

1H image-guided localized 31P MR spectroscopy of the human liver

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INTRODUCTION

Phosphorous-31 MR spectroscopy has been used to study liver phosphate metabolism. Up to now, the vast majority of measurements has been performed on animal preparations, either on isolated subcellular organelles (1-3), on perfused rat or mouse livers (4-16), or in-situ on the liver of the living rat or rabbit (17-24).

The availability of high field whole body imagers, and the progress made in the acquisition of localized MR spectra (25), has recently made it possible to measure 31P MR spectra of volumes of interest (VOI) located within the human liver (26-29).

31P MR spectra of a particular tissue provide useful information about the energy state of that tissue. Spectra obtained in resting conditions may vary for one particular tissue type, however (30). These variations may be due to biological variability, but also may arise because of differences in the experimental protocol applied, or because of magnetic field inhomogeneity.

31P MR spectroscopy becomes much more informative when applied to observe temporal changes which may be induced by some metabolic perturbation. This approach has been used in studies of muscle metabolism 31P MR spectroscopy. The clinical protocols established so far all rely upon the observation of temporal changes induced by exercise aerobic or ischemic conditions (31).

It has recently been suggested that a similar approach can be followed for the investigation of human liver metabolism (27). It has been demonstrated that I.V. fructose injections (250 mg/Kg body weight) lead to changes of the high energy phosphates in the human liver that can be monitored by 31P MR spectroscopy, with adequate time resolution. These results raised the hope that this type of measurement might provide the basis for clinical tests of liver function.

The clinical potential of the fructose load test will critically depend upon the ease and speed with which localized 31P MR spectra of the human liver can be obtained. The first 31P MR measurements of fructose metabolism in the human liver (27) were performed by means of

Topical Magnetic Resonance (32). With this technique the regions of interest are fixed, and centered at the isocenter of the magnet. This requires positioning of the patient with respect to the isocenter, which is undesirable in a routine clinical examination. Furthermore, the acquired spectrum is contaminated by a broad signal arising from the boundaries of the volume of interest, so that deconvolution techniques (33) have to be applied.

We have recently implemented a 1H image-localized 31P MR spectroscopy technique, that has proved to be applicable, in a clinical setting, to 31P MR spectroscopy examinations of the human brain (34). An essential feature of the method is the possibility to identify and delineate the volumes of interest for the 31P MR spectroscopy measurements on the basis of a set of 1H images acquired immediately before, in the same examination session. Imaging was performed with the standard 1H head coil, whereas the 31P MR spectroscopy measurements were performed with a small 31P MR head coil, which was inserted into the 1H imaging coil.

In the present study we have followed an approach to liver 31P MR spectroscopy which is similar to the procedure applied to brain. We have implemented, and tested on the liver of volunteers, a 1H image-localized 31P MR spectroscopy technique, that satisfies the requirements for clinical application of the fructose load test.

METHODS

The technique has been implemented and applied on a Philips 1.5 Tesla whole body imager installed at Erasme Hospital. A 15 cm diameter circular surface coil tuned at the 31P resonance frequency (25.9 MHz) was placed on the patient support, in a slightly tilted position. Volunteers were positioned prone with the liver centered over the coil. The regular body imaging coil was used for 1H imaging. Both imaging and spectroscopy coils remained in place during the complete examination session, so that switching times between imaging and spectroscopy measurements could be minimized. Volumes of interest, centered within the liver, were identified on a set of 1H images and chosen as large as possible (up to 1 liter), so as to optimize signal-to-noise of the liver spectra and to improve the time resolution of the serial 31P MR spectroscopy measurements. Following 1H imaging, the magnetic field homogeneity was optimized over the sensitive volume, by monitoring the water 1H MR signal observed with the 31P surface coil. The shimming procedure was performed interactively, and required no more than a few minutes. After switching the instrument from the 1H to the 31P MR frequency, the pulse power for the 31P MR measurements was optimized using the signal collected from a small sample of 2-carboxyethylphosphonic acid which was centered just below the coil plane. This substance generates a signal in the 31P MR spectrum, outside the spectral range spanned by biological tissues. Finally, the localized liver 31P MR spectra were acquired, with adequate signal-to-noise, in 1.6 minutes of total acquisition time. The averaged results were processed by Lorentz-Gauss filtering, Fourier transformation, and linear phase correction.

The volumes of interest were defined by means of a pulse sequence derived from ISIS (35-36). With this sequence, volume selection is achieved by addition and subtraction of 8 free induction decays (FID) obtained in response to identical non-selective read pulses. The read pulses are preceded by 3 orthogonal slice selective inversion pulses which are cycled through all 8 possible on/off combinations. An appropriate linear combination of the FIDs then provides a localized signal originating from a VOI at the intersection of the slices as defined by the selective inversion pulses.

Optimal performance of the ISIS sequence requires perfect spin inversion. We therefore applied frequency-modulated inversion pulses of the hyperbolic secant type (37-42), rather than the more familiar amplitude-modulated inversion pulses. With the former type of pulses, perfect spin-inversion is achieved provided that the pulse power exceeds a certain threshold level. The Bloch equations were solved in order to determine this threshold. With a pulse area corresponding to a 500 degree flip angle, perfect spin inversion was achieved. Hence, provided that enough RF power is delivered to the surface coil, perfect spin inversion is achieved over the entire sensitive volume of the coil. In order to shorten the selection time, the inversion pulses were truncated to 60% of their original length (43). Detrimental effects due to this truncation were reduced by multiplying the pulse envelope by a Gauss function. The bandwidth of the inversion pulses was 3200 Hz.

An additional difficulty arises when applying ISIS with a surface coil, rather than with a homogeneous B1 coil, as was the case with the localized 31P MR spectroscopy measurements on human brain (34). Residual longitudinal magnetization is left after the application of block-shaped read pulses, as a result of intrinsic RF inhomogeneity. Hence, imperfect suppression of signals from regions outside the VOI will occur, unless each measurement is performed on the spin system in complete thermal equilibrium. The long longitudinal relaxation times of some of the 31P metabolites in human muscle (T1 of PCr about 7 seconds) (44) make the acquisition of the 31P MR spectra under these conditions very time consuming. In addition to imperfections in localization, the intrinsic pulse angle inhomogeneity precludes optimal excitation of the entire VOI, leading to a reduction in signal-to-noise. Finally, it has been recognized that the B1 inhomogeneity of the surface coil also leads to spectral distortion when ISIS is applied with standard block-shaped read pulses (29).

We have overcome the problems due to inhomogeneity of the read pulse angle by implementing an adiabatic rapid half passage read pulse (45), rather than a standard block-shaped pulse. As a result, we achieved uniform excitation (with a 90 degree pulse angle) over a bandwidth of 1000 Hz and over variations in B1 intensity up to a factor of 4, as was demonstrated by phantom experiments.

RESULTS

Figure 1a displays a sagittal 1H image of the liver of a normal volunteer. The image has been selected among a set of sagittally and

axially oriented images acquired immediately before the measurement of the 31P MR spectrum displayed in Figure 1b. This localized image was obtained in a short total imaging time (1.8 min), using a rapid spin echo multiple slice sequence (TR = 600 msec, TE = 20 msec), and an acquisition matrix of 128 points in the measurement and phase encoding directions (no data filtering was applied in the measurement direction during subsequent image reconstruction on a 256 points matrix). A further reduction of 30% in scan time was achieved by partial matrix acquisition (only the profiles corresponding to the lowest spatial frequencies were measured). The volume of the region of interest indicated in the image was 1.1 liter.

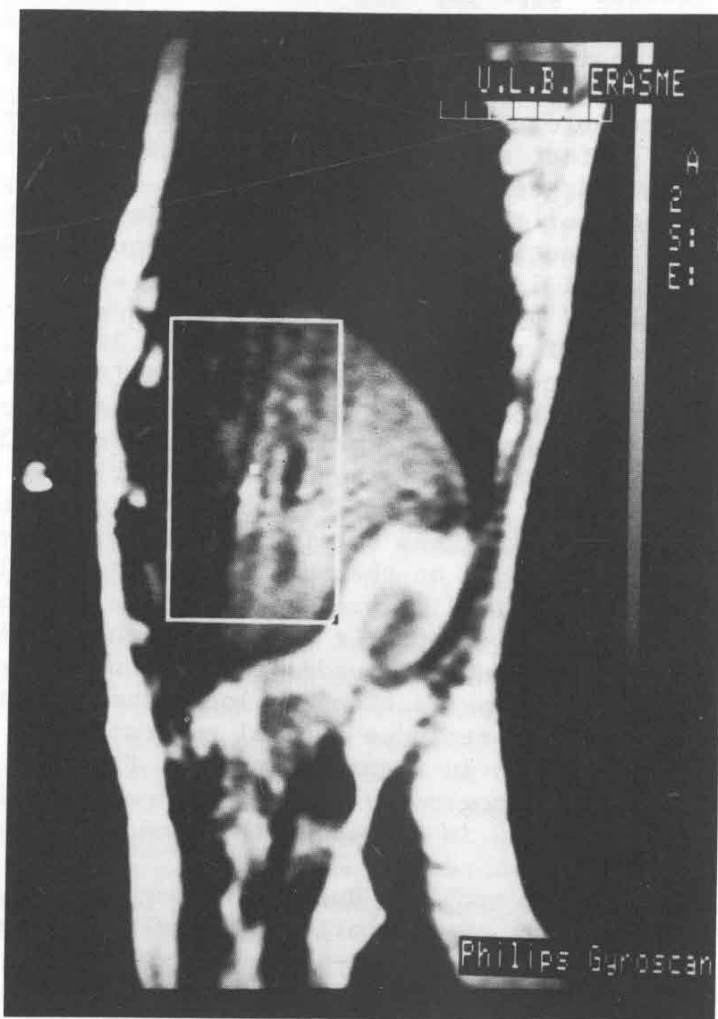


Fig. 1a. Human liver 1H image. Volume of interest (1100 cc) from which the 31P MR spectrum of b. has been obtained.

The high resolution 31P MR spectrum displayed in Figure 1b was acquired from the VOI shown. It represents a typical result for the normal, unperturbated, human liver. It has been obtained by addition of

20 serially measured spectra, acquired under the experimental conditions used during the fructose load measurement reported below. In order to obtain optimal signal-to-noise, we choose as large as possible a VOI centered within the liver. A small contamination by surrounding muscle tissue usually results. This is also the case with the spectrum displayed here, as may be concluded from the small PCr line centered at 0 ppm. The doublets and triplet of the gamma-, alpha-, and beta-ATP lines, due to spin-spin couplings, are well resolved. In addition, the phosphomonoester (PME) and sugar phosphate (SP) line as well as the phosphodiester (PDE) line exhibit some fine structure, presumably due to contributions from a.o. phosphorylcholine and sn-glycerol-3-phosphate in the PME region, and glyceryl-3-phosphorylcholine and glyceryl-3-phosphorylethanolamine in the PDE region (12). Other compounds may contribute as well.

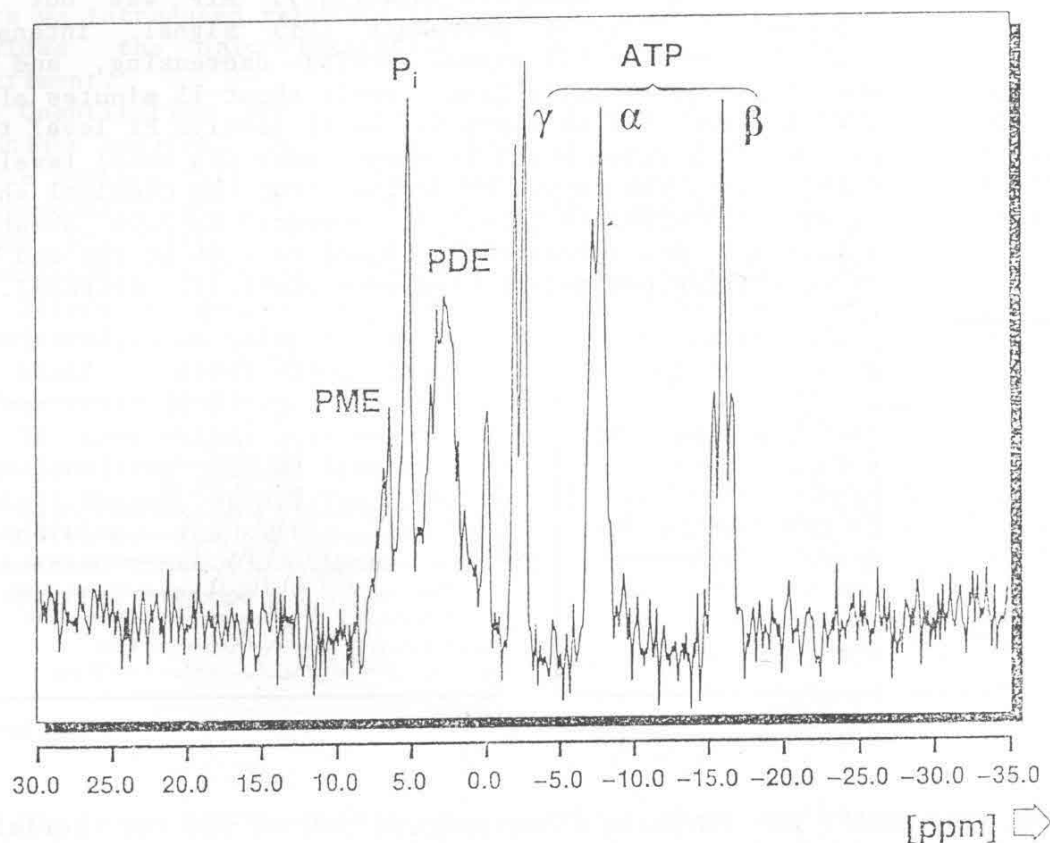


Fig. 1b. Localized ^{31}P MR spectrum from the VOI displayed in a. For details on localization technique: see text. Acquisition parameters: Total number of measurements 1280, repetition time 1.5 seconds, sample frequency 3000 Hz, 1024 sample points. Data processing: convolution difference (exponential line broadening factor 500 Hz, scale factor 1), gaussian multiplication (6 Hz line broadening factor), exponential multiplication (5 Hz line narrowing factor), zero filling (4K), Fourier transform, linear phase correction.

Figure 2 displays the temporal changes induced in the ^3P MR liver spectrum after fructose was injected intravenously (250 mg/Kg body weight) to a second volunteer. The sequential ^3P MR spectra shown span an initial time interval of 19 minutes out of a total measurement time of 80 minutes. The fructose was injected during measurement of the second spectrum. Total measurement time per spectrum is 1.6 minutes. The volume of the region of interest was 750 cc. The temporal changes observed in the ^3P MR spectra agree qualitatively with what has been reported in the literature (6, 27). Detailed analysis of our observations on different volunteers will be published in a forthcoming paper. An early increase is observed in the intensity related to the sugar phosphates (mainly fructose-1-phosphate (F1P)), which return to their basal level 15 minutes after injection. ATP level decreases concomitantly with the increase in SP level, and slowly recovers towards its basal level when the SP level starts decreasing. At the end of the experiment (80 minutes after fructose injection), ATP was not yet completely recovered. Inorganic phosphate (P_i) signal intensity increases rapidly as soon as F1P signal starts decreasing, and it reaches a maximum (about 300% of its basal level) about 15 minutes after injection (at the time when F1P recovers its basal level). P_i level then slowly decreases towards a value which is about twice its basal level at 80 minutes post injection. The tissue pH derived from the chemical shift of the P_i line was 7.38 pre-injection. It decreased to 7.06 about 6 minutes post-injection, and subsequently raised to 7.66 at the end of the measurement (titration parameters used were $\text{pK}_a=6.77$, $\Delta\text{a}=3.29$, $\Delta\text{b}=5.68$).

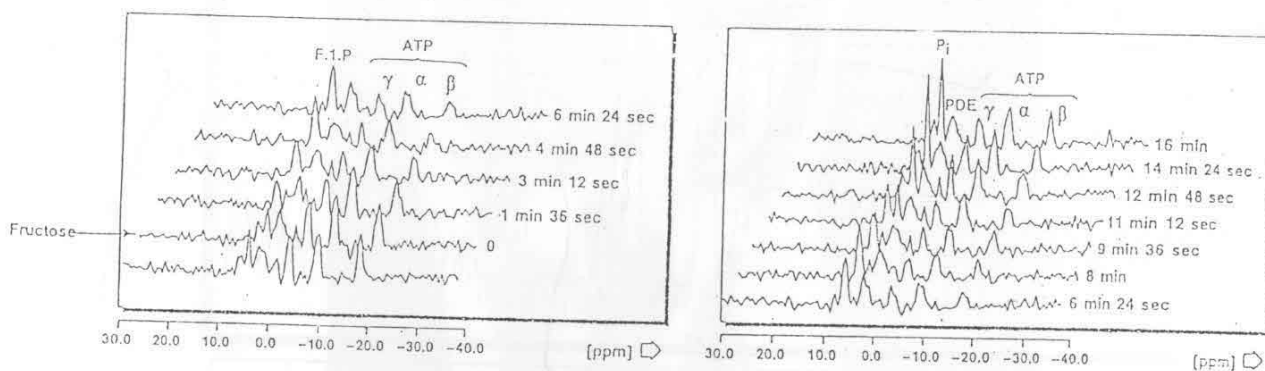


Fig. 2. Localized ^3P MR human liver spectra (VOI of 750 cc) serially measured after intravenous fructose injection (250 mg/Kg body weight). Fructose was injected during acquisition of second spectrum. Localization technique: see text. Acquisition parameters: 64 measurements per spectrum, repetition time 1.5 seconds, sample frequency 3000 Hz, 1024 samples. Data processing: convolution difference (exponential line broadening factor 500 Hz, scale factor 1), gaussian multiplication (20 Hz line broadening factor), exponential multiplication (18 Hz line narrowing factor), zero filling (4K), Fourier transform, linear phase correction.

DISCUSSION

The ^3P MR localization technique implemented has the advantage, that it fully depends upon B_0 selection. Therefore, the VOI can be centered and adjusted arbitrarily, on the basis of ^1H images acquired during the same examination, without the need of repositioning or replacing the surface coil. Hence, routine clinical applications of the fructose load or any other metabolic perturbation experiment may be undertaken. The difficulties related to the application of spectral localization by B_0 selection with a surface coil, have been overcome by the combined use of adiabatic inversion and read pulses. A further advantage of the B_0 selection is related to the reduced number of measurements required for localization, for instance in comparison with the minimum number required with the combined B_0/B_1 method (IDESSS) which we introduced recently (29). Hence, signal-to-noise of the spectra provides the only limitation to the temporal resolution of the experiment.

Quantitation of the spectral information is possible with the technique applied. It requires that the VOI be calibrated with respect to the surface coil. This can be done by placing a large container with a standard solution on the surface coil, and then select the identical volume of interest with respect to the coil as in the patient examination. By comparing the signal intensities from both the in-vivo and reference sample measurements, the in vivo spectrum can be quantitated. When using a coil with a homogeneous RF field (such as used for brain studies) (34), calibration is much less critical than with surface coils (46).

In conclusion, our results demonstrate that excellent quality ^1H image-localized ^3P MR spectra of the human liver can be obtained on a clinical imager, at 1.5 Tesla, with a time resolution of about 1 minute. In addition, the liver ^3P MR spectra accumulated during longer examination times (30 minutes) exhibit fine structure within the PME and PDE spectral regions.

SUMMARY

^1H image-localized ^3P MR spectra of the human liver have been obtained on a Gyroscan 1.5 Tesla clinical imager installed at Erasme Hospital. The volumes of interest (up to 1000 cc) for the ^3P MR spectroscopy measurements were identified on the basis of ^1H images acquired immediately before the spectroscopic examinations. The ^3P MR spectra were acquired using a surface coil for RF excitation and detection. Localized ^3P MR spectra were measured using a technique derived from ISIS, whereby only frequency modulated pulses are applied. Signal-to-noise of the ^3P MR liver spectra allows monitoring of metabolic perturbations induced by fructose loading with a time resolution of about 1 minute.

KEY WORDS: In-vivo, Human liver, Phosphorous, Localized MR spectroscopy, Image-guided.

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