We have developed a method that can measure high-energy phosphate metabolite concentrations in humans with 1D resolved surface-coil NMR spectroscopy. The metabolites are measured by phosphorus \( ^{31}P \) NMR spectroscopy, and the tissue water proton \( ^{1}H \) resonance from the same volume serves as an internal concentration reference. The method requires only the additional acquisition of a \( ^{1}H \) data set, and a simple calibration, performed separately, to determine the ratio of the signal per proton to the signal per phosphorus nucleus. The quantification method is particularly useful for human cardiac spectroscopy, where it eliminates image-based tissue volumetry and the corrections for signal sensitivity and phase nonuniformity necessary in prior approaches.

Corrections are introduced to account for blood and fat contributions to the spectra. The method was validated on phantom studies of varying concentrations and on the human calf muscle. In calf, the adenosine triphosphate (ATP) and phosphocreatine (PCr) concentrations were 5.6 ± 1.6 (mean ± SD) and 26 ± 4 mmol/kg wet wt, respectively. In normal heart, [ATP] was 5.8 ± 1.6 and [PCr] was 10 ± 2 mmol/kg wet wt. These values are in excellent agreement with prior NMR studies and biopsy data. The protocol is easily accommodated within existing 1D cardiac patient protocols, and the same approach is advantageous for eliminating tissue volumetry and sensitivity corrections when measuring concentrations by 2D and 3D resolved spectroscopy.

**Key words:** heart; metabolite; quantification; phosphorus.

**INTRODUCTION**

Phosphorus \( ^{31}P \) NMR spectroscopy is unique in its ability to provide nondestructive, noninvasive measures of tissue high-energy phosphates, including those of the heart (1). The relative amounts of cardiac high-energy phosphates are measured by the ratio of phosphocreatine (PCr) to adenosine triphosphate (ATP) resonances, which are altered by common pathological conditions including transient ischemia (2, 3) and congestive heart failure (4, 5). The absolute high-energy phosphate concentrations are technically more difficult to measure, but may provide new insights into heart disease.

For example, in human myocardial infarction, 1D spatially resolved \( ^{31}P \) NMR often shows no appreciable difference in PCr:ATP ratio from that of normal myocardium (5–8). Because dead myocytes can contribute no metabolite signal to the observed spectrum, the hypothesis is that the observed PCr and ATP signal derives from surviving myocytes surrounding, or interspersed with, the infarcted ones (6). The surviving myocytes may exhibit high-energy phosphate metabolites in essentially normal proportions or in proportions altered by heart failure or other dysfunction (6, 9). In this picture, the mere presence of metabolite in a region of tissue is indicative of living or viable cells. Cell loss through infarction will reduce the metabolite concentration, especially ATP, when it is measured as a regional average (9).

Evidence for reduced metabolite levels in human myocardial infarction is provided by a \( ^{31}P \) NMR study of patients showing significant reductions in 1D-resolved myocardial PCr and ATP signals that are normalized by an external reference signal and by the left ventricular (LV) weight estimated by approximating the heart by two spherical surfaces (7). This work has been extended recently by 2D-localized surface coil spectroscopy studies showing significant reductions in the concentrations of PCr and ATP in patients with myocardial infarction (10). In addition, biochemical assays of biopsies from open-heart surgery suggest reduced PCr concentrations in nonscar tissue in patients with LV hypertrophy and in coronary artery disease (11).

Absolute human cardiac metabolite concentrations have been measured by 3D-resolved spectra and an external concentration reference, with appropriate corrections for nonuniformity in the excitation field and the detection coil’s sensitivity, relaxation times, and the volume of tissue present in the volume element (voxel) being assayed (12). Accurate tissue volumetry with NMR imaging (MRI) is, however, difficult because of the curvature and complexity of cardiac anatomy and regional wall thinning associated with myocardial infarction, especially given the relatively large voxels that are essential for providing adequate \( ^{31}P \) spectral signal-to-noise ratios in the heart. For example, with \( 20 \text{ mm} \times 20 \text{ mm} \times 50 \text{ mm} \) 3D resolution, voxels are typically only about half-filled with myocardium (12). In addition, MRI volumetry does not account for nonuniformity in the \( ^{31}P \) coil sensitivity and phase variations in the signal from within the voxel. Moreover, with the sheer number of corrections and measurements that must be made and applied to derive a metabolite concentration, there is ample opportunity for large systematic and random errors to arise in the final estimates (13).

To eliminate some of the correction factors and potential errors in volumetry and to expedite the protocol for cardiac metabolite concentration measurements, we have devised a method of measuring metabolite concentrations from 1D-resolved cardiac spectra that incorporates...
the effects of heterogeneity in NMR sensitivity across the voxel. The method, in fact, obviates the need for image-based tissue volumetry. To a conventional 1D surface coil, $^{31}$P protocol for patient heart studies, the method requires only an additional $^1$H 1D acquisition, and is therefore easily incorporated into these widely successful protocols (1–9, 14).

**THEORY**

An ideal solution to the problem of measuring cardiac metabolite concentrations from NMR spectra would be to use an independent, disease-invariant, marker resonance of known concentration in myocardium as an internal reference. This would eliminate the need for MRI or other image-based tissue volumetry and automatically compensate for nonuniformity in phase and sensitivity across the voxel, to the extent that the reference and the metabolite are distributed the same. Such an endogenous homonuclear marker doesn't currently exist for in vivo $^{31}$P studies. However, the tissue water $^1$H resonance has been used as a concentration reference for deriving metabolite concentrations from unlocalized surface coil $^{31}$P spectroscopy studies (15, 16), and for measuring $^{31}$P metabolite concentrations in 3D-resolved voxels completely filled with brain tissue (17). Our new method uses the water resonance from a 1D-resolved $^1$H data set acquired from the same location(s) and with the same spatial resolution characteristics as the $^{31}$P data set, as a concentration reference. In applying the technique to the measurement of human cardiac metabolite concentrations, we introduce corrections to account for fat and blood contributions to the water reference. Because of the high signal-to-noise ratio of $^1$H in $^{31}$P-sized voxels, the $^1$H spectra can be acquired under fully relaxed conditions in short acquisition times.

When the excitation and detection fields for the $^{31}$P and $^1$H experiments have the same spatial dependence, the concentration of a metabolite, $[P]$, in one slice of a $^{31}$P data set is given by:

$$[P] = \frac{S_p [W] C_{PH} \left[ F_p E_p \right]}{S_w [W]} \left[ F_p E_p \right]$$  \hspace{1cm} [1]

where $S_w$ is the reference $^1$H NMR signal from water in the metabolite-bearing tissue, $S_p$ is the $^{31}$P signal from the same slice in the sample as $S_w$, $[W]$ is the concentration of tissue water protons, $C_{PH}$ is a constant scaling factor accounting for the difference in $^1$H and $^{31}$P NMR sensitivity, as defined previously (17), $F_p$ is the usual spin-lattice relaxation saturation factor for the $^{31}$P metabolite signal (14, 18), and the $E$'s are decay factors that account for any differences between the water and metabolite signal loss through transverse decay or missing data points. The $E$'s are often neglected when acquisition delays are kept short (12). The simpler form of Eq. [1] compared with that given in Ref. 12 results from the use of the internal reference that leads to cancellation of the factors that account for differences in the surface-coil excitation and detection fields at the location of the metabolite and the reference, and those that relate to voxel volume. The equation is similar to that used in a recent brain study using 3D-resolved voxels (17).

It is important to note that the concentration measurements depend on $S_w$ being a good estimator of tissue water. In 1D surface-coil studies of the heart, there are two sources of water signal that do not originate from myocardium but which could potentially contribute to the $^1$H spectra and for which a correction might be considered. The first is pericardial fat, which is very low in high-energy phosphates but contributes some water. When a sizable fat (CH$_2$) resonance is evident in the spectrum, the water signal, $S_w$, can be corrected for fat by subtracting an amount, $L S(CH_2)$, where $S(CH_2)$ is the lipid $^1$H signal, and $L$ is the water content of fat, which is about 15% (19). The second, blood, is more prone to occur when the 1D surface-coil voxels intersect substantial portions of the ventricular chamber. Blood contains no PCr, but a small amount of ATP. The blood water contribution is additive to $S_w$ and will therefore tend to lower tissue concentration estimates. Following the example of “black-blood” cardiac MRI, we first explored the use of a spin-echo sequence with balanced gradient pulses for $^1$H acquisition to substantially eliminate blood contributions to $S_w$. Unfortunately, this had some undesirable consequences: with the spin-echo sequence, $E_w$ is a much stronger factor in Eq. [1] and cannot be avoided, and the echoes are more motion-sensitive and increase the random error in cardiac assays when signal averaging is kept to a minimum to expedite the study protocol.

An alternative approach is to utilize the fact that the presence of blood in the $^{31}$P spectrum is characterized by the resonances of 2,3-diphosphoglycerate (DPG) at 5.4 and 6.3 ppm. DPG has previously been used to correct PCr:ATP ratios for the presence of ATP in blood, based on its known concentration (20, 21). The $^{31}$P DPG signal can be used to correct the water $^1$H signal for blood water contributions by inverting Eq. [1]:

$$S(blood) = \frac{S(DPG) [W_B] C_{PH} \left[ F_{DPG} E_{DPG} \right]}{2 [DPG]} \left[ F_{DPG} E_{DPG} \right]$$  \hspace{1cm} [2]

where $S(blood)$ and $S(DPG)$ are the $^1$H water and total $^{31}$P DPG signals from blood, respectively, $[W_B]$ is the water proton concentration of blood, and the factor of 2 accounts for the two phosphorus nuclei of DPG. For short acquisition delays, and where the moving blood has insufficient time to partially saturate, the bracketed term approaches unity. The correction assumes that blood DPG and blood water are NMR visible to the same extent. If this correction is applied, the myocardial [ATP] estimates should also be corrected for the small contribution of ATP from blood by replacing the ATP signal, $S_P$ in Eq. [1], by:

$$S_P = S(\text{ATP}) - 0.14 S(\text{DPG})$$  \hspace{1cm} [3]

in the usual way (9, 20, 21).

The fat- and blood-corrected water signal to use in Eq. [1] is thus:

$$S_w = S(H_2O) - L S(CH_2) - S(blood),$$  \hspace{1cm} [4]
where \( S(H_2O) \) is the observed water signal. Note also that once the tissue concentration of PCr or ATP are known, the effective fraction of the voxel filled by blood, \( V_B \), can be deduced from the ratio of the metabolite signal to the DPG signal (when this can be reliably quantified) and [DPG]:

\[
V_B = \frac{[P]}{[P] + 2 \cdot S_P [DPG]/S(DPG)} \times 100 \%.
\]

assuming that the signals are fully relaxed.

**EXPERIMENT**

All experiments were done on General Electric Signa 1.5T whole-body MRI systems with a standard 6.5-cm-diameter distributed-capacitance surface receiver coil tuned to \(^{31}\)P. The coil was used for both \(^{31}\)P and \(^1\)H reception, thereby satisfying the condition that the spatial dependence of the sensitivity is the same for both \(^{31}\)P and \(^1\)H NMR spectroscopy, albeit at the expense of non-critical \(^1\)H performance. All \(^1\)H spectra were acquired under fully relaxed conditions. Averaging was varied for \(^{31}\)P studies to accommodate apparent variations in the signal-to-noise ratio with concentration and to minimize acquisition time. All \(^{31}\)P data were acquired under partial saturation conditions, excited by a separate, larger, transmitter coil, producing a uniform flip angle over the sensitive region of the receiver coil (12, 14, 18). Saturation factors \( F_p \) were measured directly from the ratio of partially saturated to fully relaxed unlocalized surface-coil spectra, or were calculated using a calibrated flip angle and best estimates of the metabolite \( T_1 \) values (14, 18). To eliminate flip-angle calibration and \( F_p \) measurements during patient studies, a 1D phase-encoding sequence employing adiabatic BIRP \((B_1\)-independent rotation phase-cycled) pulses at the optimum angle of 34.9° for the heart, was developed (18). The slice thickness was 10 mm throughout. Acquisition delays were 0.5 or 1 ms, so \( E \) corrections were omitted. \( C_pH \) was determined by acquiring 1D \(^1\)H and \(^{31}\)P data sets from 15-liter plastic bags of 0.167 M phosphate solution as a function of depth with 1-cm resolution. The ratio of signals from the same slices was used to calculate \( C_pH \) for two cardiac quantification exams performed during the same session.

mM, and with bottles of varying diameters from 50–135 mm. The reference proton concentration was assumed to be that of water (111 mol/kg). A series of identical-looking bottles containing five different phosphate concentrations were prepared and assayed blindly with respect to the concentration, the numbers being revealed only after assay values were declared. The results are summarized in Table 1. The values agree with the correct values within experimental error. There are no significant systematic differences \((P > 0.1, \text{paired } t \text{ test})\). The average standard deviation (SD) expressed as a percentage of the measurement is about 14%, reflecting predominantly the cumulative effect of random errors in \( S_P, S_H, \) and \( C_pH \). \( C_pH \) values were determined on seven occasions and were observed to vary by about 17\% \((C_pH = 0.0018 \pm 0.0003 \text{ SD, mean } \pm \text{ SD, with the untuned } \text{H} \text{ coil) over the course of several months, indicating that an entirely stable value could not be assumed over an extended period. We used \( C_pH \) values derived from an average ratio of the \(^1\)H and \(^{31}\)P signals from multiple slices in the

| Table 1 Phosphate Concentrations Measured in Test Phantoms |
|-----------------|-----------------|-----|
| True concentration | Measured concentration (mmol/kg wet wt) | n\(^a\) |
| Test phantoms | | |
| 50 | 51.7 ± 4.2 | 6 |
| 50 | 55.4 ± 4.4 | 6 |
| 20 | 22.8 ± 3.9 | 7 |
| 20 | 18.3 ± 2.0 | 5 |
| 20 | 24.2 ± 4.8 | 4 |
| 10 | 12.1 ± 1.8 | 4 |
| 10 | 8.5 ± 1.1 | 3 |
| 7.5 | 8.1 ± 0.6 | 6 |
| 5 | 4.1 ± 0.7 | 2 |
| 5 | 4.6 ± 1.2 | 2 |
| 25 | 22 ± 2.9 | 5 |
| 10 | 11.2 ± 1.6 | 4 |

\(^a\) Values are mean ± SD.

\(^b\) Number of measurements averaged for determination.

\(^c\) Samples coded and blinded for \(^{31}\)P evaluation.

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1. The spatial dependence of the magnetic field of the surface coil is independent of its tuning provided that the lengths of coil conductor are short compared with the wavelength.
15-liter phantom. If individual \( C_{PH} \) values for each slice being assayed were used, the mean values of the concentration measurements remain unchanged, but the SDs in Table 1 approximately doubled to an average of 26% of the concentration measurement, illustrating the importance of maximizing the accuracy of a \( C_{PH} \) determination. The measured concentrations showed no significant systematic variation with depth.

In vivo experiments were first performed on the calf muscles of human male volunteers (35–45 years of age), for which metabolite concentrations are fairly well known. These experiments also provided an opportunity to introduce the fat correction [Eq. (2)]. With \( W = 67.33 \) mol/kg, and \( L = 0.153 \), based on skeletal muscle and adipose tissue water contents of 78.6% and 15.3% by weight (19), respectively, the method yielded \([PCr]\) concentrations of 25.6 ± 4.1 mmol/kg wet wt, and 5.6 ± 1.6 mol/kg for [ATP] (Table 2). Most importantly, these values were constant across the leg despite dramatic variations in the amount of muscle and fat tissue contributing to the spectra, as evidenced by the large changes in \( S_P \) and \( S_W \) as a function of depth exemplified in Fig. 2. Because of the low water content of fat, correcting the reference for water contributions to fat did not significantly alter the overall concentrations despite the fact that \( S(CH_2) \) varied from 2%–120% of \( S(H_2O) \); the uncorrected values were only 5% lower (Table 2). The largest effect of the fat correction on \([PCr]\) in any individual slice (corresponding to a 120% lipid signal) was an increase from 23.4 mmol/kg to 28.6 mmol/kg.

Cardiac metabolite quantification was performed in 2–4 sections of the anterior LV myocardium of 8 healthy male volunteers without heart disease. Subjects were positioned prone on the NMR coil set, rotated slightly on the left side to center the heart beneath the anterior LV and septum (1, 2, 6, 9, 20). Coil location was checked by MRI, then \(^1\)H and \(^{31}\)P 1D phase-encoded data sets were acquired. \(^{31}\)P acquisition times were approximately 12 min, gated at the heart rate. Myocardial tissue water content was taken as 72.7% by weight (19). The values used for the blood correction were: \( W_{bl} = 89.67 \) mol/kg, based on a water content of 80.7% (16); and \([DPG]\) = 1.64 mmol/kg, taking the red cell DPG concentration as 4.08 mM/liter and assuming a 40% hematocrit (22, 23).

![FIG. 2. Muscle PCr concentration (bottom curve, circles), \(^1\)H water signal, \(S(H_2O)\), (squares, top curve, short dashes), and \(^{31}\)P PCr signal, \(S(PCr)\), (triangles, center curve, long dashes) as a function of depth in the calf of one subject. Concentration units are mmol/kg wet wt; NMR signal is in arbitrary units.](attachment:image)

![FIG. 3. A typical cardiac-gated data set acquired during a patient exam for quantifying myocardial metabolite concentrations comprises an axial MRI to locate the \(^{31}\)P and \(^1\)H 1D spectra relative to the heart. Superficial \(^1\)H spectra are dominated by fat CH\(_2\) resonances, whereas water dominates the deeper spectra. Variations in the intensities of the \(^1\)H and \(^{31}\)P peaks with depth reflect the contributions of nuclear spins in tissue distributed throughout the entire 3D extent of the sections corre-](attachment:image)
sponding to each spectrum, including, for example, the apex and base of the LV in Slices 28 and 29. Variations in linewidths with depth also reflect varying sample distribution and susceptibility effects. This is more pronounced in ^1H spectra because of the narrower natural linewidths, smaller ^1H chemical shift range, and because remote fat distributions contribute water and CH, signal to ^31P spectra. Where ^1H peaks are split, quantification was performed by separately fitting then adding the components.

The quantitative results for chest skeletal muscle and the heart, with and without the fat and blood corrections, are listed in Table 2. The [ATP] estimates are based on quantification of the β-phosphate, which is relatively free of other nucleoside phosphates (1): In chest and heart, the ratio of α- to β-phosphate was 1.16 ± 0.23 (12 spectra from three subjects). Because the errors in the NMR signals from the eight subjects used in Eq. [1–4] are random in nature, and because C_{ref} and the phosphate reference concentration were separately determined on four occasions (thereby effectively randomizing any systematic error therein), the error in the determinations listed in Table 2 should be free of additional systematic error, except for those arising from the particular choice of values for [W]. In the chest, the assays are consistent with the calf-muscle assays but are much more scattered, apparently as a result of variability in chest composition and, occasionally, ischemia resulting from the prone orientation. The correction for water in chest fat is larger than for calf muscle, increasing the chest skeletal muscle [PCr] estimates by 19% on average.

In the heart, the fat correction was less significant, representing a 5%–14% increase for [ATP] and [PCr], respectively, whereas the blood correction produced a further 11%–17% increase in the assays, consistent with prior observations for DPG-based blood corrections of ATP (9). The net effect of both corrections was a 17% increase for [PCr], and a 34% increase for [ATP] that includes the additional blood correction of Eq. [3]. Note that the blood correction of Eq. [2] should be applied cautiously when DPG is the dominant peak in the ^31P heart spectrum and the signal-to-noise ratio is poor, such as may occur for the deepest spectra intersecting large volumes of blood in the LV. If the error in the measurement of S(DPG) is comparable to S(ATP) or S(PCr), the subtraction in Eq. [4] can produce a zero or negative tissue-water signal, implying that the tissue contribution is too small and the signal-to-noise ratio inadequate to reliably distinguish tissue from blood in this manner. Usually, the uncertainty in S(ATP) and S(PCr) in such situations prohibits reliable quantification of [ATP] and [PCr], anyway. Note also that because [DPG] in blood is only about 16% of [PCr] in myocardium, whenever S(DPG) > S(PCr), Eq. [5] shows that the spectroscopy voxel is more than 76% occupied by blood.

The fully corrected myocardial PCr:ATP ratio was 1.80 ± 0.34 SD.

**DISCUSSION**

We have developed a convenient method of measuring cardiac ^31P metabolite concentrations from 1D spatially resolved NMR spectra. The method uses the tissue-water ^1H resonance as an internal concentration reference, thereby avoiding image-based tissue volumetry and eliminating correction factors for tissue volume and nonuniform NMR sensitivity and phase (12), as well as the assumptions associated with approaches that model cardiac geometry as a spherical shell (7, 8, 10), in methods using external concentration references. Eliminating these factors results in assays that are inherently more accurate, at least with respect to the errors associated with deriving these parameters. We introduced corrections to account for fat and blood contamination of heart and muscle ^1H and ^31P spectra, which, when combined, can amount to up to about a 30% increase in the metabolite assays. We validated the method using blinded phantoms, consistently deriving the correct values.

The method was used to assay [PCr] and [ATP] in normal human calf muscle, chest skeletal muscle, and the heart. The results are compared with prior ^31P NMR measurements in Table 3. Many other NMR measurements of PCr and ATP levels in skeletal muscle reported as concentrations have been excluded from Table 3 because they were derived by setting the ATP signal level to a concentration of 5.5 mmol/kg wet wt (or 6.2 mM intracellular), a generally accepted value from biochemical assays, and they are therefore not independent determinations.
Cardiac Metabolite Quantification

Our NMR values are consistent with prior independent work: The muscle [ATP] value is the same as the accepted assay value, and values for heart exhibit the smallest random error yet seen. For the human heart, biochemical assays yield values of 33 μmol/g protein for both ATP and PCr in biopsies taken during heart surgery (11). This would correspond to 5.5 mmol/kg wet wt for ATP, entirely consistent with our value, assuming a protein content of 16.5% (19). On the other hand, the absolute value of the biopsy assay of PCr may not be reliable because of rapid PCr loss during sampling. There is strong independent NMR evidence that the myocardial PCr:ATP ratio is 1.83 ± 0.12 (9). With the biopsy value of 5.5 mmol/kg for ATP, this would imply a myocardial [PCr] of 10.1 mmol/kg, again consistent with our determination. Also, if the intracellular ATP level is maintained at the same level in myocardium as it is in muscle, we would expect myocardial [ATP] = 5.95 mmol/g wet wt, assuming that the muscle concentration is 5.5 mmol/kg and recalling the 8% difference in water contents (19). Applying the NMR PCr:ATP ratio would again yield about 10.9 mmol/kg for [PCr].

Intracellular ATP appears to be tightly regulated within the cell: Its concentration is maintained within a narrow range in all but extremes in acute stress (29). In the biopsy study of patients with coronary artery disease undergoing surgical intervention (11), areas of apparent fibrosis were avoided by inspection, and no significant reduction in [ATP] was found in regions of myocardium perfused with diseased vessels. Thus, given that infarcted cells will contain no ATP, the reductions in ATP levels observed by 31P NMR in chronic myocardial infarction patients (7, 10) probably represent a corresponding reduction in the fraction of living myocytes per unit volume, rather than a reduction in intracellular [ATP] within viable myocytes, although nonuniform wall thinning may also contribute to these observations. The new method should compensate for such wall-thinning effects in infarction, and for variable myocardial anatomy in general, via the blood correction and the use of the tissue water reference. Although all of the NMR concentration measurements lack intracellular spatial resolution, no other noninvasive techniques for measuring and investigating myocardial high-energy phosphate metabolite concentrations in disease states currently exist.

Aside from the random errors in the NMR signal measurements reflected in the SDs of the measurements, the myocardial tissue water content and the 31P metabolite spin-lattice relaxation times are other potential sources of systematic variability among different patient groups. If [W] were to increase a few percent, reflecting edema, for example, we might expect metabolite concentrations to decline. In Eq. [1], S_W would also increase, so the direct effect is neutral if the change in [W] is accounted for, or results in a decline of a few percentage points in the concentration estimates if [W] is left unchanged. The effect of any disease-associated changes in relaxation times is minimized by the small flip angle used: Under such conditions we have been unable to detect any significant differences in partial saturation effects in groups of patients with coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy or transplanted hearts compared with normal controls (14).

Finally, it should be noted that the method is not inherently limited to quantitation of 1D-resolved spectra. The problem of tissue volumetry remains for 2D- and 3D-resolved voxels whenever the tissue volume is significantly less than the voxel volume, and especially where the tissue morphology is complex and difficult to define within the voxel. The blood and fat corrections for 31P spectra are applicable to studies of other organs containing a mixture of these tissue types. The protocol for human studies requires only the additional acquisition of a 1H data set that is usually readily incorporated within existing localized spectroscopy protocols, and a measurement of the scaling factor, C_1H, before or thereafter.

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