown. In VOI 2 the ML resonance at ~ 1.3 ppm is contaminated by Lac, which can be seen by the signal decreasing when the pulse is applied. The occurrence of Lac in this tumor region was additionally checked by a Lac editing scheme (Sel-MQC[7]). The intensity of the Sel-MQC edited Lac in Fig. 3c has additional signal loss from the MQC filter. The diffusion weighting of the MLs by different b-values for VOI 1 are shown in Fig. 4.
Conclusion: Extending a selective spin-echo method with an additional selective pulse enables single scan ML measurement without contamination from Lac/Ala CH_3 signals. The dephasing of the metabolites is based on their J-coupling and is therefore independent of relaxation times. The single scan character minimizes respiratiory artefacts. A drawback of the sequence is that only MLs with long T_2 relaxation times can be detected. The sequence is suitable for diffusion measurements of MLs.
References: [1] Hakumäki et al. Trends Biochem. Sci. 2000, 25: 357-362. [2] Pérez et al. Cancer Res. 2002, 62: 5672-5677. [3] Rémy et al. Cancer Res. 1997, 57: 407-417. [4] Lin et al. J. Neuro-Oncol. 1999, 45: 69-81. [5] Hakumäki et al. Nat. Med. 1999, 5: 1323-1327. [6] Lahrech et al. Magn. Reson. Med. 2001, 45: 409-414. [7] He Q et al. J Magn Reson B 1995, 106: 203-211.
Acknowledgement: This work was funded by the DFG cooperative project: Ad 132/3-1, Ba 1433/4-1, Fl 225/3-1, Mu 576/14-1.