Multiband Excitation Pulses for Treatment Response Studies with Hyperpolarised 13C Fumarate

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Introduction: ^{13}C-labeled fumarate is a promising candidate for hyperpolarised in-vivo applications because it could allow the early detection of necrosis [1]. When the cell membrane integrity breaks down due to necrosis, the fumarase enzyme can be accessed by the injected fumarate and is rapidly converted to malate which therefore can be used to quantify the amount of tissue damage. This could for example be used to assess treatment response for various types of cancer. The goal of this work was to design and implement an efficient sequence for the in-vivo quantification of fumarate and its metabolite. The proposed sequence combines a multiband excitation pulse specifically tailored to the spectrum of fumarate and malate with IDEAL spiral imaging. Saturation recovery spectra are acquired for malate to analyse the metabolic kinetics. First measurements in an orthotopic rat hepatocellular carcinoma (HCC) model were successfully performed before and after transcatheter arterial embolisation (TAE) to validate the effectiveness of the method.

Materials and Methods:
A new spectral-spatial multiband pulse with 10mm slice thickness was designed based on [2] and tailored to the spectrum of fumarate and malate. The ratio of fumarate to malate excitation was chosen to be 1:5 to preserve fumarate polarisation for further conversion (see fig.1). The pulse was designed with a flyback gradient modulation with 9 sublobes and a total duration of 21ms. Experiments were performed on a 3 T HDx clinical scanner (GE Healthcare, USA) using a quadrature ^{13}C volume coil. [1,4-$^{13}C_2$]fumaric acid was polarised using a HyperSense polariser (Oxford Instruments, UK) resulting in about 25% polarization level in liquid state. After dissolution, 1ml of 20mM fumarate solution was injected in the tail-vein of 6 male Buffalo rats bearing a unifocal orthotopic HCC tumor (McA-RH7777) one day before and one day after transcatheter arterial embolisation with EmboCept® (1ml of 50% EmboCept® administered through the gastroduodenal artery). Acquisition was started 20s after injection at the estimated maximum of malate concentration. First, a breathing-triggered IDEAL spiral [3] image was acquired using 5 echoes with a single-shot spiral readout (FOV 8cm, nominal resolution 32x32) and an echo-shift of 1.05ms. The flip angle was chosen between 35° and 90° for malate in different animals to find the optimal settings. Subsequently, a spectrum was acquired with a repetition time of 3s and a nominal flip angle of 90° for malate to quantify the overall malate increase and the metabolic dynamics. In the image reconstruction, the double resonance of the non-symmetric malate molecule was accounted for by including the condition of equal spin density for both isomers in the least squares chemical shift imaging separation approach, thereby gaining SNR by a factor of √2.

Results and Discussion:

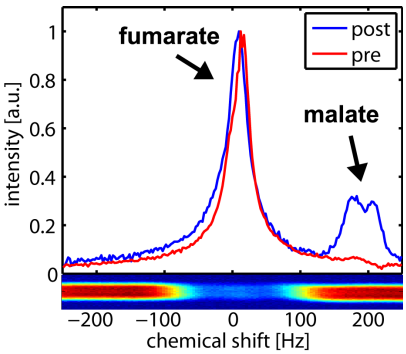

Fig. 1: Exemplary spectrum before (red) and after embolisation (blue) and measured pulse profile

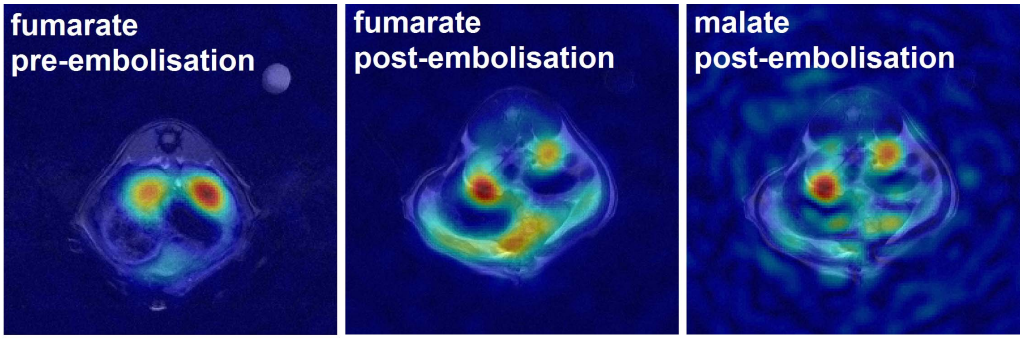

Fig. 2: Metabolite images acquired with 90° nominal flip angle for malate, 13° for fumarate

There is a significant increase of malate production 24h after the embolisation. The malate level rises to about 25% of the fumarate signal compared to about 5% before embolisation (uncorrected for pulse). The images show that the malate and fumarate maps are very similar and the signal in the tumour is low due to decreased perfusion. Also, there is a significant malate signal present in neighbouring slices (not shown). This indicates that the main malate signal most likely stems from the blood pool and that the washing-out effect of the fumarase enzyme is probably severe with this treatment. Comparing the fumarate images before and after embolisation, a clear reduction in perfusion can be observed which is a good indicator for the success of the treatment. This finding is consistent with a separately acquired perfusion image using hyperpolarised urea (not shown).

Conclusion: Metabolic acquisitions of fumarate with a specially tailored multiband pulse sequence were successfully demonstrated in a treatment setting used also clinically. As shown in the anatomical overlay, reliable images with adequate resolution of fumarate and malate could be acquired. This is an important step towards further studies and human applications. Multiband pulses are particularly favorable for fumarate compared to pyruvate because of fewer constraints to the spectral profile due to the fact that fumarate has only one metabolite. The ability to excite malate with a higher flip angle and at the same time preserve hyperpolarised fumarate signal is especially useful in this scenario since for the conversion to malate, no cell transporters are required for the conversion. The multiband approach with 90° flip angle for malate therefore allows an efficient quantification of metabolite dynamics via saturation recovery [4].

References: [1] F.A. Gallagher et al. *PNAS.* 2009;106(47):19801–19806. [2] P. Larson et al. *JMR.* 2008;194:121-127 [3] F. Wiesinger et al. *MRM.* 2012;68(1):8–16. [4] R.F. Schulte et al. *MRM.* 2012;in print.

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