Optimized semi-LASER 3D MRSI sequence for lactate detection in the prostate

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Introduction:
Lactate is an important potential biomarker in cancer, as a reporter of the Warburg effect and/or hypoxic conditions in tumors. In a prostate cancer mouse model, hyperpolarized ^{13}C pyruvate was used to image lactate production. In this model, lactate SNR levels showed a significant increase with prostate cancer development and progression (1). Detection of lactate in human prostate *in vivo* using ^{1}H MRSI is complicated by the presence of periprostatic fat, since the chemical shifts of lactate (1.3 ppm) and lipids overlap. Conventionally, frequency-selective refocusing pulses and gradient crushers are included in prostate MRSI to suppress periprostatic lipid signals. As a consequence, the lactate resonance is affected as well. When a sequence without frequency-selective suppression is used to study lactate, periprostatic lipid contamination can only be prevented by accurate volume selection within the prostate and spatial saturation slabs. Together with a wider frequency range of interest of the spectrum, this demands for high bandwidth refocusing pulses with near-perfect slice profiles. For that reason, the semi-LASER sequence (2) was adapted to enable simultaneous detection of citrate, lactate and other metabolites of interest in the prostate using 3D ^{1}H MRSI.

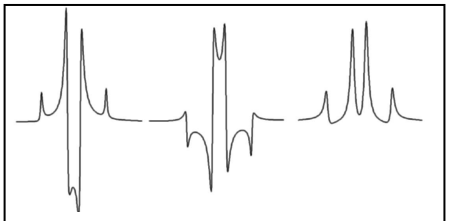

Fig 1. Spectral results from simulations of citrate using the semi-LASER sequence (TE = 144 ms) with different inter-pulse timings

Methods:
The echo time (TE) of the semi-LASER sequence was set to 144 ms to obtain an inverted lactate signal due to J-coupling. Citrate is a strongly coupled spin system and the spectral shape is highly dependent on TE and the timing of the adiabatic full passage (AFP) pulses. Using Bruker NMR-SIM software, the timing between the AFP pulses was varied and the corresponding simulated citrate signals were studied in Bruker Topspin. After optimization of the timing, the sequence was tested on two phantoms. For phantom and patient measurements a Siemens Trio 3T system was used. Phantom 1 contained citrate, choline, creatine and spermine, and phantom 2 held lactate and creatine. Next, 5 patients with high-Gleason prostate cancer (3+4 or higher on biopsy) were measured using a body-array coil and endorectal coil for signal reception. High resolution T2w images were obtained in three directions. Diffusion weighted images were made to assist in tumor localization. The T2w images were used to place the volume of interest of the 3D spectroscopy grid completely inside the prostate. Spatial saturation slabs were placed around the prostate to saturate periprostatic lipid signals. The spectra were analyzed with jMRUI v3.0 software and peak fitting was performed with the AMARES algorithm with prior knowledge about chemical shift, coupling and phase. When no lactate was detected with the algorithm, the minimal detectable lactate level was determined using creatine as an internal reference signal. Creatine was used since no significant differences for creatine were observed in different prostate tissues (3). A simulated lactate signal was added to a *in vivo* spectrum to estimate the minimum detectable lactate level. The amplitude and Cramer-Rao standard deviation (CRSD) were calculated for the lactate fit. Lactate was considered detectable if the CRSD was smaller than 20% of the amplitude. The amplitude of the simulated lactate signal was repeatedly lowered by 10% until lactate was not detectable anymore. The lowest simulated amplitude with a detectable signal was used to calculate the minimum detectable metabolite level (4), assuming lactate relaxation times of 1550 ms (T1, (5)) and 225 ms, (shortest T2 found in literature (6)). Both values were obtained in brain measurements on 1.5T. For the T1 and T2 of creatine relaxation times obtained in the prostate at 1.5T were used of 864 and 209 ms, respectively (7). One *in vivo* assessment of creatine concentration in prostate was found in literature: 4.4 mM (7).

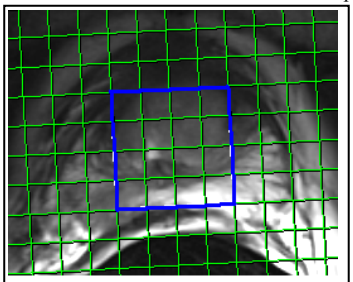

Fig. 2 T2w image of the prostate with the volume of interest for 3D MRSI

Results:
Figure 1 shows the simulation of the spectral shape of citrate at a TE of 144 ms with different timings between the AFP pulses. The timing of the third spectrum (AFP pulses of 8ms duration centered at 11, 32, 61 and 112 ms after excitation) was used as the optimized semi-LASER sequence for all experiments, producing the desired shape of interest for the coupled spin systems (Figures 3 [phantom] and 4 [*in vivo*], semi-LASER compared to conventional PRESS). The strong influence of the semi-LASER sequence on citrate is clear: while the difference in TE with the PRESS sequence is minimal (145 and 144 ms respectively), the shape of citrate is very different. An interesting detail is the decrease of the spermine signal between the choline and creatine resonances obtained with the semi-LASER sequence (Fig. 3B and 4B). The spectrum in figure 4C is a typical tumor spectrum from one voxel of a 3D MRSI experiment with the optimized semi-LASER sequence: lactate was not detectable (arrow). To select tumor voxels in the patients, the T2w images and DWI images were used as guidance. From the 5 patients, 3 patients had voxels containing tumor tissue that had good spectral quality without lipid signals in the 1.3 ppm region. In these 3 patients no lactate signals were detected using jMRUI. The calculation of the minimal detectable lactate levels gave the following results: 1.2, 0.5 and 1.2 mM for the 3 patients.

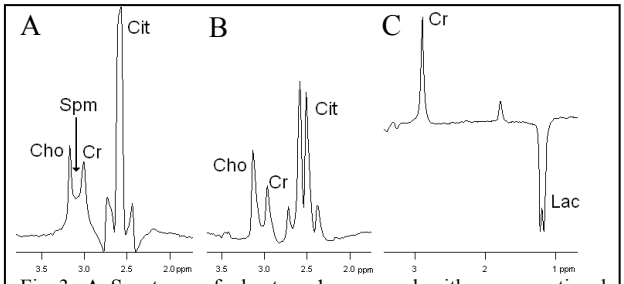

Fig 3. **A** Spectrum of phantom 1 measured with a conventional PRESS sequence at TE = 145 ms. **B** Spectrum of phantom 1 measured with the optimized semi-LASER-sequence at TE = 144 ms. **C** Spectrum of phantom 2 measured with the optimized semi-LASER sequence

Discussion and conclusion:
In this study we optimized the semi-LASER 3D MRSI sequence for lactate detection in the prostate. With phantom measurements we confirmed optimal citrate and lactate spectral shapes with the proposed sequence timing. 3D MRSI without frequency-selective lipid suppression produced lipid-free spectra in suspected cancer tissue in 3 out of 5 patients with prostate cancer. However, *in vivo* lactate levels remained below the worst-case minimum detection limit of 1 mM in these patients with high-Gleason prostate cancer. Further optimization of spatial saturation pulses could increase the number of patients with lipid-free spectra in cancer tissue, and possibilities for lactate detection could be increased in studies of patients with more advanced disease.

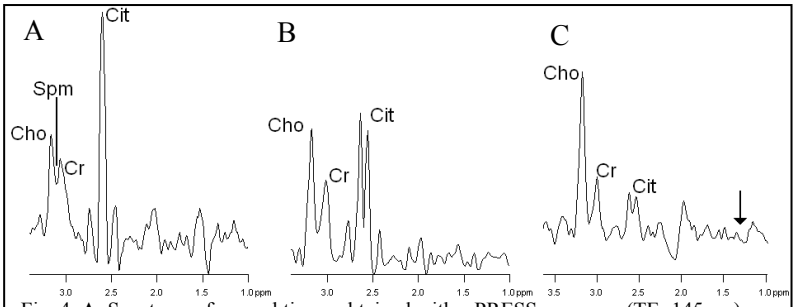

Fig. 4. **A**: Spectrum of normal tissue obtained with a PRESS sequence (TE=145 ms)
B: Spectrum of the same normal tissue measured with the semi-LASER sequence.
C: Semi-LASER spectrum of tumor tissue.

References: [1] Albers, Cancer Res (2008) 8607 [2] Scheenen, MRM (2008) 1 [3] Swanson, MRM (2006) 1257 [4] Bolan, MRM (2003) 1134 [5] Frahm, MRM (1989) 47 [6] Sappey-Marinier (1992) 313 [7] Heerschap, MRM (1997) 204 **Acknowledgement:** Dutch Cancer Society: KUN 2007/3971, ERC Grant agreement n° [243115]