Selective Saturation NMR Imaging

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Abstract: The application of selective saturation (or solvent suppression) techniques in nuclear magnetic resonance (NMR) imaging offers the opportunity to significantly expand the range of NMR studies. Data acquired at 1.44 T are presented using a two-dimensional spin-echo sequence preceded by a selective (saturating) radiofrequency pulse. Individual water or lipid proton resonances were eliminated (>90% reduction in signal intensity) resulting in images of H_2O or $-CH_2-$ distribution with resolution and imaging time equivalent to conventional proton images. Data are also presented demonstrating the feasibility of using selective saturation to image proton metabolites at low concentrations with a three-dimensional chemical shift imaging approach. Lactate was investigated because of its importance in the pathophysiology of ischemic insult. Phantom studies without solvent suppression failed to detect lactate at 80 mM; however, with solvent suppression, lactate at 40 mM was imaged in a reasonable time (approximately 50 min). With the favorable NMR characteristics of the methyl protons of lactate and with improvements in imaging systems, this technique may play an important role in the noninvasive evaluation of tissue ischemia using ^{1}H NMR. **Index Terms:** Nuclear magnetic resonance, techniques—Chemical shift imaging—Nuclear magnetic resonance.

One of the great advantages of nuclear magnetic resonance (NMR) over other imaging modalities is the wealth of information contained within the parameters determining the NMR response of tissue Most NMR imaging studies to date have focused on the parameters of proton density and relaxation times T1 or T2 (1). The NMR signal also contains specific chemical information that has been used for decades by NMR spectroscopists. Recently techniques have been developed to acquire NMR chemical shift data *in vivo* within an imaging context, with the goal of increasing the sensitivity and specificity of NMR imaging. Although primitive by spectroscopic standards, these studies have successfully demonstrated the ability to visualize low and high energy phosphorous compounds (2) and lipid and water containing regions in both normal and pathologic states *in vivo* (3,4).

Over the last several decades NMR spectroscopists have developed a number of sophisticated techniques to extend the versatility and usefulness of NMR studies. This paper will focus on one of these, selective saturation or solvent suppression, and discuss two areas in which NMR imaging can use these techniques. The first is familiar to spectroscopists and allows for imaging of pathophysiologically important moieties such as intracellular lactate using NMR. The second is a new application to increase contrast and flexibility in conventional NMR imaging.

Selective Saturation in Proton Chemical Shift Imaging

Using chemical shift imaging, we have previously demonstrated the ability to obtain NMR spectral data from all pixels within an NMR image of complex phantoms with frequency resolution better than 1 ppm and spatial resolution approaching 1 mm. *In vivo* the water resonance dominates in most soft tissues, such as brain and muscle, with only aliphatic CH_2 protons from lipids having sufficiently high concentrations to contribute to the measured chemical shift spectra (3,4). However, within biologic tissues many distinct chemical moieties exist at lower concentrations (<50 mM) which have well identified proton resonance spectra. Studies of the brain, for example, have demonstrated via NMR spectroscopy increasing tissue lactate concentra-
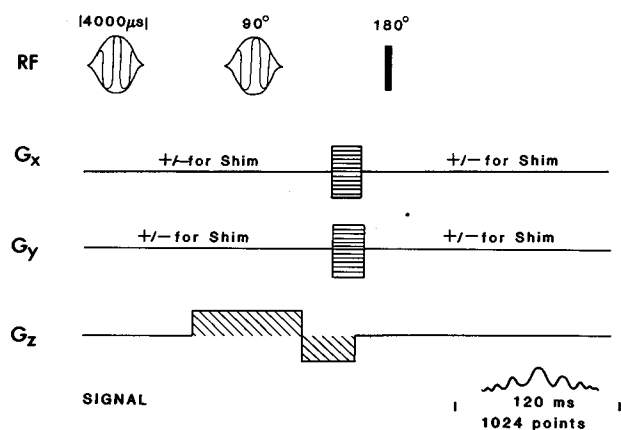
FIG. 1. Pulse sequence used for selective saturation chemical shift imaging experiments. Both saturating and plane selection pulses are gaussian in profile. Repetition time is variable, and echo time is fixed at 136 ms. Slight gradients G_x and G_y are used to perform B_0 shimming for first-order variations. Data acquisition time is approximately 120 ms.

tion with hypoxic stress (5). The key to performing these and previous *in vitro* studies is the need to suppress the overwhelming water signal to overcome dynamic range and digitization problems. Selective saturation suppresses the magnetization of the unwanted water protons so that it produces no signal. A number of techniques, using both soft and hard pulse methods, have been developed to accomplish this in the NMR spectrometer (6–8). We discuss below the application of a simple selective saturation method within an imaging context, which allows the visualization of lactate concentrations in the pathophysiologic range in phantoms.

Methods

All studies reported here were acquired using a prototype 8 cm bore Technicare NMR imaging system operating at 61.4 MHz (1.4 T). Our imaging method modified a three-dimensional chemical shift imaging technique (9), whereby two dimensions are spatially determined via phase encoding, and the third dimension represents chemical shift data. Selective saturation is achieved by the application of a narrow-banded 90° selective pulse applied in the absence of any magnetic field gradients. Following this preparatory pulse, plane selection and refocusing pulses are applied in a manner discussed previously (3), allowing for spin-echo (SE) data acquisition. The echo delay time (TE) was set at 136 ms to allow for more complete refocusing of the methyl protons of lactate in the face of their homonuclear

spin coupling. Spoiler gradients are used to dephase any residual transverse magnetization from the saturating pulse prior to plane selection. One thousand twenty four data points are collected and sampled every 120 μs. The pulse sequence is schematically shown in Fig. 1.

To demonstrate the feasibility of applying this technique to form images of dilute chemical substrates, a series of imaging experiments on aqueous lactate phantoms were performed using this sequence. Lactate was chosen for its importance as a metabolite of tissue under anoxic/ischemic stress. In these experiments spatial resolution was 2.6 mm² (32 × 32 pixels across our 8 cm bore), with a slice thickness of 6 mm (full width at half maximum). Imaging time was 53 min, with eight signal averages per projection and a pulse repetition rate (TR) of 360 ms. Serial dilutions in lactate concentration from 160 to 40 mM were tested, both with and without H_2O saturation. Because of B_0 nonuniformities in the image plane of our magnet, only a single 2 cm diameter phantom could be imaged at a time when using solvent suppression, since the technique requires homogeneity of approximately 2 ppm across the imaged region.

Results

The effect of the saturating pulse is demonstrated in Fig. 2. Four chemical shift spectra, acquired by Fourier transformation of the SE signal generated using the pulse sequence of Fig. 1 are presented.

FIG. 2. Chemical shift spectra of a 6 M aqueous lactate sample. Pulse sequence described in Fig. 1 is used, with phase encoding gradients off. **a** and **d**: The entire spectrum (H_2O peak to the right of the smaller lactate peak) is shown since the saturating pulse frequency (center line) is well offset (high and low) from either peak. By adjusting the saturating frequency to coincide with either the water resonance frequency **(b)** or the lactate frequency **(c)**, these lines can selectively be removed from the resulting spectra.
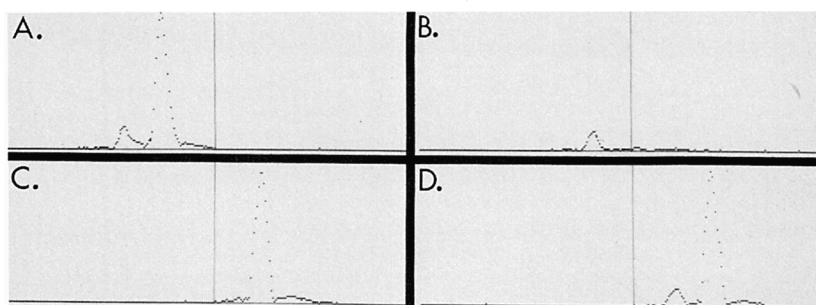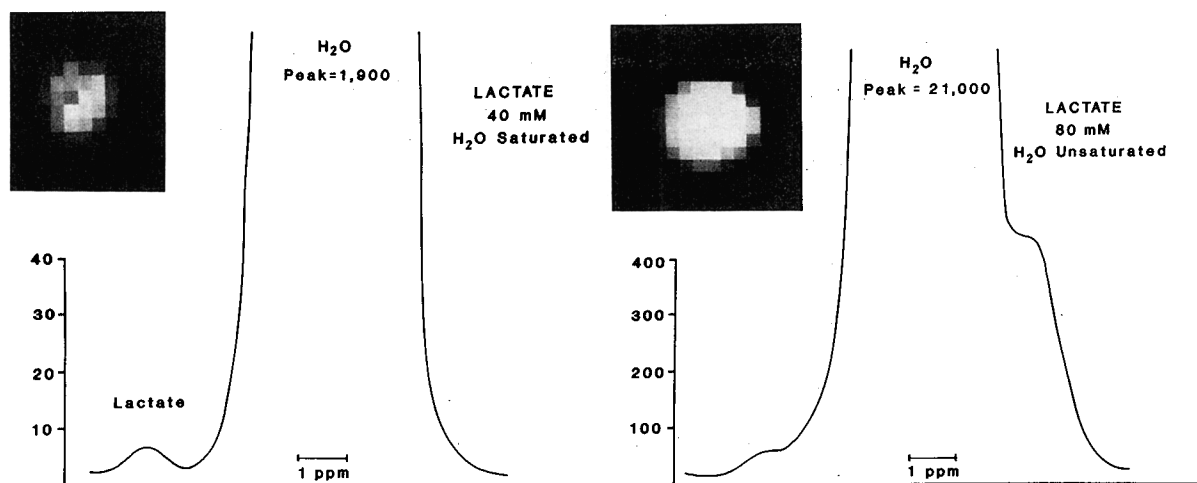
FIG. 3. Total proton (lactate + water) images and chemical shift spectra extracted from a 2 × 2 pixel region centered within 2 cm diameter aqueous lactate phantoms. **Left:** Results from 40 mM lactate with water suppression. Note a clear lactate peak to the left of the central water remnant. **Right:** Results obtained from 80 mM lactate, this time without water suppression. Note the relative water signal is increased (>10 ×), and no clear lactate signal is visible.

(Spectra displayed by our imaging system have frequency increasing from left to right, the opposite of the usual spectroscopic convention.) These spectra can be generated and displayed prior to performing an imaging experiment. Two signal averages were acquired, and the pulse TR was set to 1 s. The sample consisted of a single 2 cm diameter tube filled with a 6 M aqueous lactate solution. Note that, with phase encoding gradients off, the chemical shift spectra of this high concentration lactate and water phantom clearly demonstrate the two distinct chemical moieties (Fig. 2a and d). By changing the frequency of the saturating pulse to correspond with one or the other spectral peak, it is possible to remove either the water or the lactate peak from the acquired spectrum (Fig. 2b and c). When set at the water resonance (Fig. 2b), more than 90% of the signal from water protons is eliminated (saturated). Similar results are obtained from actual imaging experiments on the more dilute lactate phantoms.

The results of our imaging experiments showed that with serial lactate dilutions down to and including 40 mM, a clear image of the methyl protons of lactate was visible when the water signal was suppressed (Fig. 3a). Without suppression, the lactate signal was not clearly visualized at or below 80 mM (Fig. 3b). These results point to the potential of imaging physiologic metabolites with proton NMR.

Selective Saturation in Conventional NMR Imaging

The selective saturation technique just discussed has application in conventional NMR imaging as well. The most important is enhancing contrast in NMR studies. In particular, although NMR imaging does offer a high degree of soft tissue contrast via differences in relaxation times, chemical shift information is usually neglected in conventional studies. Chemical shift contrast can be either intrinsic (e.g., tissue lipid versus water) or can be obtained through the use of an extrinsic chemical shift contrast agent (mineral oil in the bowel is a simple example). To increase the overall flexibility of NMR imaging, solvent suppression techniques can be applied to enhance both intrinsic and extrinsic chemical shift contrast. Significantly, this can be done with otherwise conventional NMR imaging techniques, bypassing the need for slower (multiaxis phase encoded) chemical shift techniques in some circumstances.

Methods

Using the 1.44 T small bore system, selective saturation techniques were applied in conjunction with two-dimensional (2D) SE single slice NMR imaging. In this imaging protocol the frequency selective (saturating) pulse is applied just before performing a conventional 2D imaging experiment. As before, saturation is via a 90° narrow-banded pulse applied in the absence of field gradients (Fig. 4). The TE for this sequence is 30 ms, with 512 points acquired with a sampling interval of 30 μs. These correspond to values used in our routine 2D imaging pulse sequences. The x axis of this scan is frequency encoded, whereas the y axis spatial information is derived from phase encoding.

Results

The use of selective saturation to enhance intrinsic chemical shift contrast was tested on a
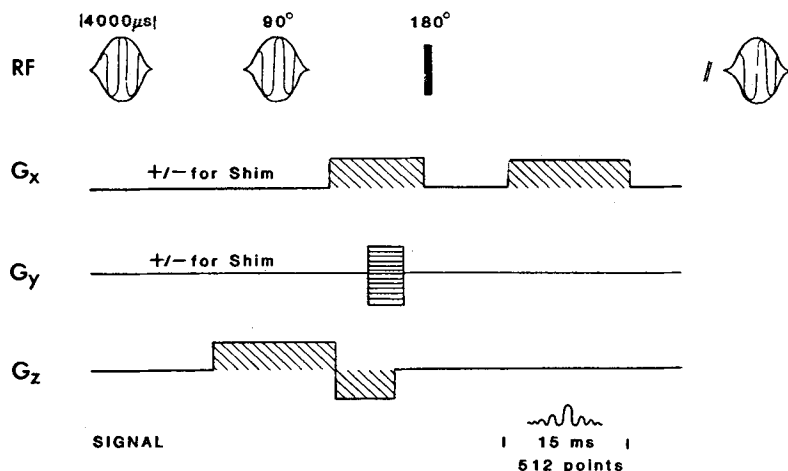
FIG. 4. Pulse sequence used for selective saturation in conjunction with conventional two-dimensional Fourier transform imaging. Repetition time can be varied, and echo time is held fixed at 30 ms. Note the x axis is frequency encoded, whereas the y axis is phase encoded. Total data acquisition time is approximately 15 ms.

simple *in vivo* model, the human forearm. Previous chemical shift studies have demonstrated the presence of two chemical moieties in high abundance, lipid and water, within cross sections through the forearm (3). By selectively saturating the protons of one of the two constituents, it becomes possible to produce an image that reflects only lipid or water proton distribution. Relaxation weighting within this distribution is unaffected. The results are demonstrated in Fig. 5. The pulse TR was 750 ms, and image time with two signal averages was 3 min. The 128 phase encoded steps were applied along y, leading to spatial resolution of <1 mm. With image times no greater than conventional NMR methods, the chemical shift contrast within diverse tissues is thus easily demonstrated.

Discussion

Two distinct applications of a single NMR technique, selective saturation, have been introduced. In using this technique to visualize dilute chemical moieties such as lactate, proton NMR imaging will take the significant step toward providing physiologic as well as anatomic information. The role of lactate in the etiology of irreversible central nervous system damage during ischemic insult makes imaging of this metabolite particularly important (5,10). The association between lactate concentrations approaching 25 mM and both a decrease in high energy phosphates (11) and cerebral edema and necrosis (12) emphasize the clinical impact anatomic mapping of this compound may have. Lactate levels are also known to be significantly elevated in other ischemic tissues, in particular ischemic myocardium (13).

Although other nuclei, such as phosphorus (^{31}P), can provide similar information on cellular energy metabolism (14), the ability to use proton NMR with water suppression offers distinct advantages.

These include the intrinsic greater sensitivity of the hydrogen versus phosphorous nuclei (>6× for constant B_0) and more favorable relaxation times for image data acquisition. The protons in lactate, for example, have a longer T2 (>150 ms versus <20 ms for α and β ATP) and shorter T1 (~500 ms versus >1 s) than high energy phosphates, allowing for more efficient collection of imaging data. Imaging times can thus be substantially less with better spatial resolution, ultimately making these examinations practical with field strengths of 1.5 T and higher. From our initial experience with lactate, a goal of <20 mM sensitivity with imaging times of 30 min should be attainable with the new generation of NMR imagers under construction. This should be sufficient to study *in vivo* the response of both brain and muscle to ischemia and infarction.

Using selective saturation with conventional imaging methods also opens new possibilities. Although probably not applicable for imaging very dilute compounds such as lactate, the ability to form distinct lipid and water images with resolution and in times completely comparable with total proton images should find application in quickly evaluating the fat content of mass lesions and fatty livers (4). Also, the high degree of contrast afforded by using chemical shift differences can rival that found in contrast enhanced X-ray studies. This offers the opportunity to develop NMR contrast media, for example, intraluminal bowel agents, that act either as chemical shift reagents to shift the resonance frequency of water or that have intrinsic chemical peaks offset from those of surrounding tissue. These can then be used in planar or projective studies as with radiographic agents. We are currently exploring these possibilities.

These experiments impose stringent instrumental requirements. Most important (and costly) is the need for high magnetic field homogeneity, where approximately 2 ppm over the whole imaged region will be necessary with optimum technique. This de-
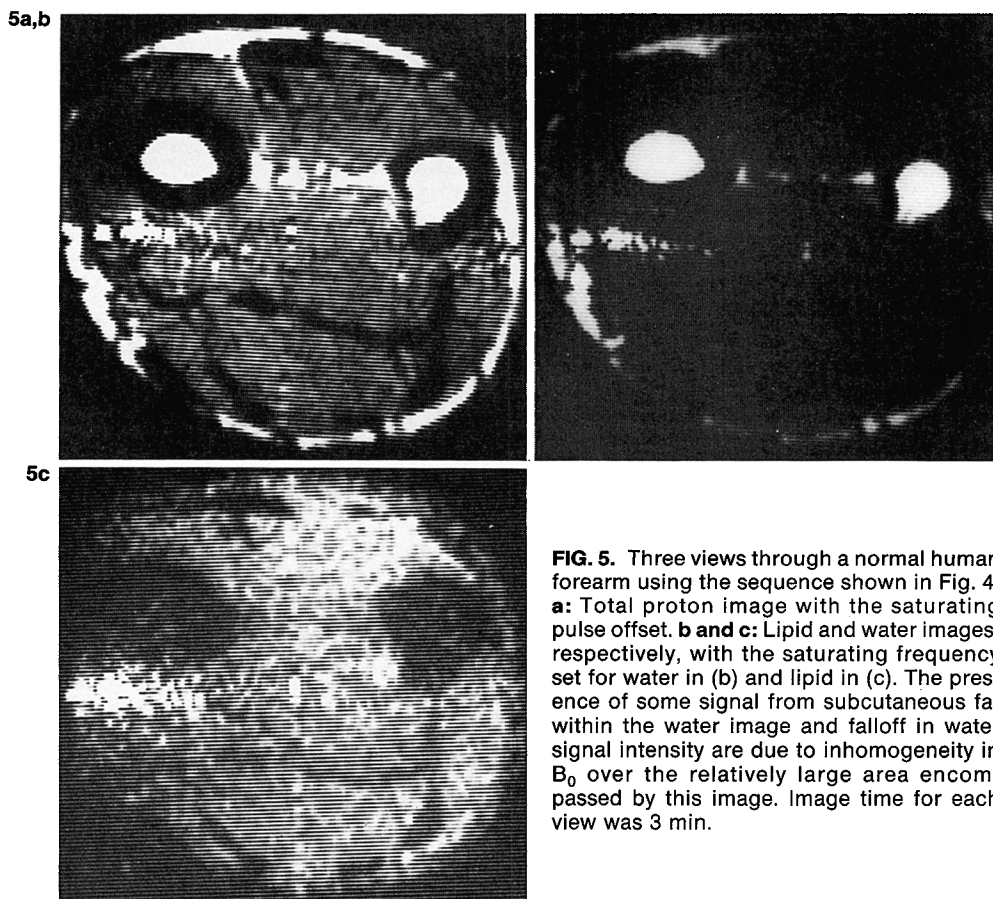
5a,b

5c

FIG. 5. Three views through a normal human forearm using the sequence shown in Fig. 4. **a:** Total proton image with the saturating pulse offset. **b and c:** Lipid and water images, respectively, with the saturating frequency set for water in (b) and lipid in (c). The presence of some signal from subcutaneous fat within the water image and falloff in water signal intensity are due to inhomogeneity in B_0 over the relatively large area encompassed by this image. Image time for each view was 3 min.

gree of homogeneity is required so that suppression of the water signal in one region does not saturate the lactate protons from another area. Because the natural line widths of both water and the methyl protons of lactate are quite narrow, homogeneity much greater than this is unnecessary. Unambiguous identification of the chemical shift can be made in the face of any B_0 inhomogeneity by reference to the residual signal from water protons remaining due to imperfect presaturation. Signal-to-noise ratio and threshold sensitivity will also be influenced by B_0 heterogeneities, although here the important quantity will be homogeneity over each voxel, which should be much better than that over the whole volume. Two parts per million homogeneity is certainly greater than that found in most imagers currently in use; however, newly designed machines with spectroscopic capabilities should meet this requirement. In addition, results in our laboratory using a cat head show that the effects of diamagnetic susceptibility variation *in vivo* are not prohibitive. The presence of significant ferromagnetic implants may, however, distort the field quite significantly.

A number of pitfalls do exist. In efforts to image lactate, an important consideration will be the pres-

ence of free lipid, with its dominant chemical shift frequency closely juxtaposed to the methyl protons of lactate. At least in the brain, the lack of significant mobile lipid should lessen this concern (3,5). Signal influx by regions of surrounding subcutaneous fat can also be lessened by applying selective excitation schemes used routinely today to perform magnification or "zoom" imaging. Although fat and water imaging produce no new obstacle besides B_0 homogeneity, efforts to make wider use of chemical shift contrast depend both on the ability to develop safe and effective contrast agents and on efforts to increase image resolution and speed. The use of agents with high lipid content, such as mineral oil, may find some important applications. Contrast media with chemical shifts distinct from either lipid or water will be more generally useful, because of the large amount of lipid (fat) present in and around many normal tissues.

Despite these obstacles, it seems likely that NMR spectroscopic tools will become increasingly important for imaging as well. The application of basic physical principles, so characteristic of advances in magnetic resonance imaging to date, should continue to expand the role of NMR within the imaging community.

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