Simultaneous Detection of Choline and Other Metabolites using SEE-SelMQC for Spectroscopic Imaging of Human Breast Cancer

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INTRODUCTION. ^{1}H NMR detection of metabolites and drugs in human breast tissue is challenging due to the intense water and lipid signals that dominate the proton chemical shift range.[1] Since initial observation of increased choline level in breast cancer by Roebuck *et. al.* using spin-echo MRS techniques,[2] choline has become a potential MR biomarker for breast cancer diagnosis with improve specificity. In most breast MRS studies, the incomplete lipid and water suppression often obscure the quantitative evaluation of tissue choline concentration. Other biochemicals are usually not detectable in breast tissue by MRS due to overlapping lipid and water resonances. In this report, we present data to address this issue with our previously demonstrated SEE-SelMQC (Spin Echo Enhanced Selective Multiple Quantum Coherence transfer) technique developed for multiple metabolite detection *in vivo* in animal EMT6 tumor models.[4] Complete suppression of lipid and water signals was achieved in a single scan by the Selective Multiple-Quantum Coherence transfer (Sel-MQC) pulse sequence component, which makes it possible to observe metabolites and antineoplastic agents in tissues containing high concentration of mobile lipid.[3-6] The Sel-MQC method has been adapted for simultaneous detection of lactate and antineoplastic agent Iproplatin in RIF-1 tumors.[5] In addition, the T_1- and T_2-Sel-MQC sequences have also been developed to determine the relaxation times of the edited lactate signals for tissue metabolite quantification.[7] Modified Sel-MQC sequences are available to detect neuronal glucose, GABA and glutamate.[8, 9] Recently, we have developed the volume selective Sel-MQC techniques using 1331 composite pulses,[11] as well as a multi-slice Sel-MQC method for 3D mapping of metabolites using the Hadamard matrix approach.[10] The efficiency for robust multi-slice spectroscopic imaging or 3D volume detection were recently improved for the SelMQC techniques using spatial-spectral (SPSP) selective RF pulses.[14,15] Here we present the results from a GE 3T clinical scanner for SEE-SelMQC implementation to demonstrate its potential in simultaneous detection of multiple metabolites in human breast tissue or other lipid abundant tissues to study extracranial cancers. Thus, the MRSI studies of breast cancer can be expanded to detect multiple biomolecular markers. Although high-field is preferred for the SEE-SelMQC method, the application of the sequence at lower-field would also enhance lipid and water suppression for choline quantification in the clinical breast MRSI settings.

METHODS. The SEE-SelMQC sequence was modified from the original Sel-MQC CSI pulse sequence for lactate editing, $90^0_{\phi}(C\underline{H}_3,lipid)$ -1/2J- $90^0_x(C\underline{H},\underline{H}_2O)$ - $t_1/2,g_1$- $180^0_x(C\underline{H}_3,lipid)$ - $t_1/2,g_2$ - $90^0_x(C\underline{H},\underline{H}_2O)$ - $g_3,\tau\pm t_1$ - acq, which excites lactate into the MQ-states and leaves lipid and water in the SQ modes for single scan suppression by the MQC-selection gradient pulses (g_1: g_2: g_3 =0:-1:2 or 1:0:2).[3] In the SEE-SelMQC sequence, an additional 90º-selective pulse was added to excite choline and other metabolites outside the lactate CH_3 (1.3 ppm) and CH (4.2ppm) regions (Fig. 1a). Slice localization was accomplished using the 180º pulse, which also refocused the choline signal as in the clinical spin echo sequences for elevated choline detection in human breast cancer. Phase-encoding gradients are applied to map metabolite distributions in two-dimensions in the selected slice or volume. In this work, Shinnar-Le Roux (SLR) pulses were used as the 90° pulses to achieve highly efficient frequency selection (~100Hz). All SLR pulses were designed as described in reference 14. Specifically, pulses with linear-phase or minimal phase typically had a time-bandwidth product of 2-4, with pass-band and stop-band ripples to be less than 1-2%. After each pulse design, a Bloch equation simulator was used to verify and optimize the performance of the SLR pulse.

RESULTS AND DISCUSSIONS. Mapping of multiple metabolites with SEE-SelMQC on clinical scanners was demonstrated on a GE 3T scanner using a commercial GE phantom of brain metabolites (Fig. 1b). Data were acquired with the GE 3T quadrature head coil. Multiple brain metabolites were detected, although lactate lost one half of its signal with the SEE-Sel-MQC editing. Excellent water suppression was evidenced by the flat spectral baseline for most of the voxels. When lipid was present in the inner phantom compartment (Fig. 2a), SEE-SelMQC sequence also gave a flat baseline in an experiment to simultaneously detect choline and lactate using an in-house breast coil.[16] To clearly show this effect, we deliberately applied insufficient multiple-quantum selection gradients and did not apply the slice-selection gradients. The residual lipid signals from the center test tube compartment appeared in the spectra of choline and lactate from the outer phantom compartment (Fig. 2b). This result demonstrated the feasibility to improve choline spectral baseline in breast cancer studies using spin-echo detection, with enhanced lipid and water suppression by Sel-MQC. Further validation on human breast tissues in a breast cancer trial is in progress in our laboratory. When spsp RF pulses are employed, the SEE-SelMQC sequence will be capable of interleaved multi-slice mapping of multiple metabolites within a desired 3D volume, as suggested by an earlier study.[15]

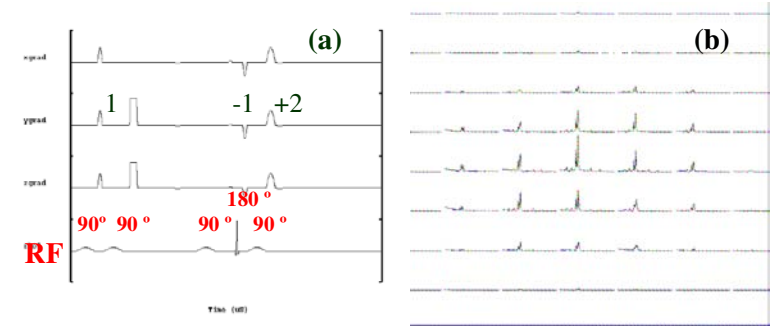

Fig. 1 (a) The SEE-SelMQC sequence from GE EPIC simulator with the first pulse being a SLR 90º pulse for choline excitation. Slice localization and choline refocusing can be achieved by a broadband slice-selective SINC 180 º pulse. Phase-encoding was applied in two-dimensions to map the cross-section of the sample. (b) Detection of multiple brain metabolites with excellent water suppression from the GE Brain phantom on a GE 3T MRI scanner using a head coil.

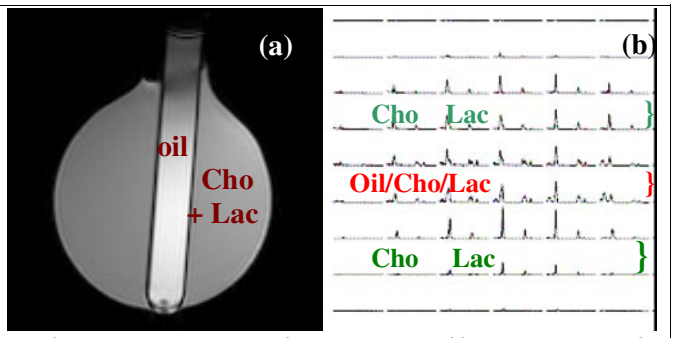

Fig. 2 (a) A two-compartment phantom constructed by inserting a test tube of vegetable oil into a 250mL flask containing a mixture of choline (Cho) and lactate (Lac) aqueous solution. (b) The SEE-SelMQC CSI mapping of metabolites without slice selection. Insufficient MQ-selection gradient was applied to allow residual lipid and water resonances appearing in the spectra of choline and lactate. Excellent baseline was obtained due to superior lipid and water suppression by Sel-MQC at 3T.

CONCLUSIONS. We have demonstrated the feasibility to employ SEE-SelMQC sequence for multiple metabolite detection in human breast cancer on a MRI 3T GE clinical scanner. The method gives excellent spectral baseline due to effective suppression of water and lipid signals by MQ-filtering. The method will play an important role in an on-going breast cancer trial to improve breast cancer diagnostic specificity using MR metabolic markers.

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