Effect of J coupling and T2 Relaxation in Assessing of Methyl Lactate Signal using PRESS Sequence MR Spectroscopy

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Abstract

Purpose: This work was aimed at quantification of lactate concentration using proton MR spectroscopy (MRS). We carried out a basic study to clarify the characteristics of signal change and T2 relaxation time of lactate that occur by J coupling in point resolved spectroscopy (PRESS) sequence.

Materials and Methods: Proton MRS was done for a water phantom containing 10 mmol/L creatine and lactate on a clinical 1.5 T MR system by using an asymmetric PRESS sequence. The coupling constant J was 7.35 Hz. In acquisitions, TE was varied from 68 ms up to 544 ms, with an increment of 68 ms (1/2J) and TR was fixed to 10000 ms.

Results: The shape and signal intensity of the lactate signal vary depending on its phase. The lactate signal intensity at TE 272 ms was higher than at TE 136 ms despite the longer TE. T2 relaxation times of lactate in the negative in-phase (TE 136 ms, TE 408 ms) and positive in-phase (TE 272 ms, TE 544 ms) were 1033 ms and 1042 ms, respectively (no significant differences), so that when the same phase was used, regardless of the phase condition, T2 relaxation behavior was not different. We
considered that our results included over expression and loss of lactate signal depending on the phase.

Conclusions: For evaluation of the lactate peak, we recommend the use of the positive in-phase signal because it is larger than the negative in-phase signal. The influence of the asymmetric PRESS sequence, which may cause loss and over expression of lactate signal, should be considered in the calculation of the quantification. The T2 relaxation time should be also considered in the calculation of the lactate value since it affects the value considerably.

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Introduction

Lactate is a redox partner of pyruvate, which is a metabolic intermediate between glycolysis and the tricarboxylic acid (TCA) cycle. When oxygen availability is low, due to a perfusion deficit or other metabolic stress, the TCA cycle rate drops, pyruvate is produced during glycolysis and it is converted to lactate. Although lactate cannot be resolved in the adult human brain under normal conditions, high concentrations of cerebral lactate are often seen in disease states associated with an increased energy demand, impaired cellular capability for oxidative phosphorylation, or both. Examples of such situations are tumors (1-3), ischemia (4, 5) and congenital metabolic deficiencies (6). Therefore, in clinical examinations, the detection of lactate may provide useful information for the evaluation of the state and/or response to a therapeutic intervention.

In proton MR spectroscopy (MRS), the lactate molecule has two peaks, a doublet at 1.33 ppm due to the methyl protons, and a quartet at 4.12 ppm due to the methine proton. The methine quartet peaks are very near the water resonance peak (4.7 ppm), and generally cannot be observed in human studies in vivo. These two peaks are weakly coupled with a coupling constant of J, which has typically been given in the range of 6.9 Hz - 7.35 Hz (7-13). The present study used the value of 7.35 Hz, i.e., 2/J = 272 ms. This J coupling causes a phase modulation of the methyl lactate signal with a refocusing interval of 136 ms, thus the lactate peak becomes a negative in-phase signal (inverted signal) for 1/J (= TE 136 ms) and 3/J (= TE 408 ms) and a positive in-phase signal for 2/J (= TE 272 ms) and 4/J (= TE 544 ms). This is the reason for using echo times of 136 ms and 272 ms in conventional clinical proton MRS examinations.

Several methods for obtaining volume-localized proton MRS are currently in use. These include stimulated echo acquisition mode (STEAM) (14) and point resolved spectroscopy (PRESS) (15) sequences, which generate a stimulated echo and a spin echo of magnetization inside the volume of interest, respectively. PRESS sequence offers several useful attributes for localized in vivo spectroscopy. The advantages are specificity in volume localization, ability to achieve high-quality local shimming, and doubled signal intensity compared with STEAM. We have used the PRESS methods considering these points. However, in the PRESS method, we often found that the inverted signal at TE 136 ms was smaller than that at 272 ms.
Our aim for the present work was to establish a quantification method of lactate concentration using proton MRS by PRESS Sequence. For that purpose, we examined and evaluated the signal changes due to phase modulation and we obtained T2 relaxation time calculation method in vitro as basic data for further use in lactate quantification in clinical cases.

Materials and Methods:

The following experiments were done using a water phantom which was a large cylindrical acryl bottle (diameter 20 cm, length 40 cm) filled with 10 mmol/L of lactate and 10 mmol/L of creatine.

1. We examined the phase changes of lactate and creatine peaks in relationship to the changes of TE. Data were acquired with variable TE from 68 ms to 544 ms, with an increment of 68 ms (1/2J) and TR was fixed at 10000 ms.

2. We evaluated the signal intensity of lactate and creatine in relation to changes of TE. Data were acquired for the negative in-phase (TE 136 ms and 408 ms) and positive in-phase (TE 272 ms and 544 ms) signals. Moreover, T2 relaxation time of lactate was calculated for the negative in-phase and positive in-phase, respectively according to Eq.1:

\[
M_s = M_0 \times \exp \left( \frac{-2\tau}{T2} \right)
\]

where \(M_s\) denotes the signal intensity to a given TE, \(M_0\) denotes the signal intensity at TE = 0, and \(\tau\) denotes TE/2. TR was fixed at 10000 ms.

Proton MRS was performed on a clinical 1.5 T super-conducting MR whole body system (Gyroscan, Philips Medical Systems) using a circularly polarized head coil. Data were acquired by using the PRESS sequence (known as PRIME (Proton Regional Imaging of Metabolites) in Philips's instruction manuals), which generates a spin echo. The PRESS sequence consisted of one slice selective 90° RF-excitation pulse and two slice selective 180° RF-refocusing pulses. The timing scheme was defined as TE = 2 \(\tau_2\) where \(\tau_2 = \tau_1 + \tau_3\), and between the 90° pulse and the first 180° pulse was defined as \(\tau_1\), between the first 180° pulse and second 180° pulse was defined as \(\tau_2\), and between the second 180° pulse and total echo signal was defined as \(\tau_3\). We used an asymmetric timing scheme, in which the fixed delay between the 90° pulse and the first 180° pulse was always 6.89 ms (Fig.1). RF pulse used in this sequence was a sinc pulse, which is the default pulse set in our clinical machine. The number of acquisitions was 64. We
used a coupling constant of $J = 7.35$ Hz ($2/J = 272$ ms). The number of points sampled was 512 and the spectral width was 1000 Hz. Water suppression was done using a chemical shift selective (CHESS) pulse with 60 Hz bandwidth. The field homogeneity was maximized over the selected volume of interest (VOI) by automatic shimming on water proton signals using PRESS sequence without a saturation pulse, resulting in a line width of 3 Hz (FWHM). Spectral processing involved zero filling to 1024 data points followed by Gaussian filtering of 2 Hz, exponential filtering of $-1$ Hz, Fourier transformation, manual zero– and first– order phase correction, and integration of the peaks by means of standard Philips software. The VOI was a single voxel of 15 mm $\times$ 15 mm $\times$ 15 mm in the center of the phantom.

**Results:**

Fig. 2 reproduces the magnitude spectra obtained from the water phantom containing lactate and creatine with the PRESS sequence as depicted in Fig. 1. The spectra were obtained with different TE values (68 ms increments). There was no change of the signal phase for creatine, but the lactate peak changed with TE.

Fig. 3 shows the relationship between signal intensity of lactate and creatine and different TE. The lactate signal intensity at TE 136 ms was about 60% of the lactate signal at TE 272 ms despite the shorter echo time. The lactate signals at TE 408 ms and TE 544 ms showed the same tendency. The creatine signal at TE 136 ms was higher than that at TE 272 ms due to the simple T2 decay. T2 relaxation times of lactate calculated from the negative in-phase signal (TE 136 ms and 408 ms)
and positive in-phase signal (TE 272 ms and 544 ms) were 1033 ms and 1042 ms, respectively (no significant differences in Mann-Whitney U-test).

Discussion:
Detection of lactate by in vivo proton MRS may provide useful information on metabolic stress in brain and other human tissue, potentially identifying the degree of ischemia or growth potentiality of tumors. Therefore, if lactate can be quantitatively evaluated, it could have a substantial clinical impact. However, lactate signal change is complicated because of J coupling. In this study, we have demonstrated that the lactate quantification could be performed when several important factors regarding the lactate signal changes were considered.

There was no change of phase for the creatine signal, with various TE. However, the phase of the lactate signal changed with TE (Fig.2). Namely, the lactate signal was periodically transformed into the negative in-phase or the positive in-phase due to J coupling; this is called J modulation. This characteristic is widely used in clinical proton MRS studies to distinguish the lactate signal from a lipid signal, since the lipid signal sometimes overlaps that of lactate at 1.33 ppm. Lipids do not show J modulation, so that the negative in-phase signal at TE 136 ms and positive in-phase signal at TE 272 ms indicate the presence of lactate.

When selecting the positive in-phase signal (TE 272 ms, TE 544 ms), the transverse magnetization produced by the 90° RF pulse, becomes in-phase and the magnetization will be completely equivalent to transverse magnetization occurring in an uncoupled spin system (7). For the negative in-phase signal (TE 136 ms, TE 408 ms), the transverse magnetization produced by the 90° RF pulse becomes anti-phase and the magnetization is not equivalent to transverse magnetization occurring in an uncoupled spin system (7).

In the present study, the creatine signal for the TE 136 ms spectrum was slightly higher than that of the TE 272 ms spectrum due to the simple T2 decay, while the lactate signal was higher for TE 272 ms than TE 136 ms despite the longer echo time (Fig.3). In other words, signal loss occurred with the negative in-phase signal or over expression occurred with the positive in-phase signal.

In our MR machine, a strongly asymmetric PRESS sequence is used as shown in Fig.1. This sequence is characterized by application of a very short $\tau_1$. Schick et al. (9) studied the change in lac-
tate signal by using the Hann-fit sinc pulse, which is the same RF pulse as the sinc pulse that we used. They reported that when a short $\tau_1$ in PRESS sequence with a Hann-fit sinc pulse is used, the lactate signal becomes small for the negative in-phase signal (TE 136 ms, TE 408 ms) and higher for the positive in-phase signal (TE 272 ms, TE 544 ms) compared to a pure absorption signal. Therefore, we may consider that in our results over expression and loss of lactate signal occurred depending on the phase. Consequently, due to the higher signal intensities, using the lactate signal at TE 272 ms (positive in-phase) is preferable for quantification.

Lactate signal loss resulting from the PRESS sequence arises from anti-phase magnetization (negative in-phase) being refocused less efficiently than in-phase magnetization (positive in-phase). In order to more efficiently refocus in the anti-phase magnetization, exactly rectangular 180° pulses and adjustment of the flip angle are needed. Moreover, signal intensity of lactate depends on the sequence timing. It is not possible to change these parameters on the console in clinical machines.

In our study, T2 relaxation times for negative in-phase and positive in-phase signals were 1043 ms and 1050 ms, respectively (no significant differences in Mann-Whitney U-test). Namely, if the same phase is used, the T2 measurement of lactate is possible in each phase. However, in clinical cases the lactate peak will be is smaller than in a phantom study and if the negative in-phase is used, the lactate peak will disappear at longer echo time (TE 408 ms). Therefore, we recommend using the positive in-phase signal to obtain the lactate peak at longer echo time (TE 272 ms, TE 544 ms) for calculation of the T2 relaxation time and further quantification.

Conclusions:

We confirmed that loss of lactate signal occurred for the negative in-phase (TE 136 ms, TE 408 ms) and over expression of lactate signal occurred for the positive in-phase (TE 272 ms, TE 544 ms), when short $\tau_1$ was used in PRESS sequence. Such signal changes should be kept in mind when evaluating lactate signals in clinical settings.

As for the calculation of T2 relaxation time of lactate, it is necessary to set the negative in-phase signal or set the positive in-phase signal separately to achieve the same signal decay in each phase.

In the future, we want to examine the quantification of lactate in clinical cases such as evaluation of the malignant degree of a brain tumor, the severity of a cerebral infarction and/or the extent of the penumbra zone.

References:


