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A general chemical shift decomposition method for hyperpolarized ^{13}C metabolite magnetic resonance imaging

Jian-xiong Wang^{a,*}, Matthew E. Merritt^b, Dean Sherry^a, and Craig R. Malloy^a

^a Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

^b Department of Biochemistry and Molecular Biology, University of Florida, Gainesville, FL, USA

Abstract

Metabolic imaging with hyperpolarized carbon-13 allows sequential steps of metabolism to be detected *in vivo*. Potential applications in cancer, brain, muscular, myocardial, and hepatic metabolism suggest that clinical applications could be readily developed. A primary concern in imaging hyperpolarized nuclei is the irreversible decay of the enhanced magnetization back to thermal equilibrium. Multiple methods for rapid imaging of hyperpolarized substrates and their products have been proposed with a multi-point Dixon method distinguishing itself as a robust protocol for imaging $[1-^{13}\text{C}]\text{pyruvate}$. We describe here a generalized chemical shift decomposition method that incorporates a single-shot spiral imaging sequence plus a spectroscopic sequence to retain as much spin polarization as possible while allowing detection of metabolites that have a wide range of chemical shift values. The new method is demonstrated for hyperpolarized $[1-^{13}\text{C}]\text{pyruvate}$, $[1-^{13}\text{C}]\text{acetoacetate}$, and $[2-^{13}\text{C}]\text{dihydroxyacetone}$.

Keywords

hyperpolarized; ^{13}C MR; metabolite imaging; chemical shift; decomposition

Introduction

Hyperpolarized (HP) ^{13}C overcomes the poor sensitivity characteristic of conventional ^{13}C MR imaging and spectroscopy.^[1] Since the initial demonstration, successful applications *in vivo* by numerous laboratories in experimental animals^[2-4] and human patients^[5] have been reported. $[1-^{13}\text{C}]\text{pyruvate}$ is often selected for a study because of the central role of pyruvate in intermediary metabolism, the relatively long T_1 and its ease of polarization. However, many other molecules involved in glycolysis, the citric acid cycle and ethanol metabolism have been studied *in vivo*, including fumarate,^[6] dihydroxyacetone,^[7] lactate,^[8] glucose^[9] and ethanol.^[10] Detailed information about fluxes in individual enzyme-catalyzed reactions is accessible in principle, but a limiting factor is the relatively short period available for data acquisition because of T_1 decay. Because data are ideally presented in image format, fast chemical shift imaging of ^{13}C in a limited time is a critical objective for clinical translation.

* Correspondence to: Jian-xiong Wang, Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, USA. jianxiong.wang@utsouthwestern.edu.

Numerous approaches have been suggested for rapidly acquiring metabolite-specific ^{13}C images. The multi-point Dixon concept was originally developed for separating water and fat.^[11] A more general method, termed iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL), has been investigated for ^{13}C imaging.^[13-15] The paper by Wiesinger et al.^[12] in particular demonstrated a framework for using spiral IDEAL to image metabolites labeled by HP $[1-^{13}\text{C}]$ pyruvate (Fig. 1) and that inspired the work described herein. In this work, we describe an efficient and flexible generalized chemical shift decomposition method based on these earlier approaches. Applications of the more general chemical shift decomposition method are presented for imaging HP $[1-^{13}\text{C}]$ pyruvate, $[1-^{13}\text{C}]$ lactate and $[1-^{13}\text{C}]$ alanine. In this context, the general chemical shift decomposition methods yields results similar to earlier reports. A more complex phantom using a compound not present in biological systems, $[1-^{13}\text{C}]$ formate, was used to test the generality of this decomposition method. To achieve the advantages of the general decomposition, chemical shifts *in vivo* must be known precisely, a strategy to acquire and integrate measured chemical shifts *in vivo* with image reconstruction is described. Finally, applications of this method in rat models using the HP ^{13}C imaging agents $[1-^{13}\text{C}]$ pyruvate, $[1-^{13}\text{C}]$ acetoacetate and $[2-^{13}\text{C}]$ dihydroxyacetone (DHA) are described on a clinical MRI scanner.

Theory

Metabolite decomposition

For a sample composed of multiple molecules or metabolites with resonances at distinguishable frequencies, the MR signal acquired following a radio frequency (RF) excitation can be written as

$$S = \sum_{m=1}^M \rho_m e^{j\omega_m TE} \quad (1)$$

where ρ_m is the MR signal contribution from the metabolite m that is proportional to its quantity, ω_m is the difference between the chemical shift frequency of metabolite m and the center of the RF excitation frequency, and TE is the echo time. Each $e^{j\omega_m TE}$ can also be geometrically represented as shown in Fig. 2A. The phase caused by field inhomogeneity can be added into the phase term empirically.

To decompose M metabolites ρ_m , the same excitation-acquisition sequence is repeated N times ($N > M$) by shifting the echo time TE_n . The Eqn (1) can be expanded as

$$\mathbf{s} = \mathbf{E} \boldsymbol{\rho} \quad (2)$$

where $\mathbf{s}$ is the acquired MR signal vector of N echoes and $\mathbf{E}$ is a matrix of size $(N \times M)$ with each element $e^{j\omega_m TE_n}$. In practice, the echo times are equally spaced as $TE_n = TE_1 + (n-1) \times TE$. The MR signals that contributed from the M metabolites are then decomposed as a vector

$$\rho = E^+ s \quad (3)$$

where E^+ denoted the Moore-Penrose pseudo-inverse of the matrix E that computes a ‘best fit’ (least squares) solution to the linear equations.

Optimization of the echo time shift TE

When the number of echoes is defined, the choice of the echo times, particularly the echo time shift TE, becomes critical. Choice of an inappropriate TE will cause an ill-conditioned matrix E and therefore an inaccurate solution for decomposition of the metabolite vector ρ . For this purpose, the two-norm condition number inverse (CNI) is used to insure that the matrix E is well-conditioned:

$$CNI(E) = \frac{1}{\|E\|_2 \|E^{-1}\|_2} = \frac{\sigma_n}{\sigma_1} \quad (4)$$

where $\|\cdot\|_2$ denoted two norms and σ_n and σ_1 are the smallest non-zero singular value and largest singular value in the singular value decomposition of E respectively. For an ill-conditioned matrix E , the CNI is close to zero, and for a well-conditioned matrix, CNI would approach to 1.

After injection of a HP ^{13}C -labeled substrate, an increasing number of downstream metabolites make the decomposition more complex. For example, for HP $[1-^{13}\text{C}]$ pyruvate, the number of *in vivo* metabolite resonances that might be detected could have three, four, five or more components namely pyruvate, pyruvate hydrate, lactate, alanine, bicarbonate and others depending upon the tissue under investigation.^[17] Because of physiology, pH and other condition differences, the chemical shift of the same metabolite, for example, $[1-^{13}\text{C}]$ pyruvate, can vary from organ to organ. In general, the correct and tolerable TE is estimated by calculating CNI as function of TE in a relatively wide range with *a priori* known or estimated chemical shifts of metabolites to be imaged. In certain situations, TE needs to be readjusted quickly according to observed chemical shifts for more accurate component decomposition. With the single value, CNI is intuitive for picking up the most suitable TE for overall system performance. In theory, arbitrary TEs can also be implemented by applying a multi-dimensional CNI optimization process to find an optimum set of echo times. This will be addressed in a future study.

The CNI as function of TE for a five-metabolite system calculated for 3 T is shown in Fig. 2B. In this example, the metabolites likely to arise from a commonly used HP agent $[1-^{13}\text{C}]$ pyruvate include $[1-^{13}\text{C}]$ lactate, $[1-^{13}\text{C}]$ pyruvate-hydrate, $[1-^{13}\text{C}]$ alanine, $[1-^{13}\text{C}]$ pyruvate and $[^{13}\text{C}]$ bicarbonate with 5, 7 and 9 echoes. Results from a simpler three-metabolite pyruvate system are also shown ($[1-^{13}\text{C}]$ lactate, $[1-^{13}\text{C}]$ pyruvate-hydrate and $[1-^{13}\text{C}]$ pyruvate) with 3, 4 and 5 echoes. These results illustrate that with the proper selection of TE and with increasing number of echoes, the CNI approaches unity and a well-conditioned matrix E in Eqn (2) is obtained.

Design of the spiral encoding trajectory

For fast imaging and to conserve hyperpolarization, the single-shot uniform density spiral was chosen and the encoding trajectory that in k-space can be described as

$$k(t) = r(t) e^{i\theta(t)} \quad (5)$$

Each step along the spiral path should not exceed the maximum gradient strength G_{max} and the slow rate S_{max} of the MRI scanner system. The outcome of an example is shown in Fig. 3. Because of the lower gyromagnetic ratio of ^{13}C , the gradient strength requirement is much higher compared with proton imaging. Our experience suggests that about 80% of the maximum value can be used. The continuous operation at fully specified maximum gradient strength and slow rate may cause system halt. The k-space trajectory (Fig. 3b) is used for image reconstruction, and the gradient waveform (Fig. 3c) is encoded into the pulse sequence.^[16]

Spiral-based multi-point Dixon sequence scheme and image reconstruction

The n -echo sequence scheme is shown in Fig. 4. Each echo is an independent sequence with its own excitation pulse. For the first echo, the spiral gradient and data acquisition follow the excitation pulse with an echo time (TE) as short as the system permits typically 1.4 ms from the center of the RF pulse if 1.8 ms width pulse is used. For the following echoes, the TE is increased sequentially by an echo time shift TE .

To perform the chemical shift decomposition image reconstruction, each acquired data set at the same k-space position from n -echoes (Fig. 4b linked solid dots) is collected as vector $s(\mathbf{k})$, and the metabolite intensity vector $\rho(\mathbf{k})$ is resolved with Eqn (3). Then, the phase of each metabolic element is corrected to the acquisition starting time t_0 by

$$\rho_m(k_0) = \rho_m(k_t) e^{i\omega_m t_k}. \quad (5)$$

This is repeated for all n -echo spiral trajectories to form m -metabolic phase-corrected spiral trajectories. The spiral trajectories for each metabolite are then gridded into Cartesian k-space data and reconstructed into images by 2D Fourier transform as shown in Fig. 4c-f. Brodsky *et al.*^[25] combined this phase correction into matrix E of Eqn (3) for their k-space IDEAL water-fat decomposition that has the same effect as this two-step correction with Eqns (3) and (5).

Methods

To validate the method, a multiple component phantom was used. This phantom consists of four chambers filled with 1 M ^{13}C -labeled lactate, alanine, formic acid and bicarbonate solutions. These chambers were 40 mm in length and 10 to 20 mm in diameter. Variable diameter reservoirs allow easy identification of the chemical components visually for the phantom and the image.

All ^{13}C agents were hyperpolarized in a homemade dynamic nuclear polarization pre-polarizer^[18] at 4.6 T and 1.15 K for about 90 min. Trityl OX063 free radical was used for all experiments. A total of 14.4 M $[1-^{13}\text{C}]$ pyruvic acid, 1.3 M $[1-^{13}\text{C}]$ acetoacetate or 4 M $[2-^{13}\text{C}]$ dihydroxyacetone dimer were polarized for different experiments. In the case of pyruvic acid, the neat compound was used; no additional glassing solvents were added. DHA was polarized according to the method of Moreno *et al.*^[19] Gadoteridol (Prohance, Bracco Diagnostic, Inc., Cranbury, NJ) was added to the samples to a 1.2 mM concentration to improve the total sample polarization.^[20] After an appropriate time was allowed for polarization, the solid was dissolved with ~4 ml phosphate-buffered saline heated to 200 °C at 10 bar pressure. The final solution is ~37 °C and has a pH value of ~7.4. In the case of pyruvic acid, a commensurate amount of 1 M NaOH is added to dissolution media to assure the correct pH. All experiments were approved by the University of Texas Southwestern Medical Center Animal Care and Use Committee. About 3 ml of such solution was injected into rats and 0.3 ml into mice through either jugular vein or tail vein catheter, while mice or rats were anesthetized with an isoflurane-oxygen gas mixture.

Imaging was performed on a MR750W wide bore 3 T clinical scanner with ^1H - ^{13}C dual tuned rat or mouse coils (General Electric Company, Milwaukee, WI). Shimming and slice selection were conducted with ^1H imaging. RF power calibration for ^{13}C was performed with an enriched ^{13}C -labeled chemical phantom by searching for a change in phase and the minimum signal amplitude at 180° with proper transmit gain. Depending on the goals of the experiment, a slice thickness of 8 to 18 mm and a field of view (FOV) of 8 to 12 cm were used. The single-shot RF spiral sequence has a typical repetition time (TR) of about 100 ms. Four to 7 echoes were normally used for the chemical shift decomposition imaging experiments. For the purpose of correctly identifying the frequencies of each metabolite, an optional fid acquisition was implemented either before or after each n -echo sequence set. This is done by turning off the spiral acquisition gradient pulse, and the fid is then converted into a spectrum in frequency domain. Together with a spectroscopic fid, one time course set of sequences takes 0.4 to 0.8 s to obtain one set of metabolite images. Flip angles of 5°, 7° and 10° were typically used. When a total time course time is defined, a time course delay was automatically calculated and inserted after the n -echo sequence set. Normally, a waiting time of 2.0 to 2.5 s was implemented between each sequence set to form a 3-s ‘total time course delay’ as shown in Fig. 5. To validate the gradient delay correction and the image geometry, a fiducial mark (^{13}C -labeled propionate, urea, etc.) was sometimes placed adjacent to the subject. Our experiments showed that the chemical shift of metabolites may drift during the time course and the metabolism may vary at different body parts of subject.

Raw data are sent to a desktop computer for image reconstruction with a Matlab script. All necessary imaging control variables are implemented in the raw data header, and the script will produce the slice selective time course spectra and images for every metabolite, slice and time course. The accurate metabolite frequencies ω_m are defined manually or semi-automatically based on the summed spectrum and then automatically adjusted for each different slice of the time course. B_0 corrections are only performed when it is needed. In general, it is done by applying a linear phase gradient along one physical direction or along the spiral trajectory.

Results

The chemical shift decomposition imaging protocol that incorporates the single-shot spiral imaging sequence plus the spectroscopic sequence is shown in Fig. 5. The spectrum for the purpose of chemical shift referencing may be performed prior to image acquisition (5A), after image acquisition (5B) or not at all (5C). These option choices were implemented after various requests from researchers to suit different metabolic studies. After a delay, typically 3 s, fresh product metabolite signals continue to increase in intensity. If 5A is chosen, better spectra could be acquired for more accurate overall slice dynamic analysis such as heart and large liver slice imaging. 5A is best suited for metabolic research without abnormal metabolite chemical shifts. Method 5B is better suited for tumor metabolism studies where abnormal chemical shifts and possibly double peaks, pyruvate for example, can occur. Method 5C is best used for well-known models in order to save an excitation for each time course and obtain longer dynamics. Figure 5d shows the time course of spectra acquired from brown fat in a rat after injection of HP [1-¹³C]pyruvate. As anticipated, [1-¹³C]lactate, [1-¹³C]alanine, [1-¹³C]pyruvate hydrate and [¹³C]bicarbonate were observed.^[21] The frequencies of each metabolite from each n-echo set were separately determined semi-automatically. In this way, more accurate chemical shift decomposed images can be obtained for each time course point and slice.

Spectra and images from the validation phantom are shown in Fig. 6a. The double peak of formic acid arising from J_{CH} was reconstructed into two images of the same physical object. A reference spectrum and ¹³C image of [1-¹³C]pyruvate and downstream metabolites from a rat heart are shown in Fig. 6b. Note that the [¹³C]bicarbonate signal reconstructs to form a usable image even though the attending spectrum shows that the bicarbonate signal is ~1/10th the intensity of the lactate signal. A reference spectrum and image of brown fat after injection of [1-¹³C]pyruvate are shown in Fig. 6c. Images from the heart were also acquired in these axial slices; ¹³C images were scaled to emphasize the metabolites in the brown fat area that revealed all metabolites from the brown fat at accurate triangular shape and location. These experimental results, Fig. 6a-c, illustrate applications of the generalized chemical shift decomposition method to imaging of [1-¹³C]pyruvate and its products.

Figure 6d shows the image set acquired after injection of [2-¹³C]DHA with imaging of the rat liver. For this experiment, a RF pulse with narrow frequency bandwidth selectively excites the product metabolite [2-¹³C]glycerol-3-phosphate (G3P) and the naturally occurring [2-¹³C]DHA-hydrate. G3P images illustrate the phosphorylation of DHA in the liver. Using this method, the DHA-hydrate actually serves as a useful marker of substrate delivery, with the advantage that excitation of the resonance does not rapidly deplete the polarization of the DHA parent molecule normally resonating at 212 ppm. Figure 6e shows ¹³C images of HP [1-¹³C]acetoacetate from a rat heart and the metabolic products [3-¹³C]acetoacetate and [1-¹³C]acetate. Major imaging parameters for previously mentioned *in vivo* experiments are listed in Table 1.

Discussion

Dynamic nuclear polarization is of general use for enhancing the NMR signal of almost any organic compound. This work demonstrates that the generalized chemical shift decomposition pulse sequence is flexible and easily extended to accommodate, in principle, virtually any HP ^{13}C -enriched compound and its metabolic products. Although the echo time shift TE must be selected for every situation, one can determine a reasonable range of TE by calculating the CNI with possible ranges of chemical shift for the metabolites under study before the *in vivo* experiment. However, for optimal reconstruction, the chemical shifts of each metabolite under *in vivo* conditions must be known. The precise chemical shift varies from subject to subject and at different regions within a single subject because of susceptibility-induced B_0 variations. For this reason, acquisition of a separate spectrum in an interleaved manner establishes the exact frequencies needed to perform the matrix inversion described by Eqn (3). The exact determination of the shifts has been incorporated into the IDEAL reconstruction in a straightforward manner. A semi-automatic peak search establishes the exact frequencies. This step can be bypassed if the shifts are not changing across the kinetic data set.

In HP ^{13}C experiments, real-time kinetics is potentially accessible through either the time course or the integrated intensities of the metabolic resonances.^[22] This information provides previously unobtainable insights into metabolic flux in healthy or diseased tissues. The paradigm demonstrated here provides both images and slice-localized spectra in the same protocol, which aids in overall experimental flow. The large majority of kinetic data obtained with hyperpolarization to date has been acquired using slice selective spectroscopy alone.^[23] By collecting the spectroscopic measurements, comparison of new data with that previously acquired is facilitated. Combined with the increased accuracy of the reconstruction, we believe that this protocol is a significant advance in terms of collecting useful information from *in vivo* HP experiments. Our data show that slice selective excitation does not impede the acquisition of kinetic data.

The *n*-echo sequence is repeated for the entire lifetime of the hyperpolarization, which is about 2 min. The dynamic repetition time of about 3 s is typically used for the detection of kinetic data without depleting the HP magnetization prematurely. Because the metabolic images are based on the entire *n*-TE course, changing physiological conditions over the repeat time will cause distortions in the data. For this reason, achieving a minimal TR for the sequence is necessary. To balance these competing considerations, a time course delay mechanism is implemented into the pulse sequence. The shortest repetition time for each excitation-acquisition sequence is about 100 ms. Extension of the time course delay to 3 s has two advantages: It allows the completion of the *n*-echo sequence in a minimal time period and allows the metabolite signals to build up during enzymatic processes during the remaining portion of the defined TR. The image reconstruction computation is very fast (10 to 30 s), even for long time course and multiple slice experiments.

Because the readout time of the spiral acquisition is relatively long (about 50 ms), each metabolite may experience different point spread function (PSF) caused by T_2^* signal loss during the long readout. In that case, the partial volume effects may cause metabolite signals

from different volume. In order to estimate this effect, we calculated the PSF for spirals and the effects caused by T_2^* decay. Yen *et al.*^[24] estimated that T_2^* of *in vivo* HP $[1-^{13}\text{C}]\text{pyruvate}$ is ~ 100 ms. Figure 7 and Table 2 show the PSF of the spiral and the effects of T_2^* decay. The results indicated that for a wide range of T_2^* values (from 40 to 100 ms), the increase in PSF is only a few percent and the caused partial volume effect is negligible; only when T_2^* is as short as 20 ms, minor distortions begin to appear. Therefore, even if each HP ^{13}C metabolite signal has a different T_2^* , the signal of each metabolite will appear in the same pixel volume and quantitative kinetics can be obtained from the targeted volume under study.

Gordon *et al.*^[26] proposed a spiral trajectory splitting strategy to reduce the number of echoes or use the same number of echoes to increase the image reconstruction quality by increasing the spiral field of view by a factor of 4 or 7 for small animal such as rodent imaging. For large animal and human ^{13}C metabolite imaging, more simulations experiment would be needed to validate the method.

Conclusions

We have demonstrated a modification of the IDEAL sequence for imaging of HP carbon-13-labeled metabolites. The method is suitable for imaging not only $[1-^{13}\text{C}]\text{pyruvate}$ and its metabolic products but also $[2-^{13}\text{C}]\text{dihydroxyacetone}$, $[3,4\text{-}^{13}\text{C}]\text{glucose}$, $[1-^{13}\text{C}]\text{butyrate}$ and $[1-^{13}\text{C}]\text{acetoacetate}$. Despite the large chemical shift ranges of these precursors and their products, the chemical shift decomposition method produces images in a robust manner. By inclusion of an intermediate pulse-acquire element in the sequence design, we can simultaneously acquire kinetic data for each metabolic product. This serves multiple purposes: It increases the information yield gained from each HP injection, and it provides a spectrum for accurate measurement of chemical shifts. This new method should prove superior for chemical shift decomposition reconstruction.

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Figure 1. Diagram of pyruvate metabolism in oxidative tissues. The chemical shift of each commonly observed metabolite is shown. ALT, alanine aminotransferase; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; CA, carbonic anhydrase.

Figure 2.

Panel A shows the phase relationships of $[1-^{13}\text{C}]$ pyruvate, $[1-^{13}\text{C}]$ pyruvate hydrate, $[1-^{13}\text{C}]$ lactate, $[1-^{13}\text{C}]$ alanine and $[^{13}\text{C}]$ bicarbonate for a field of 3 T. In this example, the relative phases at delta TE 1.1 and 1.4 ms are shown. Panel B illustrates the condition number inverse (CNI) as a function of echo time shift. The left column shows the CNI of a five-component system generated by $[1-^{13}\text{C}]$ pyruvate (lactate, pyruvate hydrate, alanine, pyruvate itself and bicarbonate). For 9 and 7-echo schemes, TE can be around 1.2 ms, while in 5-echo case, 2.27 ms would be a better choice. The right column represented a three-component system (lactate, pyr-hydrate and pyruvate). For 3, 4 and 5 echo schemes, optimized TE should be 1.70, 1.91 and 1.53 ms respectively.

Figure 3.

An equivalent of $\text{FOV} = 8 \text{ cm}$ and $\text{resolution} = 2 \text{ mm}$ spiral trajectory. Panel (a) represents the trajectory in k_x - k_y space; panels (b, c and d) are k -space value, gradient and slow rate as function of time. Solid line is for x -axis and dashed line for y -axis. The envelop line is the length u . G_{max} and S_{max} were set to 26 mT/m and 96 T/m/s respectively for this design.

Figure 4. Sequence and chemical shift decomposition metabolite imaging reconstruction procedure; (a) single-shot spiral RF pulse, (b) n -echo pulse set with echo time shift ΔTE , (c) n -echo converted into m -metabolite k-space data, (d) phase correction along the k-space time line, (e) non-Cartesian spirals are re-gridded into Cartesian k-space, and (f) image of each metabolite is reconstructed via Fourier transform.

Figure 5. Chemical shift decomposition imaging protocol; each solid bar represents a single-shot spiral imaging sequence and hollow bar a spectroscopic acquisition by turning off all gradient pulses. (a) Pre-imaging spectrum, (b) post-imaging spectrum and (c) no spectrum acquisition and (d) a hyperpolarized $[1-^{13}\text{C}]$ pyruvate *in vivo* rat spectrum set with a 3-s 'time course delay'.

Figure 6.

(a) Phantom spectrum and images reconstructed with a 7-echo chemical shift decomposition method; both spectrum peaks and images from left to right: lactate, alanine, formate1, formate2 and bicarbonate. (b) Metabolite ^{13}C image set of a rat heart. (c) Metabolite ^{13}C images of a rat brown fat. Part of the heart is in the axial slice, images are scaled up to emphasize the metabolites in brown fat. (d) ^{13}C images of a rat liver using $[2-^{13}\text{C}]\text{DHA}$ as HP agent; beside the aorta, part of the right kidney and tip of the left kidney are shown in the $[2-^{13}\text{C}]\text{DHA-hydrate}$ image; (e) ^{13}C images of a rat heart using $[1-^{13}\text{C}]\text{acetoacetate}$ as hyperpolarized agent.

Figure 7.

Point spread function of the spiral and the effects caused by T_2^* decay. The results demonstrate that spurious effects because of differences in T_2^* should be negligible. Only when the T_2^* is 20 ms, noticeable effects begin to appear.

Table 1

Imaging parameters of experiments corresponding to rows in Fig. 6

	¹³ C agent	Dose	f_0 (ppm)	nTE	TE (ms)	TR (ms)	Fig. 5 scheme	Time course
(a)	Phantom	1 M	170	7	1.0	5000	(b)	35 s
(b)	1C-pyruvate	14M	170	7	2.4	150	(a)	3 s
(c)	1C-pyruvate	14M	170	7	1.5	125	(b)	3 s
(d)	2C-DHA	4M	70	5	1.0	120	(b)	3 s
(e)	1C-AcAc	1.3M	185	5	1.5	120	(a)	3 s

¹³C agent doses are initial hyperpolarization concentrations (refer in the texts). The last two columns showed the scheme in Fig. 5. Time course and delay is automatically adjusted according to requested imaging time.

f_0 , RF pulse center frequency; nTE, number of echoes; TE, echo time increment.

Table 2

Increase of resolution by measuring the spiral point spread function because of decrease of the T_2^* at bottom and FWHM of the center lobe in unit of percentage relative to $T_2^* = 100$ ms

	$T_2^*(\text{ms})$	100	80	60	40	20
FOV = 80 mm	Lobe Bottom	0%	1%	4%	11%	36%
	FWHM	0%	1%	4%	8%	25%
FOV = 300 mm	Lobe Bottom	0%	3%	5%	10%	32%
	FWHM	0%	1%	4%	8%	24%

FWHM, full width at half maximum; FOV, field of view.