Single-shot, Frequency and Time Specific, 3D Imaging Method for Measuring Hyperpolarized 13C Biomarkers In-Vivo at 14.1 Tesla

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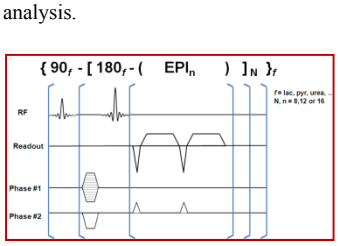
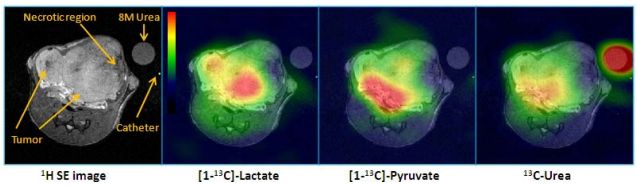
Hyperpolarized, ^{13}C labeled biomarkers can provide unique biochemical and physiological information *in-vivo* and have been used in animal models to detect and characterize tumors (1,2). This is made possible by the unprecedented signal enhancement achieved by the dynamic nuclear polarization (DNP) technique (3). However, special pulse sequences are needed for MRSI applications because the hyperpolarized magnetization is rapidly and irreversibly depleted due to relaxation, RF pulse saturation and metabolism. MRSI studies at high fields pose further challenges because T2*, motion and flow related artifacts are increased. The increased chemical shift spread at high fields is beneficial in resolving the resonance peaks in MRSI but may cause spatial errors in the slice and readout dimensions. The wide spectral dispersion may also result in lower digital resolution and in aliasing of outlying peaks in the frequency dimension. In this project we developed a novel, single-shot, 3D imaging sequence for hyperpolarized MRI studies on high field systems and investigated its performance by obtaining ^{13}C images of lactate, pyruvate and urea in a transgenic mouse prostate cancer (TRAMP) model.

Experimental Methods and Materials

The pulse sequence used for the single-shot, chemical shift specific method is shown in Figure 1. It is based on a 3D spinecho EPI sequence and, as in the GRASE (4) method, uses additional 180 degree pulses during the echo train to minimize the effect of T2* related signal loss and artifacts. Flyback EPI readout gradients are applied during the blipped gradient duration and the data acquired during the positive gradients to avoid the Nyquist ghost artifact. SLR pulses, with 6msec duration and 500Hz bandwidth, were designed to selectively excite only the resonance of interest. 3D images, with a data size of 16x12x12, were acquired in 153msec and provide high temporal resolution. The maximum gradient strength used was about 300mT/m. The experiments were done using a vertical, 14.1T Varian 600WB micro-imaging system equipped with 55mm 1000mT/m gradients and 40mm diameter proton and carbon RF coils. The animals were placed in a temperature controlled animal holder and anesthetized using isoflurane. An animal monitoring system (SA Instruments) was used to monitor respiration and trigger the scanner during all protocols. The proton coil was used for shimming and anatomical imaging and then the carbon coil was used for ^{13}C imaging. A mixture of [1-^{13}C]-pyruvate and ^{13}C-urea was polarized using an Oxford Hypersense™ DNP instrument and 400ul of the resulting dissolution mixture containing 80mM pyruvate and 74mM urea was administered via a jugular vein catheter. 44s after injection, ^{13}C image datasets corresponding to lactate, pyruvate, and urea were acquired in 0.46s (153msec per image). After acquiring the image, a portion of the dissolution mixture was injected into a second catheter placed inside the RF coil and a 4mm slab spectrum taken to measure the level of polarization and normalize the image intensities for quantitative analysis. In some cases, we have used the signal from the kidney as an internal reference to normalize image intensities for analysis.





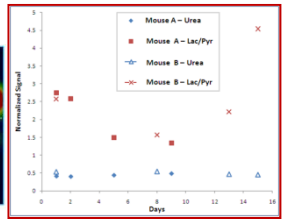


Figure 1 (Left): Single-shot, frequency specific imaging sequence.
Figure 2 (Middle): ^{13}C (color) images acquired 44s after injecting a mixture of pyruvate and urea into a TRAMP mouse with prostate tumor.
Figure 3 (Right): Urea and Lac/Pyr (ratio) signals measured over several days in the tumors of two TRAMP mice following radiation treatment.

Results

Figure 2 (left) shows an axial spinecho image taken from a TRAMP mouse with a large prostate tumor. The corresponding ^{13}C slices from the 3D volume data are shown in color and superimposed on the anatomical image. Urea is an inert agent and was used in this study to investigate blood perfusion in the tumor. Pyruvate is delivered to the tumor by the vascular system and converted to lactate by the enzymatic reaction catalyzed by lactate dehydrogenase (LDH). High levels of lactate were seen in the active regions of the tumor whereas regions of necrosis showed low perfusion and low production of lactate. The large vessels in the lower part of the tumor showed high levels of pyruvate. Figure 3 (right) shows the changes occurring in the urea signal and the lactate/pyruvate ratios in the prostate tumor following low level radiation treatment in two TRAMP mice. The signal intensities in each image were normalized with respect to the signal in the kidney. Note that the urea signal in the tumor is similar across different studies because of the normalization. The lac/pyr ratio show an initial decrease followed by an increase due to the low level radiation dose treatment.

Discussion and Summary

We have demonstrated a new, fast and efficient pulse sequence for acquiring HP ^{13}C signals in-vivo at 14.1T. The high temporal resolution (153msec) is ideal for studying dynamic processes such as metabolism and perfusion in-vivo. Selective pulses are used to excite only the resonance of interest, therefore, the frequency and time of acquisition can be independently specified. For 3D encoding, the digital resolution will be limited to about 12 or 16 in each dimension to reduce the overall acquisition time and minimize T2* related signal loss. The GRASE type acquisition scheme helps to minimize T2* related effects which can be problematic at high fields. Since the RF pulses used are chemical shift selective pulses it is essential that peaks are well separated and resolved to prevent signal contamination from neighboring resonances. Shimming is therefore critical and it helps to narrow the linewidth of the spectral peaks. The hyperpolarized signal enhancement can vary due to a number of factors. Therefore, calibrating the signal at the time of delivery into the mouse using the spectrometer allows us to normalize the image intensities for quantitative studies. At present, we are using this ^{13}C imaging method, at 14.1T, to routinely study various disease models in mice (PTEN prostate tumor N=8; TRAMP prostate tumor N=16; fatty liver disease N=26). During the same study, proton imaging (DWI, DCE-MRI, etc.) and spectroscopy data is also collected to complement the ^{13}C study.

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