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Correlation between Metabolite Peak Area Ratios on the Influence of Poor Shimming by ^{1}H MR Spectroscopy

Hyun-Man Baik , Bo-Young Choe*, Tae-Suk Suh, and Hyoung-Koo Lee

Department of Biomedical Engineering, College of Medicine, Catholic University, Seoul 137-040, Korea

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Abstract: Using ^{1}H magnetic resonance spectroscopy (MRS), we quantitatively evaluated correlation representing linear relationship between the metabolite peak area ratios associated with poor shimming conditions. The inadequate shimming due to linear shim offsets directly affected overall MR spectral quality as well as peak area for each metabolite. Three major peaks such as N-acetylaspartate (NAA), creatine (Cr), choline (Cho) were used as a reference for data analysis. Despite considerable variations of metabolite peak area, a significant correlation between the metabolite peak area ratios relative to Cr was established while the correlation between the peak area ratios relative to Cho and NAA was not. The present study suggested that metabolite peak area ratios based on the metabolite of Cr could be an acceptable quantification method even under the poor shimming in clinical MRS examination.

INTRUDUCTION

The use of proton magnetic resonance spectroscopy (^{1}H MRS) in quantitative analysis of the brain metabolite stems from the fact that the peak area (or peak intensity) is directly proportional to the number of spins contributing to the peak. Thus, under appropriate conditions in MRS evaluation, assessment of metabolite concentrations can be reduced to calculate peak areas that are able to aid in the interpretation of clinical MRS data [1, 2]. The most refined approach to peak area calculation requires spectral curve fitting that is widely used in reporting clinical MRS results. Since the absolute quantification of poorly separated peaks in clinical low-field spectra poses much more formidable problems [3, 4], the metabolite peak area ratio method is currently used in clinical MRS mostly because it provide the simplest MRS patient assessment. The ratio method is calculated from a spectrum of lesion and then compared to the corresponding ratios from contralateral normal

with the corresponding ratios from contralateral normal region, if available. Otherwise, it may be compared with normative values from healthy volunteers. In order to improve the precise and accurate quantification, one of the measured metabolites must fulfill the requirement of a reference that does not vary with the physical conditions and/or diseases. In general, the ratio method relies on the assumption that the metabolite of creatine (Cr) of the brain is stable enough to use as an internal reference in reporting relative concentrations of other metabolites such as *N*-acetylaspartate (NAA) and choline (Cho).[5] However, recent reports suggest that this assumption should be used with care.[6, 7] In reality, a stable internal reference may be unavailable for some pathophysiological conditions. Nevertheless, knowledge of biochemical processes with MRS techniques has contributed to the successful use of ratios in the interpretation of clinical MRS data.[8, 9]

Proton MRS is to detect signals from small concentrations of metabolites in the presence of the large concentration of water contained in a small volume over a narrow frequency range. Thus, it is critical to secure practical and precise localization techniques, the best field homogeneity possible and the effective water peak suppression. On the other hand, in the present study the peak area of each metabolite is measured to examine the strength of the linear relationship between the metabolite peak area ratios under poor shimming which degrades the water signal suppression significantly, hence decreasing the quality of the resultant proton spectra. The physical environments such as the poor shimming are found to affect peak broadening and/or baseline distortions due to incomplete water suppression. Thus, the present study aims for quantitative investigation of whether there exists any considerable correlation between metabolite peak area ratios relative to a certain reference under poor shimming. Three major peaks such as NAA, Cr, and Cho were used as references for data analysis.

MATERIALS AND METHODS

Liquid Human Brain Phantom

A phantom containing *in vivo* levels of metabolites at concentrations that were found in the adult human brain was used to study *in vitro* ^1H MRS. The homemade phantom (liquid brain) contains 12.5 mM, CH_3 of NAA, a marker for neuronal tissue; 10.0 mM, N-CH_3 of Cr, an indicator of energy status; 3.75 mM, N-$(CH_3)_3$ of Cho, a metabolite involved in membrane synthesis and degradation; 7.5 mM, H_4 and H_6 of myo-inositols (Ins), an intracellular signal transduction; 12.5 mM, γ -CH_2 of glutamate (Glu), metabolism of neurotransmitter; 5.0 mM, CH_3 of lactate (Lac); 50.0 mM KH_2PO; 0.1% sodium azide and 0.1% Gd-DTPA (reference). ^1H MRS is a non-invasive technique that allows the concentration of a number of cerebral metabolites to be measured *in vivo*. Biochemical information may be obtained about local cellular metabolism by determining peak metabolite ratios of the neurochemicals detected in the spectra.

Experimental Theory

Assuming local optimal field homogeneity in a localized volume of interest in case of ^{1}H MRS with stimulated-echo acquisition mode (STEAM) followed by water suppression, free induction decay (FID) signal, $S(t)_{opt}$ can be written in the time domain as follows,

$$S(t)_{opt} = f \cdot \int_{ROI} dxdydz\rho(x,y,z)\exp[i\gamma B_{opt}(x,y,z)t]\exp[-t/T_2] \tag{1}$$

where ρ is the spin density at any point (x, y, z) and T_2 is the transverse relaxation time constant, and the weighting function, f contains pulse sequence parameters such as TR and TE,

$$f = \exp[-TE/T_2]\exp[-TM/T_1](1-\exp[-TR/T_1]) \ . \tag{2}$$

Let us consider the results of poor shimming through linear shim offsets to produce inadequate physical environments given by

$$B(x,y,z) = B_{opt}(x,y,z) - \sum_{i=1}^{N} I_i F_i(x,y,z) \tag{3}$$

where the magnetic field B is expressed with two terms, one due to the optimized homogeneous field and one due to the locally inhomogeneous field function, F_i of the i-th shim coil at unit current I_i. Therefore, assuming a uniform distribution of spins in a localized single voxel, the new FID signal, $S(t)$ can be written

$$S(t) = \rho f \cdot \int dxdydz \exp[i\gamma B(x,y,z)t]\exp[-t/T_2] \tag{4}$$

The local deviation from the average field value B_o is

$$dB(x,y,z) = B(x,y,z) - B_o \tag{5}$$

where the B_o component that needs to be considered is only the z component. By substitution of $B(x, y, z)$ from Eq.(5) into Eq.(4), then, the FID signal can be rewritten as Eqs.(6a, 6b),

$$S(t) = \rho f \cdot \int dxdydz \exp(i\gamma[dB(x,y,z) + B_o]t)\exp[-t/T_2] \tag{6-a}$$

$$= \rho f \cdot \int dxdydz \exp[i\gamma dB(x,y,z)t]\exp[i\gamma B_o t - t/T_2] \tag{6-b}$$

with a poor shimming, the inhomogeneous field, dB is sufficiently small for the quadratic approximation of the exponential to be valid,

$$\exp[i\gamma dB(x,y,z)t] \cong 1 + i\gamma dBt - \gamma^2 dB^2 t^2 / 2 . \tag{7}$$

When this is substituted back into Eq.(6b), and the summation performed over all x, y, z, the second term of Eq.(7) will disappear because the sum of dB is zero from Eq.(5).

$$S(t) = \rho f \cdot \int dxdydz[1 - i^2 dB^2 t/2]\exp[i\gamma B_o t - t/T_2]. \tag{8}$$

the exponential term represents the FID that would be obtained from all points of the same field B_o, thus, the observed FID amplitude is at every time t less than the theoretical value by an amount which depends dB^2. Hence, maximizing

$$\int_{ROI} dxdydzdB^2(x,y,z) \tag{9}$$

yields a minimum of the observed FID, where $dB = (\nabla B)_x\, dx + (\nabla B)_y\, dy + (\nabla B)_z\, dz$ indicates a physical interpretation of the gradient of a scalar function, which the maximum value of local deviation results when the gradient and displacement are in the same direction.

Poor Shimming

It is often necessary to distinguish compounds that differ in chemical shift by only a fraction of a part per million (ppm). Thus, it is important to emphasize the homogeneity of the magnetic field since the homogeneity directly affects the spectral resolution. In particular, it is crucial for *in vivo* ^{1}H MRS because poor shimming degrades the water signal suppression and produces the bad quality of the resultant spectra. Consistent field homogeneity for a series of similar *in vivo* studies is also an important asset for accurate metabolic quantification.[10] Thus, in general, a local shim is applied over a selected ROI for local homogeneity improvement before water suppression in MRS experiment.[11] In the present study, however, inadequate or poor shimming due to linear shim offsets was specifically applied for optimized good shimming values within the range of permitted autoprescans. During the period of autoprescan, flip angle, saturation power, and receiver and transmitter gains were automatically adjusted. The calculated peak area included a possible concentration variation for each metabolite on the measurement.

Data Acquisition and Analysis

All localized ^{1}H MRS studies were performed on a 1.5T MRI/MRS system (GE Signa Advantage, Version 4.8; GE Medical System, Milwaukee, WI) using the short echo time (TE) STEAM pulse sequence, followed by water suppression with three chemical shift-selective saturation (CHESS) pulses and dephasing gradients.[12, 13] All spectra were obtained from a localized voxel (2 x 2 x 2 cm^3) in the center of phantom. Spectral parameters were TE 20 ms, TR 2000 ms, acquisition averages 128, spectral width 2500 Hz, and data points 2048. Total examination time per one measurement was approximately 30 minutes. Spectroscopic data were transferred to a Sun SPARC station *IPC* (Sun Microsystems, Mountains View, CA) and postprocessed by SAGE data analysis package (GE Medical Systems, Milwaukee, WI).

The residual water signal in the spectrum was subtracted during postprocessing procedures. Gaussian line broadening filtering was carried out to improve SNR and reduce truncation artifacts. Phased absorption spectra were reported directly with baseline corrections. All of the ^{1}H MRS spectra were plotted and analyzed in the absorption mode and fitted to Lorentzian lineshapes. Proton resonances in the spectra were assigned on the basis of prior assignment.[1] Resonance peak assignments of major proton metabolite were 2.0 ppm of NAA, 2.35 ppm of Glu, 3.0 ppm of Cr, 3.2 ppm of Cho, 3.5 ppm of Ins and 1.30 ppm (doublet) of Lac. Three major peaks such as NAA, Cr and Cho metabolites were used as a reference for data analysis. Peak areas for each proton metabolite were measured using a Marquart algorithm.[14] The quantitative expression of results was evaluated with correlation between metabolite peak area ratios considering major metabolites as references. In addition, in order to determine the possible concentration variations of the metabolite peak area, a coefficient of variation (COV(%)=100× standard deviation/mean) was calculated by finding the mean and standard deviation of all the metabolite peak area ratios.

Statistics

Statistical analysis was performed using Origin (Origin for Windows, Version 6.0, Microcal Software, Inc.). A linear regression curve fitting was used to find the optimal description of the correlation the metabolite peak area ratios, where $r>0.7$ was considered correlative. the P value can be obtained from the ANOVA for linear regression (the P value for the t-test of the slope=0).

RESULT

Figure 1 shows three orthogonal bases T2-weighted MR image (left), together with spectrum (right) obtained from a localized volume of interest centered on the liquid human brain phantom. For all the metabolite peak area ratios, the calculated COV values were listed in Table 1. In most cases, the COV values were showed highly large range (20-60%, 2

standard deviation), indicating that an inadequate shimming due to linear shim offsets in the external field generated considerable metabolite peak area variations.

To evaluate the strength of the linear relationship of metabolite peak area ratios, the present study investigated with correlation between the ratios on the influence of poor shimming.

Table 1. Percentage COV calculated by finding the mean and standard deviation of the peak area ratios to determine metabolite concentration variations possible under poor shimming conditions. Note. NAA = N-acetylaspartate, Cr = creatine, Cho = choline-containing compounds, Ins= myo-inositols, Glu = Glutamate, Ref. = reference. COV^1, COV^2, and COV^3 are given as the percentage

Cr Ref.	COV^1	Cho Ref.	COV^2	NAA Ref.	COV^3
NAA/C	23.8	NAA/Cho	12.6	Cho/NAA	13.9
Cho/Cr	27.5	Cr/Cho	29.3	Cr/NAA	24.9
Ins/Cr	26.1	Ins/Cho	23.4	Ins/NAA	12.1
Glu/Cr	25.6	Glu/Cho	11.9	Glu/NAA	22.3

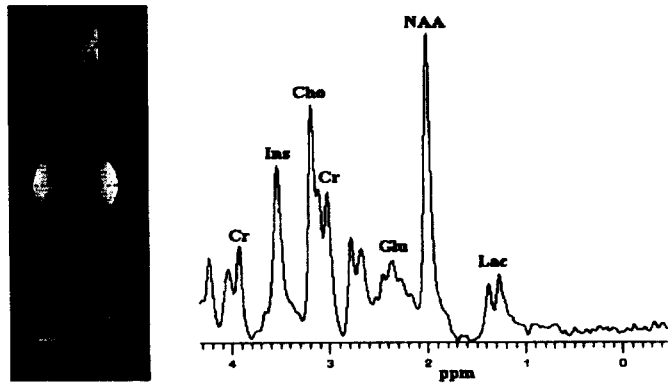

Fig. 1. shows three orthogonal bases T2-weighted MR image (left), together with spectrum (right) acquired from a localized volume of interest centered on the liquid phantom under a poor shimming, nor moving the phantom in ^1H MRS with the short echo STEAM sequence.

Figure 2 illustrates a strong correlation between NAA/Cr and Cho/Cr ratios relative to Cr, despite the metabolite peak area variations possible reflecting large COV values. (r=0.883, P<0.001). Apparently there was also a significant correlation between Ins/Cr and Glu/Cr ratios in the short TE spectra (r=0.711, P<0.001). Moderate correlation between NAA/Cho and Cr/Cho relative to Cho (r=0.480, P=0.005), and between Ins/Cho and Glu/Cho ratios (r=0.543, P=0.001) did not considered correlative. In case of NAA reference, there was no correlation between Cho/NAA and Cr/NAA ratios in the same physical environments (r=0.02, P=0.91), but a moderate correlation between Ins/NAA and Glu/NAA ratios was observed (r=0.477, P=0.005). Thus, except for the metabolite peak area ratios relative to Cr, no correlation between the metaboite ratios relative to Cho and NAA observed a significant linear relationship.

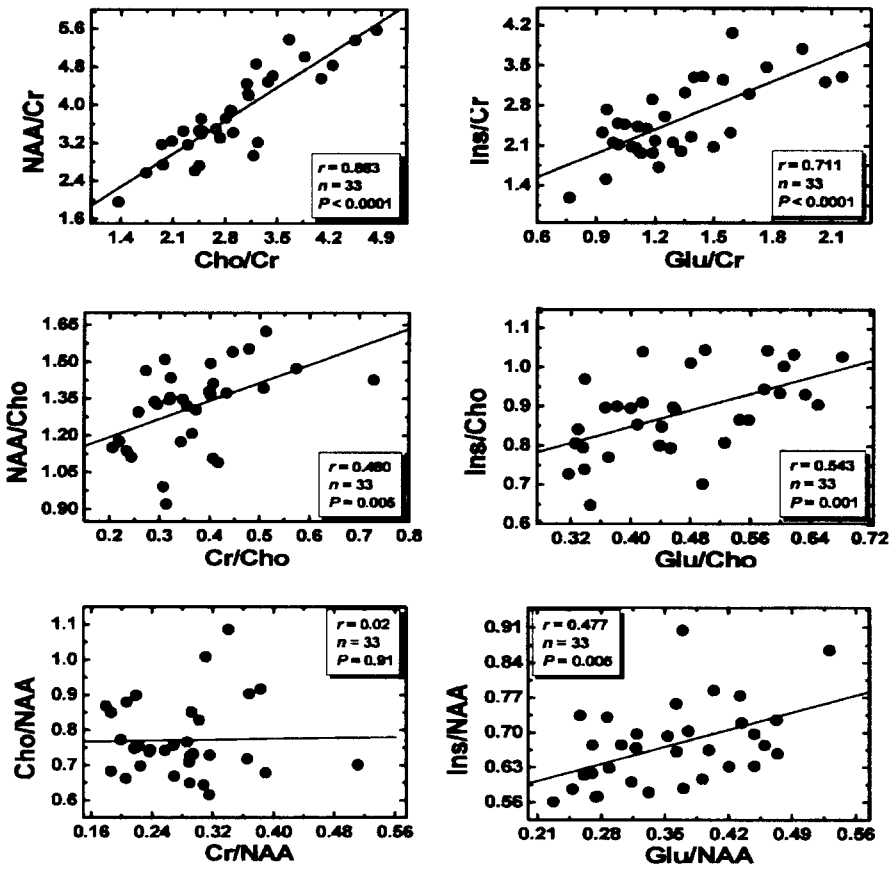

Fig. 2. Correlation between metabolite peak area ratios relative to Cr, Cho, and NAA as a reference under the influence of poor shimming conditions in ^{1}H MRS examination.

DISCUSSION AND CONCLUSIONS

Successful MRS examination depends upon a wide variety of different factors that include patient preparation, voxel shimming, water suppression, choice of acquisition parameters and data postprocessing to obtain quantitative results. Each of these factors can contribute to possible deviations in the precision of the results. The local voxel shimming among these factors is to optimize the magnetic field homogeneity specifically over the selected volume of interest. A good local shimming procedure produces narrower and sharper metabolite peaks, hence better spectral resolution and improved SNR. In our experiment, however, we used an inappropriate shimming control that can degrade the water signal suppression and the quality of the resultant spectra. The inadequate or poor shimming in accordance with linear shim offsets was applied for optimized good shimming values specifically over the selected ROI. Only linear shim offsets were manually adjustable through the shim values starting from the references and gradient hardware. Acquisition spectra were obtained from physical conditions within the range of permitted autoprescans. The peak area for each metabolite in MR spectra was affected by peak and/or baseline distortions of spectrum due to incomplete water suppression on the influence of poor shimming. The calculated peak area included a considerable possible concentration variation for each metabolite under on the measurement. When the COV values for each metabolite peak area ratios were calculated, the values showed large ranges, indicating that inadequate shimming considerably generated metabolite peak area variations in most cases. Despite the variations, a strong correlation between the NAA/Cr and Cho/Cr, and Ins/Cr and Glu/Cr ratios relative to Cr was observed (r=0.883, r=0.711). Apparently there was a significant linear relationship with the metabolite data points, representing a positive slope. This finding may reflect that a correlation actually exists between the metabolite peak area ratios on the basis of Cr. However, a linear relationship possible between NAA/Cho and Cr/Cho, and Ins/Cho and Glu/Cho ratios did not strongly reveal although it possess a positive slope, representing a moderate positive relationship (r=0.480, r=0.543). In case of NAA reference, no significant linearity between Cho/NAA and Cr/NAA, and Ins/NAA and Glu/NAA ratios was also established (r=0.02, r=0.477). Therefore, cautious interpretation of clinical data with respect to metabolite quantification relative to Cho and NAA should be considered in reporting relative concentrations acquired from short TE STEAM spectra.

In some special cases of emergent, psychiatric and/or pediatric patients even with metallic dental supplements, we could not get the acceptable shimming results. Thus, in order to use ^1H MRS data inevitably under the inadequate or poor shimming conditions, Cr peak area based on a strong linear relationship may seem to be the most desirable reference for accurate quantification in all metabolites. Furthermore, Cr peak distinctly appears at 3.0 ppm in the proton brain spectrum, and is an extremely reliable marker of intact brain energy metabolism and is imported to the brain from extracerebral sources of synthesis. Accordingly, peak area ratios relative to Cr are reasonable considerably in interpreting many

pathological MR spectra.

In conclusion, the present study suggested that peak area ratios based on the Cr metabolite could be used as a plausible quantification method for a reference, even if metabolic concentrations were subjected in determining the peak area under the inadequate physical environments in MRS examination. This peak area ratio method on the basis of Cr could be a desirable diagnostic tool to evaluate the metabolic alterations in clinical MRS studies. Further studies are in progress to establish whether there is a correlation between the metabolite peak area ratios for *in vivo* tissues, and will be expanded to longer TE values such as those used in most brain examinations.

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