Clinical double quantum filtered lactate spectroscopy of leg ischemia and non-hodgkins lymphoma in 3D

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Objective

Lactate is a metabolic product and biomarker for cancer; however its detection is difficult because lipid resonates at the same frequency. To further clinical studies of lactate, our objective was to implement 3D double quantum filtered human lactate imaging on a 3T clinical scanner.

Background

Lactate is the product of glycolytic metabolism, normally only produced in small quantities in limited cell types under certain conditions. However, in many disease states and under ischemic conditions, lactate increases. For example, tumor cells exhibit enhanced glycolytic metabolism under aerobic or anaerobic conditions as part of the malignant phenotype, increasing local lactate levels. In models, lactate production is diminished following successful treatment[1,2]. The greatest obstacle to *in vivo* NMR detection of lactate is overlap of the $-CH_2-$ resonance of lipids with the methyl resonance of lactate at 1.3ppm in ^1H MRS. As a result, the lactate resonance is often obscured by higher concentrations of free fatty acids and glycerides. The selective homonuclear multiple quantum coherence transfer (SelMQC) technique offers a potential solution for lactate/lipid separation[3]. Very recently, a 3D version (abbreviated HDMD-SelMQC-CSI) based on 1D Hadamard (HDMD) and 2D phase encoding (CSI) was implemented on small animals in a tumor model[4]. We now wish to apply the sequence to the 3D mapping of lactate in humans. At ISMRM 2008 we confirmed that this approach was possible in phantoms on a clinical 3T scanner[5]. In this work, we provide the framework for future clinical HDMD-SelMQC-CSI studies by first validating the Hadamard slice profiles *in vivo* and optimizing the gradient durations for lactate and fat separation. Then, an image of the lactate in a human tumor surrounded by superficial fat is generated in 5-20 minutes. It is also shown that SelMQC is sensitive to lactate generated in the human calf with thigh pressure cuff occlusion of blood flow.

Materials and Methods

All experiments were performed on a Siemens Trio 3T clinical scanner with body coil transmission and surface coil reception except when noted. Human experiments were approved by our Institutional Review Board. The applied pulse sequence is as described in a 2008 ISMRM abstract[5] and is very similar to a research scanner sequence[4]. Basically, HDMD-SelMQC-CSI starts with one of 4 (2 slice) or 8 (4 slice) frequency modulated hyperbolic secant (HS) inversion pulses that combine to produce slice selection (SS)[6]. A series of frequency selective Gaussian pulses select for the 1.3ppm double quantum coherence of lactate and 2D CSI is applied. Here DQ->ZQ quantum pathway selection is exclusively used. **Figure 1.** To test the slice profiles generated by the SS pulses, individual pulses preceded each TR of a spoiled GRE with the preceding SS gradient in the readout frequency encoding direction with phase reconstruction. This was performed on the 4x4x4cm core of a non-Hodgkins Lymphoma (NHL) in the thigh of a 63 year old male patient (13 sec/pulse tested). **Figure 2.** To determine optimal parameters for lactate and fat separation, two 50mL conical tubes were filled with 100mM lactate or 100% oil. To separate the phantoms, 2 HDMD slices selected either lactate or oil without phase encoding. The quantum selection gradient (QSel) amplitude was increased with a 300μs fixed duration. Then a 26mT/m QSel amplitude was fixed and the duration increased. Other parameters were 4 preparatory scans per acquisition, TR 1.5s, 1024 points, and 4kHz bandwidth. **Figure 3.** The NHL of a 34 year old female volunteer was imaged. A multi-slice axial T2-weighted series was taken for localization, and a 5 minute HDMD-SelMQC-CSI sequence was run with FoV 250x250mm, Matrix 10x10 (elliptically sampled), slice thickness 25mm, TR 1500ms, and 2 slice Hadamard encoding (4 pulses). **Figure 4.** A 67 year old healthy male was positioned with his calf in a knee coil. A non-magnetic thigh tourniquet system inflated a tourniquet to 250 mmHg of pressure and then deflated about 5 minutes later. This setup has previously abolished flow to the calf muscles of volunteers[7,8]. A series of unlocalized FIDs were acquired and the amplitudes integrated over time. The parameters were: 300μs QSel duration, 26mT/m amplitude, TR 3s (6s per plot point, phase cycles averaged together).

Results

Figure 1 A shows one of the frequency selected inversion pulses with two modulations (the two bright bands were inverted) *in vivo*, and B shows each slice after all 8 hyperbolic secants underwent Hadamard transform. C shows excellent agreement between the experimental results in B and simulation based on Fourier and Hadamard transformation of the HS pulses. This demonstrates the feasibility of human *in vivo* Hadamard selection. **Figure 2** examines the fat and lactate separation based on QSel parameters. At 26 mT/m and 300μs QSel, lactate has lost 10x its FID signal. Based on the concentration of 1.3ppm protons in the oil, the lipid is suppressed 1600 fold more than lactate. From this we estimate 3.4% lipid signal contamination for 5mM lactate based on separate estimations of lipid concentration from the PRESS spectra of NHL tumors. **Figure 3** A and C show two T_2-weighted slices of two discrete NHL lesions on the surface of the thigh (surrounded by superficial lipids). B and D show the corresponding HDMD-SelMQC-CSI lactate maps from a 2-slice, 5 minute acquisition. E shows an example spectrum from the high lactate area in B. **Figure 4** displays the results of the leg blood flow occlusion experiment, where the arrows indicate start and stop of occlusion. At 6 seconds per point (phase cycles averaged together), a rapid and clear increase is seen in the 1.3ppm peak in the calf with simple SelMQC spectroscopy that returns quickly to almost baseline levels after release.

Figure 1

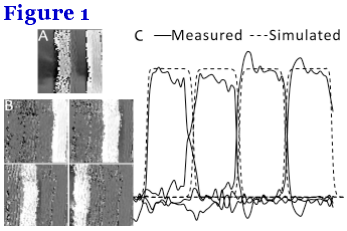


Figure 2

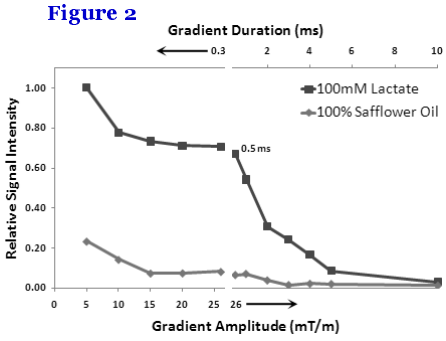


Figure 3

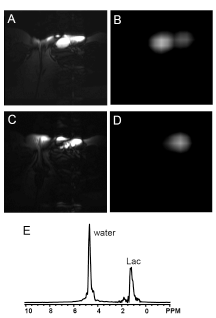
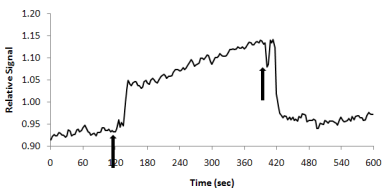


Figure 4



Conclusions **Human feasibility studies of the HDMD-SelMQC-CSI sequence confirm lactate is rapidly detected and mapped on clinical hardware. This has significant implications for studies of the response of cancer to therapy and studies of ischemic disease.**

References 1.Poptani et al NMR Biomed 16(2003):102 2.Lee et al NMR Biomed 21(2008):723 3. He et al JMR B 106(1995):203 4. Pickup et al MRM 60(2008):299 5. Mellon et al ISMRM 2008 #1577 6. Souza et al JCAT 12(1988):1026 7. Wu et al ISMRM 2008 #605 8. Wu et al ISMRM 2008 3676