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Localized Proton Spectroscopy Using Stimulated Echoes

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This paper describes a new method for spatially resolved NMR spectroscopy that takes advantage of stimulated echo signals. STEAM (*st*imulated *e*cho *a*cquisition *m*ode) sequences, already used for a variety of imaging purposes, almost perfectly match the requirements of image-controlled localized ^{1}H NMR *in vivo*. Superior spatial discrimination as well as high flexibility with respect to location, size, and shape of the volume of interest is achieved by employing only three slice-selective 90° rf pulses in the presence of orthogonal gradients. The method is a single-step procedure minimizing rf power requirements and gradient switches. It further allows accurate determinations of localized T_1 and T_2 relaxation times simply by varying the length of corresponding intervals of the STEAM sequence. In fact, the inherent T_2 weighting may be used for water suppression and/or reduction of residual eddy current effects. Here we present first results on phantoms and human extremities demonstrating the ease of image selection, localized spectroscopy, and localized determinations of relaxation times. Future steps will deal with water/lipid-suppressed metabolic spectroscopy.

INTRODUCTION

Spatially resolved NMR, in particular localized high-resolution NMR spectroscopy *in vivo,* may become an important tool not only for noninvasive biochemical and biophysical research but also for medical diagnosis. In terms of technical approaches, one may generally distinguish between "global" and "local" methods of acquiring both spatial and spectral information in a combined imaging/spectroscopy experiment. Global methods are four- (or three-) dimensional chemical-shift imaging techniques yielding data sets with three (or two) spatial dimensions and one chemical-shift dimension. Obvious problems are the long measuring times, the handling and storage of very large data matrices, and the fact that there seldom is a real interest in truly global information. Moreover, spectroscopic *imaging* techniques often sacrifice spectral resolution and spectral quantification in order to keep imaging times short. Global methods also suffer from limited B_0 and B_1 homogeneities in cases where water suppression techniques have to be applied over large volumes.

Local methods comprise *spectroscopy* techniques that attempt to focus on a selected volume of interest (VOI) ideally defined by previous imaging investigations. The most successful technique up to now has been surface coil spectroscopy (*1*), where localization is achieved by radiofrequency (rf) gradients, i.e., the B_1 profile of the surface coil or arrangement of coils. Improvements with respect to a better spatial characterization of the surface coil spectra have been obtained using rotating frame imaging techniques

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(*2, 3*) including Fourier windowing (*4*). Surface coils have also been combined with magnetic field gradients for slice selection in the DRESS experiment (*5*). More recently, approaches using magnetic field gradients in combination with homogenous rf coils have regained interest in order to make the localization of a VOI more flexible with respect to location, size, and shape. The first promising techniques are ISIS (*6*) and SPARS (*7*), the latter of which being a derivative of the VSE experiment (*8*).

In most cases new sequences have been developed to be applicable for protons as well as for heteronuclei. However, the actual requirements for proton and, for example, phosphorus spectroscopy are very different and under certain circumstances even contradictory: extremely short T_2 weightings for phosphorus to keep ATP resonances visible versus strong T_2 weightings for water-suppressed proton spectroscopy of mobile metabolites. Consequently, it would be advisable to specifically design a localization technique for proton and phosphorus spectroscopy, respectively. In this paper we describe a new technique for localized ^{1}H NMR spectroscopy taking such considerations into account. It is able to provide strong T_1 and T_2 weightings and directly allows image selection and characterization of the selected volume.

METHODS

In order to spatially select a volume of interest within a three-dimensional object it is necessary to apply at least three selective rf pulses in the presence of orthogonal magnetic field gradients. This condition is almost perfectly met by stimulated echo sequences. In fact, STEAM (*st*imulated *e*cho *a*cquisition *m*ode) imaging sequences have already been used for a variety of purposes in improving the imaging specificity (*9–16*). For localization all three rf pulses of the STEAM sequence are taken as slice-selective pulses in the presence of orthogonal gradients as demonstrated in Fig. 1. Without the slice selection gradients in the read and phase-encoding direction, i.e., rf pulses No. 1 and No. 2, the sequence is a standard single-slice STEAM imaging sequence that may be used for selection of the VOI for the subsequent spectroscopic investigation. By inclusion of these gradients the sequence in Fig. 1 allows direct image control of the VOI if desired. Another interesting application might be zoom imaging

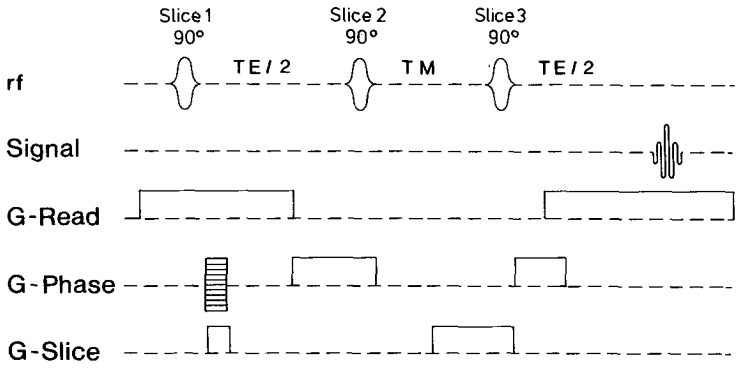

FIG. 1. Radiofrequency and magnetic field gradient sequence for volume-selective STEAM imaging.

or even localized microscopic imaging by restricting the field of view and using increased strengths for the read and phase-encoding gradients.

On the other hand, localized spectroscopy as shown in Fig. 2 is easily achieved by omitting both the phase-encoding gradient and the read gradient in Fig. 1 while retaining the slice-selective parts. In general, the procedure may include the following steps: conventional (multislice) STEAM imaging using a single slice-selective 90° pulse, selection of a VOI, imaging of the VOI using the sequence shown in Fig. 1, and localized spectroscopic examinations using the sequence shown in Fig. 2. Basically, localization on the basis of stimulated echoes is a direct "single-step" method that, for example, allows reshimming of the homogeneity over the VOI. The choice of a position or a certain size and shape of the VOI is under computer control and may be easily adjusted by changing the frequency and/or the shape of the selective rf pulses and/or the strength of the slice-selective gradients. Since only three selective 90° pulses are employed, localized STEAM spectroscopy will be applicable to any small-bore and whole-body NMR system with a very low rf load on animals or patients. Moreover, the spatial selectivity of the sequence is not affected by misadjustments of the pulse flip angles. Residual eddy current effects can be circumvented by long echo times.

At this stage the sequence shown in Fig. 2 offers elegant determinations of local T_1 and T_2 relaxation times. This can be accomplished simply by varying the length of the corresponding intervals TM or TE in a series of experiments without the need of additional pulses. Metabolic spectroscopy, however, requires a suppression of water and possibly also lipid proton signals. Also for this purpose, one may exploit the inherent suppression capabilities of the sequence, i.e., independent adjustments of strong T_1 (lipid resonances) and T_2 (water resonance) weightings. In addition, the basic STEAM sequence may be combined with any conventional suppression technique such as presaturation or frequency-selective spin-echo formation.

It should be noted that there are two extensions of the basic experiment that may improve the efficiency of the spectroscopic examinations in all cases where multiple accumulations are recommended. The first modification is a multislice or multipoint version of the sequence shown in Fig. 2 obtained by multiple applications of the third pulse while shifting its center frequency (at the expense of slightly increased TM values).

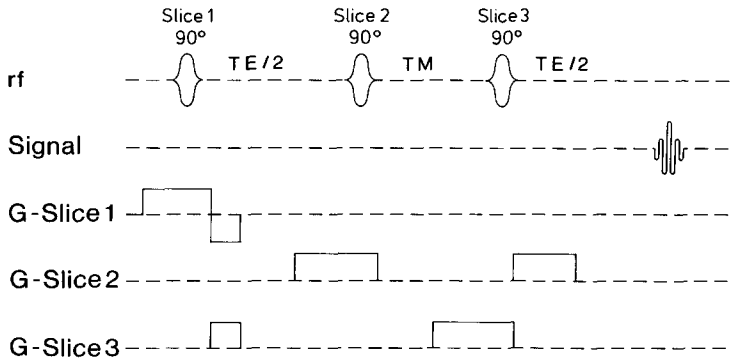

FIG. 2. Radiofrequency and magnetic field gradient sequence for volume-selective STEAM spectroscopy.

An alternative way of screening an extended VOI would be the 3D analog to multislicing: only two slice selection pulses (or a third with increased bandwidth/lowered gradient strength) are applied and combined with a phase-encoding gradient in the third direction, e.g., applied during the first interval of the STEAM sequence. This version simultaneously records spectra of an extended region ("line," compare Figs. 3b and 3c) in the form of a two-dimensional array with one (course) spatial dimension and one high-resolution chemical-shift dimension with the full signal-to-noise related to all excitations.

EXPERIMENTAL RESULTS

Proton NMR images and localized spectra (100 MHz) of phantoms and human extremities have been obtained using a 2.35 T 40 cm bore magnet system (Bruker Medspec). Both imaging and spectroscopy experiments were carried out using the standard imaging coil (slotted tube resonator) with a clear diameter of 22 cm. Figures 3a–d describe the first two steps of image-controlled STEAM spectroscopy, image selection, and characterization and gives an impression of the spatial selectivity. The images of a water bottle comprising five different test samples (2.5 cm outer diameter) show the entire object (Fig. 3a) and some selected volumes that have been recorded

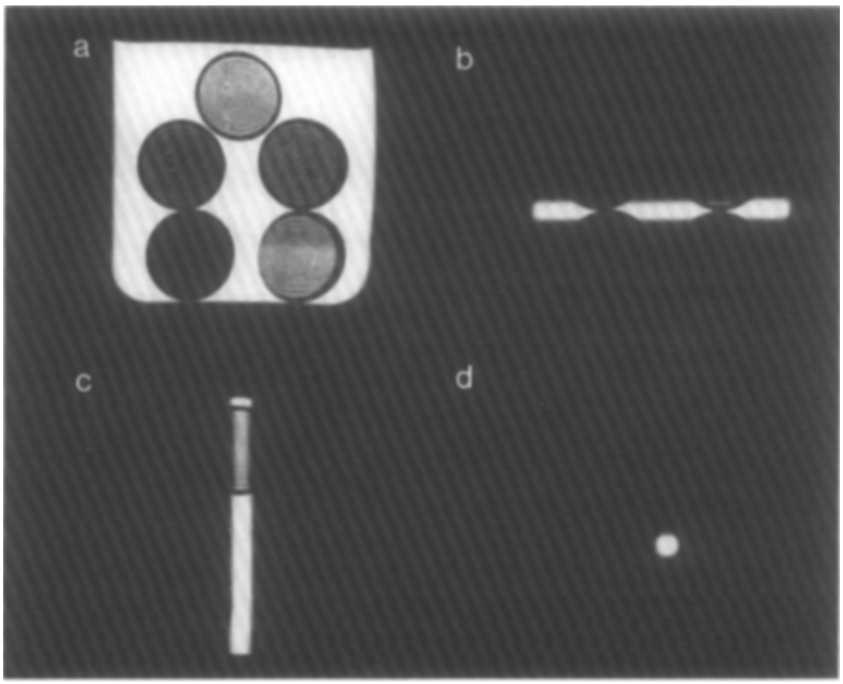

FIG. 3. 100 MHz ^{1}H NMR STEAM images of a phantom with different degrees of volume selection. (a) Conventional STEAM image with a slice thickness of 5 mm, (b and c) volume-selective STEAM images with a second slice-selective rf pulse either in the read or phase-encoding direction cutting out a line of image (a) with a thickness of 5 mm, and (d) full volume-selective STEAM image with three slice-selective rf pulses according to Fig. 1. The VOI is a 5 × 5 × 5 mm cube corresponding to a volume of 0.125 ml.

with two (Figs. 3b and c) and three (Fig. 3d) slice-selective rf pulses in accordance with the sequence shown in Fig. 1. The intervals correspond to TE = 30 ms and TM = 40 ms. For a measured resolution of 128 × 256 complex data points with a single excitation and a repetition time of TR = 2 s the imaging time was about 4.5 min. Of course, this time may be reduced using fast imaging techniques (*13, 17*). The slice thickness was adjusted to 5 mm using 2 ms Gaussian-shaped selective rf pulses and 7.5 mT/m slice selection gradients. The VOI in Fig. 3d is therefore limited to a 5 × 5 × 5 mm cube corresponding to a volume of 0.125 ml. The images clearly demonstrate the high degree of spatial discrimination achieved in a single experimental run without the need of compensation or add/subtract algorithms. In this example the spatial discrimination factor is more than 3000 with respect to the volume of the entire object. This finding also applies to the volume-selective spectra shown in Figs. 4a–e.

While the image shown in Fig. 4 represents an overlap of a conventional STEAM image with some volume-selective images, Figs. 4a–e contain the related localized proton spectra. The spectra are magnitude representations and have been recorded with two acquisitions using a 180° phase cycling of the final 90° pulse. Since our hardware has not yet been optimized to minimize eddy current effects in the magnet induced by switching magnetic field gradients, some of the spectra are slightly distorted due to the short echo time of TE/2 = 15 ms. In addition to the individual spectra, complete relaxation curves have been obtained by varying TM and TE in a series of

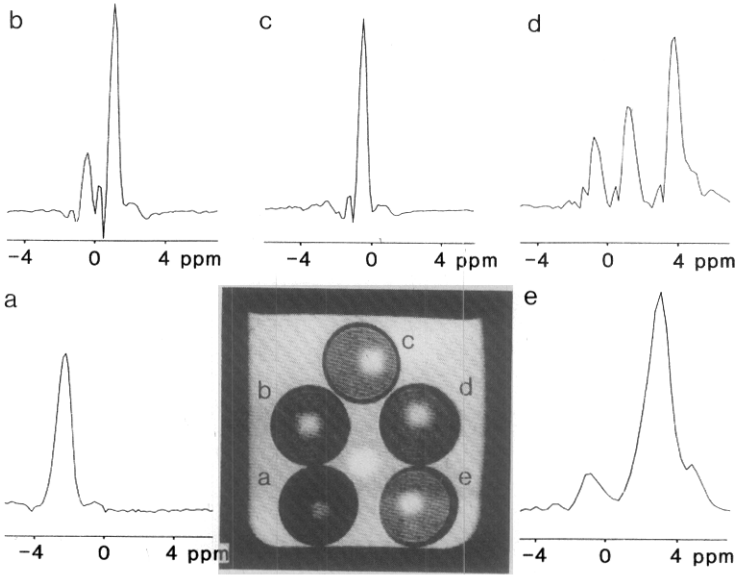

FIG. 4. 100 MHz ^{1}H NMR STEAM image and localized spectra of a phantom filled with $CuSO_4$-doped water and five different test samples containing (a) benzene, (b) methanol, (c) distilled water, (d) ethanol, and (e) vegetable oil. The conventional image is superimposed with volume-selective STEAM images to characterize the spatial selectivity of the spectroscopic examinations. The VOI is a 5 × 5 × 5 mm cube corresponding to a volume of 0.125 ml. (a)–(e) Localized 100 MHz ^{1}H NMR STEAM spectra (TE = 30 ms, TM = 40 ms, 2 acquisitions, 3 s repetition time, magnitude representations).

experiments with high accuracy. A first application *in vivo* is depicted in Fig. 5 where the VOI (0.125 ml) has been focused on the muscle tissue of a human forearm. The T_1 determination of muscle water protons yields 1.20 ± 0.05 s (2.35 T). The measuring time of the entire experiment was 30 s.

CONCLUDING REMARKS

A new method for image-controlled localized proton spectroscopy using stimulated echoes has been presented. Its initial steps include image selection and characterization, localized proton spectroscopy, and localized determinations of T_1 and T_2 relaxation times. Basically, the method is a single-step procedure with superior spatial selectivity insensitive to flip angle misadjustments and not dependent on add/subtract algorithms. The sequence allows reshimming of the homogeneity over a selected volume as well as computer-controlled adjustments of location, size, and form of the VOI. Since only three slice-selective 90° rf pulses are employed, the sequence is directly applicable to any small-bore and whole-body NMR system with a very low rf load on animals or patients.

Although the inherent T_1 and T_2 relaxation time weightings of the method become a severe drawback for the investigation of components with short relaxation times,

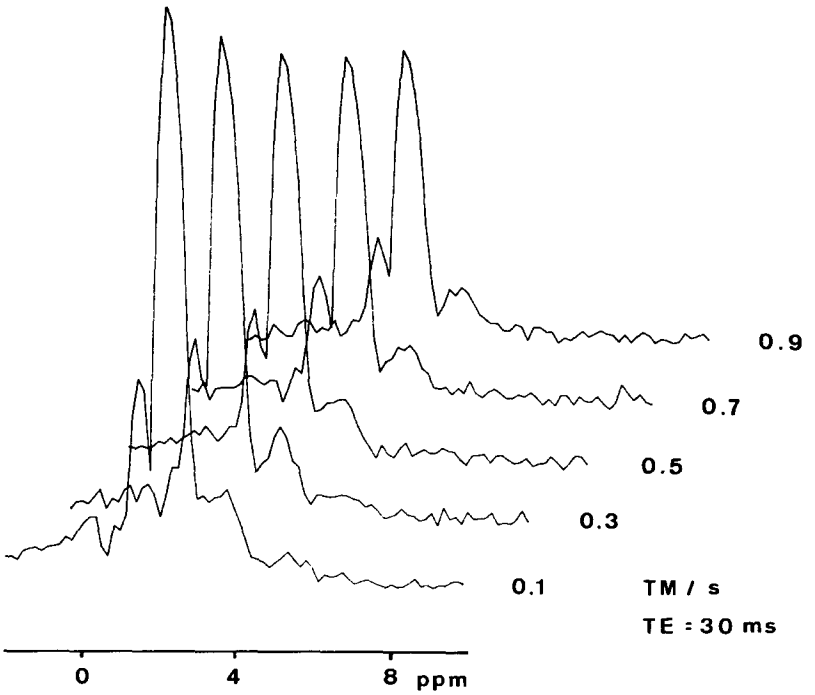

FIG. 5. 100 MHz ^{1}H NMR STEAM spectra (2 acquisitions, 3 s repetition time, magnitude representations) of a selected VOI (5 × 5 × 5 mm corresponding to 0.125 ml) within the muscle tissue of a human forearm. The series of spectra (TE = 30 ms, TM as indicated) describe the spin–lattice relaxation curve yielding T_1 = 1.20 ± 0.05 s.

e.g., ATP using phosphorus spectroscopy, they may be exploited for proton spectroscopy with respect to the suppression of water and/or lipid resonances as well as for eddy current stabilization. Our next steps in metabolic spectroscopy will include further combinations with presaturation and selective spin-echo formation as well as with the adaptation of more complex spectroscopic "editing" techniques.

A limitation in principle of stimulated echo sequences is the signal reduction by a factor of two when compared to a spin echo obtained at the same echo time. Although this does not seem to affect localized determinations of relaxation times for medical purposes, it may contribute to the sensitivity problem encountered for metabolic concentration levels. A possible alternative might be a 90°–180°–180° spin-echo sequence either using improved slice-selective refocusing pulses or compensating dual experiments (*18*).

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