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

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Introduction: The 1H 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 [6,7]. The altered glycolysis in many tumors results in a lactate (Lac) accumulation and an increased Lac CH3 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 CH3 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 CH3 resonance. Lac evolves under J-coupling and after τ = 1/(2J) = 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 CH3, 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 (Sel-MQC) [8]. The selective 180° refocusing pulse interchanges the ZQC and DQC and the second spoiler gradient Sp2 (= Sp1) rephases the 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.

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 CH3 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) [8]. 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 (Fig. 4, Δ = 80 ms, δ = 3 ms).

Conclusion: Extending a selective spin-echo method with an additional selective pulse enables single scan ML measurement without contamination from Lac/Ala CH3 signals. The dephasing of the metabolites is based on their J-coupling and is therefore independent of relaxation times. The single scan character minimizes respiratory artefacts. A drawback of the sequence is that only MLs with long T2 relaxation times can be detected. The sequence is suitable for diffusion measurements of MLs.


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