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Original contributions

Fast volumetric spatial-spectral MR imaging of hyperpolarized ^{13}C-labeled compounds using multiple echo 3D bSSFP☆

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Abstract

Purpose: The goal of this work was to develop a fast 3D chemical shift imaging technique for the noninvasive measurement of hyperpolarized ^{13}C-labeled substrates and metabolic products at low concentration.
Materials and Methods: Multiple echo 3D balanced steady state magnetic resonance imaging (ME-3DbSSFP) was performed in vitro on a syringe containing hyperpolarized [1,3,3-2H3; 1-^{13}C]2-hydroxyethylpropionate (HEP) adjacent to a ^{13}C-enriched acetate phantom, and in vivo on a rat before and after intravenous injection of hyperpolarized HEP at 1.5 T. Chemical shift images of the hyperpolarized HEP were derived from the multiple echo data by Fourier transformation along the echoes on a voxel by voxel basis for each slice of the 3D data set.
Results: ME-3DbSSFP imaging was able to provide chemical shift images of hyperpolarized HEP in vitro, and in a rat with isotropic 7-mm spatial resolution, 93 Hz spectral resolution and 16-s temporal resolution for a period greater than 45 s.
Conclusion: Multiple echo 3D bSSFP imaging can provide chemical shift images of hyperpolarized ^{13}C-labeled compounds in vivo with relatively high spatial resolution and moderate spectral resolution. The increased signal-to-noise ratio of this 3D technique will enable the detection of hyperpolarized ^{13}C-labeled metabolites at lower concentrations as compared to a 2D technique.

Keywords: Hyperpolarized ^{13}C; Chemical shift imaging; Balanced steady state free precession imaging; Spectroscopic imaging

1. Introduction

An important goal of molecular imaging is the development of non-invasive techniques for measuring in vivo metabolism. Magnetic resonance spectroscopy (MRS) has demonstrated the ability to monitor aerobic and anaerobic metabolism using isotopically enriched ^{13}C-glucose and pyruvate substrates in brain [1,2], heart [3], and animal tumor models [4–7]. The nonradioactive ^{13}C-labeled substrates are chemically equivalent to naturally occurring ^{12}C-substrates and therefore undergo the same metabolic reactions. This powerful tool for noninvasively monitoring metabolism in vivo has not been widely applied to the characterization of human cancers in vivo due to the low MR sensitivity necessitating long imaging times. Administration of a large dose of a ^{13}C-enriched substrate to increase the MR sensitivity would disrupt the endogenous metabolism defeating the purpose of using the ^{13}C-enriched substrate to probe the metabolic state of the system.

The low MR sensitivity of ^{13}C-enriched substrate metabolite imaging and spectroscopy is currently being addressed by the development of hyperpolarization methods to significantly increase the MR signal obtained from ^{13}C-labeled substrates. PASADENA (parahydrogen and synthesis allows dramatically enhanced nuclear align-

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ment) [8–11], and DNP (dynamic nuclear polarization) [12–14] methods are able to increase the MR signal of ^{13}C-labeled compounds by factors of 20,000 or more. This increase in ^{13}C polarization directly translates into increased MR signal of both substrates and metabolites since the ^{13}C nuclei retain their hyperpolarization while undergoing chemical reactions. The increased signal of hyperpolarized ^{13}C-labeled metabolic substrates has begun to allow noninvasive MR detection of the original ^{13}C-labeled substrate and metabolic products at millimolar levels using fast chemical shift imaging [15,16].

The main limitation of MR imaging and spectroscopy of hyperpolarized ^{13}C-labeled molecules is useful lifetime of the hyperpolarized spins as the spin system reverts from the hyperpolarized state back to Boltzmann polarization with characteristic relaxation time constant T_1. The T_1 relaxation times for this decay are on the order of 20 to 60 seconds for most biologically relevant ^{13}C-substrates, which limits the detection time to the order of several T_1 times ($\approx 4T_1$ or 80–240 s). Furthermore, the T1 relaxation time of the hyperpolarized metabolic product may be different from that of the hyperpolarized substrate due to a different local chemical environment. Therefore, the key requirements for metabolic imaging of hyperpolarized substrates are fast delivery and uptake by the target tissue (tumor), rapid conversion of the substrate to its metabolites, and MR imaging times which are short relative to both the T_1 of the substrate and the conversion rate of substrate to product. These requirements are the driving force behind the development of fast MR pulse sequences which are able to provide both spectral (chemical shift) and spatial (image) information.

The chemical shift induced amplitude modulation of the MR signal for gradient echo imaging was first reported by Wehrli et al. [17]. They noted that this modulation could be used to generate fat and water images by performing the Fourier transform along the echoes in a multiple gradient echo image acquisition. Recently, Wieben et al. [18] proposed a fast method for acquiring both the spatial and spectral information in one scan using a multiple-echo 2D balanced steady-state free precession (bSSFP) imaging technique. The Nyquist frequency (F_N) for this technique is determined by the echo spacing, Δt, where $F_N = 1/(2\Delta t)$, and the spectral resolution (Δf) is determined by $\Delta f = 1/(N_E \Delta t)$, where N_E is the number of acquired echoes. The multiple-echo 2D bSSFP technique is fast, has relatively high spatial resolution and is able to adjust the N_E and the echo spacing (Δt) to provide the desired spectral resolution.

Previous multiple gradient echo chemical shift bSSFP imaging was performed in a single-slice acquisition mode [17–19]. We have implemented three-dimensional multiple gradient echo bSSFP (ME-3DbSSFP) imaging in order to observe hyperpolarized ^{13}C-labeled substrates and products at lower concentrations due to the increased signal-to-noise ratio (SNR) of the 3D acquisition, and to provide multiple contiguous slice chemical shift imaging in order to measure the MR signals of the substrates and products at more than one slice in the subject. The ME-3DbSSFP technique presented here is conceptually similar to echo planar spectroscopic imaging (EPSI) [20,21], however, with much shorter 3D spatial and 1D chemical shift image acquisition time.

2. Materials and methods

2.1. PASADENA Hyperpolarization

The instrumentation and polarization transfer technique necessary for generating hyperpolarized ^{13}C molecules is described in detail by Golman et al. [9], Johannesson et al. [10] and Bhattacharya et al. [11]. Briefly, the unsaturated PASADENA precursor molecule undergoes hydrogenation by parahydrogen gas in the presence of a rhodium catalyst, producing a molecule with high proton spin order. This proton spin polarization is then transferred to the ^{13}C atoms at a low magnetic field using tailored radiofrequency (RF) pulses transmitted at both the ^{1}H and ^{13}C Larmor frequencies. The rhodium catalyst enables the transfer of the parahydrogen protons as a unit onto the precursor molecule, thus maintaining the spin order of the protons immediately after hydrogenation. The chemistry takes place at an elevated temperature (60°C) and pressure (10 bar) in a reactor vessel where a solution containing both precursor and catalyst (pH:7.8) is injected into an atmosphere of parahydrogen gas. The goal is to achieve this reaction in a timescale which is small (≈4 s) compared to spin lattice relaxation times. Relaxation losses are minimized by proton irradiation of the substrate in the reactor prior to polarization transfer, which traps the singlet state. The PASADENA precursor for the experiments presented below was [1,3,3-2H3; 1-^{13}C]2-ethylacrylate, synthesized in collaboration with Isotech, Miamisburg, OH, USA, which becomes [1,3,3-2H3; 1-^{13}C] 2-hydroxyethylpropionate (HEP) upon hydrogenation during the PASADENA hyperpolarization process as shown in Fig. 1.

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2.2. ^{13}C and ^{1}H MR imaging

All ^{13}C and ^{1}H imaging was performed on a 1.5 T General Electric Signa MR scanner (GE Healthcare, Milwaukee, WI, USA) operating with version 9.1 software. The imaging was performed using a dual purpose RF coil designed and built in our laboratory incorporating two single-turn, 12-cm diameter proton surface coils arranged in quadrature configuration which overlap a two-turn transmit/receive 11-cm diameter circular ^{13}C surface coil at an angle of 45° minimizing the mutual inductance between the proton and carbon RF coils [22].