Pitfalls in Lactate Measurements at 3T

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SUMMARY

In clinical magnetic resonance spectroscopy at higher field strengths, lactate may show reduced or absent signal at an echo time of 144 ms. Although this false negative result may be predicted from theory, experimental verification and clinical impact have not been fully established. Using scanners from three major vendors, spectra from phantoms and patients demonstrate the lactate signal loss and potential error in interpretation. Strategies are discussed to overcome, or at least alleviate, this problem.

INTRODUCTION

Lactate is a metabolite that plays a pivotal role in many brain pathologies such as tumors, stroke, cerebral ischemia, hypoxia and several mitochondrial disorders (1). The lactate concentration in healthy brain under normal conditions is about 1 mM. However, when oxygen availability is low due to metabolic stress, glucose molecules are no longer oxidized completely and pyruvate is produced. The pyruvate is converted to lactate, which can rise to concentrations above 10 mM. Lactate is therefore an important marker of anaerobic glycolysis taking place in the above mentioned brain disorders. The lactate molecule has two weakly coupled resonances in 1H magnetic resonance spectroscopy (MRS): a doublet (split by coupling to the methine (CH) proton) at 1.33 ppm arising from three magnetically equivalent methyl (CH₃) protons and a quartet (split by coupling to the protons of the methyl group) at 4.11 ppm arising from the methine proton, which is usually not visible in vivo. The scalar coupling gives rise to a phase evolution of the methyl doublet, which depends on the echo time (TE). For TE = 144 ms the resonance shows a phase of 180° leading to a negative in-phase doublet, whereas an echo time of 288 ms gives rise to a positive in-phase doublet. Since only in-
phase resonances can be quantified, echo times of 144 ms and 288 ms are preferable for lactate detection and assignment. The coupling evolution can also be exploited for difference editing techniques increasing the sensitivity of lactate detection (2).

Localization techniques such as the double spin echo method PRESS, which is the standard localization technique used on clinical MRI systems, suffer from chemical shift displacement artifacts. Importantly, this can give rise to signal misregistration for almost all metabolites, as only the signal from one specific frequency, usually the NAA frequency, originates from the selected volume of interest. Signal from protons with different chemical shifts, e.g. from other metabolites, stem from spatially shifted volumes. Furthermore, for weakly coupled resonances, there is an additional signal cancellation due to anomalous J-modulation (3, 4). This additional artifact and its effect on the interpretation of lactate levels in clinical spectra are discussed in this paper. As the chemical shift displacement roughly scales with the square of the field strength (due in part to reduced RF pulse bandwidth, as well as increased chemical shift frequency separation), a severe underestimation of lactate occurs at 3T, when PRESS localization is used with an echo time of 144 ms. A detailed explanation of the origin of anomalous J-modulation can be found in the appendix.

This paper shows in vitro and in vivo examples of signal cancellation for several MRI systems. A strategy is presented to quantify the lactate signal loss and thus validate the underlying theory. Finally, suggestions for parameter choices on clinical systems are given to avoid or at least diminish the problem of lactate underestimation at 3T.
DESCRIPTION OF THE TECHNIQUE AND RESULTS

1) Patient Measurements

Two patients with high-grade gliomas underwent MRS both with TE of 144 and 288 ms, performed on Philips Intera whole body systems using a send-receive head coil. One patient was measured at a field strength of 1.5T, while the other was measured at 3T.

Another patient with Mitochondrial myopathy, encephalopathy, lactacidosis, stroke (MELAS) was examined on 1.5T and 3T systems from a second vendor (GE Healthcare, Milwaukee, WI). Two dimensional multivoxel spectra were acquired at both field strengths consecutively the same day, repeated with both TE = 144 ms and TE = 288 ms. Standard PRESS localization was used with the region of interest centered over an acute occipital lesion. On this system VSS saturation bands (5) are placed around the volume of interest by default.

Some of the data presented here was acquired on a clinical basis, but all patients gave their written informed consent prior to participating in research experiments.

In the high-grade tumor in figure 1 the spectra acquired at 1.5T both show a prominent lactate doublet, inverted for TE = 144 ms and in phase with NAA for TE = 288 ms. The lactate peak, clearly visible as inverted doublet at TE = 144 ms, is of greater area and amplitude at TE = 144 ms than at TE = 288 ms. This signal change reflects the known T2 related signal attenuation with increasing TE.
Comparable experiments were carried out on a 3T system scanning another patient with a glioma (grade III). While for TE = 288 ms a large lactate peak is observable at 1.33 ppm, the lactate resonance has completely vanished for TE = 144 ms, due to anomalous J-modulation (Fig. 2).

The third patient example (Fig. 3), carried out on different systems, shows lactate peaks of similar relative amplitude with TE = 144 ms and TE = 288 ms at 1.5T. The lactate signal loss, which is expected with TE = 288 ms compared to TE = 144 ms due to $T_2$ relaxation, is approximately compensated by the signal loss due to anomalous J-modulation with TE = 144 ms. At 3T, however, anomalous J-modulation gives rise to a complete disappearance of the lactate peak.

2) Phantom Measurements

A standard brain metabolite phantom containing 5 mM of lactate was measured on three 3T MRI scanners from three different vendors (GE Healthcare, Philips Medical Systems and Siemens Medical Solutions). Single Voxel MRS (VOI size = 2x2x2 cm$^3$, PRESS localization) was acquired from the same volume once with TE = 144 ms and once with TE = 288 ms. The lactate peak seen at 1.33 ppm for TE = 288 ms would be expected to be smaller than the inverted doublet for TE = 144 ms due to $T_2$ relaxation. However, at 3T spectra from all three MR systems show significantly larger lactate resonances at TE = 288 ms than at TE = 144 ms. For one system the lactate peak has even disappeared completely. This demonstrates that a significant amount of the lactate signal is lost (not visible) at TE = 144 ms (Fig. 4).
To quantify the signal loss due to anomalous J-modulation on the basis of the phantom spectra acquired for TE = 144 ms and TE = 288 ms, the T₂ relaxation constant of lactate would have to be determined first. Since the relaxation constant of lactate for the used brain metabolite phantom was unknown and difficult to determine with high precision, a different approach was chosen: Spectroscopic Imaging (SI) offers the possibility to dispense with spatially selective refocusing pulses, since the SI slice can be selected only by the excitation pulse and the spatial encoding within the slice is achieved with phase encoding only. However, in a standard SI measurement protocol without PRESS localization, both the excitation pulse and the refocusing pulse, which is needed for the echo formation, are slice-selective on some scanners, leading again to some signal loss. To estimate the amount of signal loss due to anomalous J-modulation, SI data sets were acquired once with (“standard” SI sequence) and once without the slice selection gradient during the refocusing pulse. Theory predicts that the overall signal loss at TE = 144 ms is the same for a standard SI sequence as for a single voxel protocol using PRESS (see appendix). It can also be calculated that no signal loss should occur for lactate for a standard SI measurement with TE = 288 ms. Therefore, to validate the theoretical predictions experimentally, SI data sets were acquired for these two echo times. Postprocessing of the spectra included exponential filtering of the time domain signal, cosine filtering in k-space and B₀ correction.

Fig. 5 shows the results of the SI measurements without PRESS. For echo times of 144 ms and 288 ms one representative SI voxel is shown (acquired once with (Fig 5a, 5c) and once without a refocusing pulse gradient (Fig 5b, 5d), respectively).

Integrating the modulus spectra and comparing the results with and without anomalous J-modulation yielded a signal loss of 72.2 % for TE = 144 ms, whereas the signal
intensity is about the same for TE = 288 ms. Theoretical calculations taking into account the chemical shift difference of the coupled nuclei and the bandwidth of the used refocusing pulses yield a relative signal loss of 81.2 % for TE = 144 ms, whereas for TE = 288 ms no signal loss due to anomalous J-modulation is predicted (see appendix).

Thus the measured signal loss is consistent with the theoretically expected value. It should be noted that, in contrast to spectroscopic imaging without PRESS, theory also predicts a small signal loss of 6.8 % at TE = 288 ms when using PRESS localization for single voxel experiments. But this loss only needs to be taken into account when high precision quantification is desired.

**DISCUSSION**

Detection of lactate using MRS plays an important clinical role in the assessment of a number of brain abnormalities, including tumor, stroke and mitochondrial disorders. The presence of lactate in the context of a tumor can be considered diagnostic for glioblastoma multiforme. Lactate is also elevated as a consequence of mitochondrial abnormalities in neurodegenerative disorders, such as Huntington’s disease. Since for very short echo times there are often residual fat peaks visible in the spectral region of the lactate doublet, one has to resort to echo times near multiples of 1/J (J being the coupling constant) for proper lactate detection and quantification. As an inverted doublet can be discriminated more easily against other resonances like lipids, PRESS with an echo time of 144 ms is often considered the most appropriate method for unambiguous lactate detection at 1.5T. Although the effect of “anomalous J-modulation” and the potential signal loss for lactate at TE = 144 ms has been
discussed in the literature (3, 4), little attention has been given to this phenomenon in clinical routine so far. Neglecting this effect can potentially lead to a severe misinterpretation in clinical diagnosis as shown in our examples. The extent of the signal loss due to anomalous J-modulation can vary considerably depending on the field strength, the used coil and the sequence parameters. A practical recommendation for clinical MRS at 3T is to perform a phantom study at TE = 144 ms and TE = 288 ms; if the lactate signal at TE = 144 ms is less than that seen at TE = 288 ms, it is recommended not to use TE = 144 ms, but rather only TE = 288 ms in clinical examinations, although in general the sensitivity decreases with longer echo times due to T2 relaxation. However it should be noted that the quantitative influence of anomalous J-modulation can be different in specific in vivo examples, where inhomogeneous metabolite distributions can either aggravate or attenuate the effect compared to in vitro experiments.

Strategies to prevent or alleviate the signal loss due to anomalous J-modulation are discussed elsewhere in detail (3-5), but usually require changes in the scanner software. An approach implemented on several clinical scanners is to saturate the region of spin-selective refocusing with outer volume suppression (OVS) pulses prior to excitation. E.g. on some scanners, quadratic phase suppression pulses have been implemented for this purpose (6), but they suppress the effect only partially, since they are not specifically tuned for lactate detection as can be seen both from in vivo and phantom examples in this paper. However, at higher field strengths than 3 T, which have now become available for human studies as well, the chemical shift displacement will be so pronounced that this work-around will be less effective.
Another approach for high-field systems is using pulses with much larger bandwidths such as adiabatic pulses to alleviate the chemical shift displacement. However, since ordinary adiabatic pulses are usually not spatially selective, they cannot be used in PRESS sequences. LASER (Localization by Adiabatic SElective Refocusing) sequences, using pairs of large bandwidth AFP (Adiabatic Full Passage) pulses for volume selection and echo formation at the same time, will probably be the method of choice for localization in high-field spectroscopy applications in the future (7). A further popular localization technique is STEAM (STimulated Echo Acquisition Mode), which uses three 90° pulses giving rise to a stimulated echo. Since 90° pulses have much larger bandwidths than 180° pulses, the chemical shift displacement is far less severe. However, for STEAM the signal intensity of coupled resonances not only varies with TE, but also shows a strong modulation governed by the mixing time (TM) between the second and third pulse (1). Furthermore, SI (Spectroscopic Imaging) offers the possibility to dispense with spatially selective refocusing pulses and therefore prevent the signal cancellation. However, SI protocols without PRESS localization are usually not implemented on purely clinical scanners and very good outer-volume suppression is required for this approach to prevent the spectra from being impaired by subcutaneous fat signal.

APPENDIX

The signal cancellation by anomalous J-modulation for coupled resonances arises from the chemical shift displacement artifact. The relative voxel displacement for two protons with chemical shifts $\delta_1$ and $\delta_2$ equals the ratio of the chemical shift difference ($\Delta\omega_{CS} = \delta_1 - \delta_2$) and the bandwidth of the RF pulse ($\Delta\omega_{RF}$) used for volume selection.
For the signal of the methyl (CH$_3$) resonance of lactate at 1.33 ppm the signal loss can be understood as follows: Due to this chemical shift displacement the volume selected by one single refocusing pulse decomposes into a region where both the methyl and the methine (CH) protons of the lactate molecule are affected by the pulse ("non-selective" pulse) and a region where only the methyl spin is inverted ("selective" pulse) and therefore the coupling evolution is refocused. This leads to a superposition of signal with different phases giving rise to signal cancellation in the spectrum. The volume selected by a PRESS sequence, which uses two refocusing pulses, consists of four partial volumes with different phase evolutions, depending on whether none, one or both of the two refocusing pulses are spin-selective (Fig. 6). In a PRESS sequence the signal loss is also determined by the sequence timing, since the spins are inverted twice by the two spatially selective refocusing pulses (8). By adding the signal terms for the four partial volumes, the resulting signal loss can be calculated. This effect termed "anomalous J-modulation" (4) is particularly pronounced for an echo time of 144 ms, when the two superimposed signals from the partial volumes V$_1$ and V$_4$ have a phase difference of 180° and therefore the cancellation is most effective, whereas for an echo time of 288 ms almost no cancellation occurs (Fig. 6).

According to theory, the relative signal loss for lactate due to anomalous J-modulation at TE = 144 ms amounts to

$$\frac{\Delta S}{S} = 2\frac{\Delta \omega_{CS}}{\Delta \omega_{RF}},$$

(1)

where $\Delta \omega_{CS}$ is the chemical shift difference of the coupled nuclei and $\Delta \omega_{RF}$ is the bandwidth of the refocusing pulse. At 3T the chemical shift difference between the methyl and the methine proton is 355 Hz, and the refocusing pulse used in this example...
had a bandwidth of 874 Hz. This predicts a relative signal loss of 81.2 % due to anomalous J-modulation for TE = 144 ms. The theoretical signal loss for single voxel PRESS measurements at TE = 288 ms depends on the position of the two refocusing pulses within the sequence. Usually the PRESS sequence is rendered as asymmetric as possible with the first refocusing pulse being irradiated as soon as possible (at time $\tau_1$) after the excitation pulse. For the standard PRESS sequence implemented on a 3T Philips Intera Scanner theory predicts the following signal loss due to anomalous J-modulation at TE = 288 ms:

$$\frac{\Delta S}{S} = 2 \frac{\Delta \omega_{CS}}{\Delta \omega_{RF}} \left(1 - \frac{\Delta \omega_{CS}}{\Delta \omega_{RF}}\right) \cdot (1 - \cos(\pi \cdot J \cdot 2 \tau_1)) = 6.8\%.$$ (2)

For an SI sequence without PRESS localization, but with a slice-selective refocusing pulse for the echo formation, there are only two interfering partial volumes (corresponding to $V_1$ and $V_4$ in Fig. 6). For TE = 144 ms, this leads to the same relative signal loss as for a single voxel PRESS sequence, whereas no signal loss at all occurs for TE = 288 ms.

To understand the basic behavior of the lactate resonances in a PRESS sequence, it is sufficient to approximate the used pulses as ideal hard pulses. However, pulse imperfections give rise to a far more complicated evolution behavior, which was investigated analytically, simulated numerically and discussed in detail in several publications (9-13). As the chemical shift is proportional to $B_0$ and, due to $B_1$ limitations, the pulse bandwidths are approximately inversely proportional to $B_0$, the chemical shift displacement and also the lactate signal loss due to anomalous J-modulation at TE = 144 ms roughly scale with the square of the field strength.
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REFERENCES


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FIGURE CAPTIONS

Figure 1:

Single voxel spectra acquired at 1.5T from the brain of a patient with a high grade glioma using PRESS localization: a) TE = 144 ms, b) TE = 288 ms.

Figure 2:

Single voxel spectra acquired at 3T from the brain of a patient with a grade III glioma using PRESS localization: a) TE = 144 ms, b) TE = 288 ms.

Figure 3:

Multi-voxel spectra acquired at 1.5 T and 3 T one hour apart from the the same region in the brain of a patient with MELAS using a standard PRESS localization with TE = 144 ms and TE = 288 ms. An inverted lactate doublet is clearly visible at 1.5T, but not at 3T (arrows). Upright lactate peaks at TE = 288 are seen equally well at both field strengths (arrows).

Figure 4:

Proton spectra acquired from a standard brain metabolite phantom containing 5 mM of lactate. The measurements were performed on three 3T MRI scanners from three
different vendors (Philips Medical Systems, GE Health Care and Siemens Medical Solutions). Single Voxel MRS (VOI size = 2x2x2 cm$^3$, PRESS localization) was performed from the same volume once with TE = 144 ms and once with TE = 288 ms. RF pulse bandwidths for the selective refocusing pulses vary between vendors in the range 874 to 2300 Hz.

Figure 5:
Spectra from a spectroscopic imaging dataset acquired at 3 T from a phantom containing 10 mM NAA and 20 mM lactate without PRESS localization: a) TE = 144 ms, with refocusing pulse gradient, b) TE = 144 ms, without refocusing pulse gradient, c) TE = 288 ms, with refocusing pulse gradient, d) TE = 288 ms, without refocusing pulse gradient.

Figure 6:
Partial volumes and their coupling evolution for a single voxel PRESS experiment: The 90° excitation pulse is applied with a gradient in the z direction, whereas the two refocusing pulses are applied with gradients in the x and y direction respectively. The size of the partial volumes is determined by the chemical shift displacement. The signal phase of the magnetization is determined by the echo time (TE), the scalar coupling
constant ($J$) of lactate and the time interval ($t_1$) between the excitation pulse and the first refocusing pulse.
Fig. 1)
Fig. 3)
Fig. 4)

a) TE = 288 ms

b) c)
Fig. 5)
V_1 = \left(1 - \frac{\Delta \omega_{CS}}{\Delta \omega_{RF}}\right)^2 \cdot V

V_2 = V_3 = \frac{\Delta \omega_{CS}}{\Delta \omega_{RF}} \cdot \left(1 - \frac{\Delta \omega_{CS}}{\Delta \omega_{RF}}\right) \cdot V

V_4 = \left(\frac{\Delta \omega_{CS}}{\Delta \omega_{RF}}\right)^2 \cdot V

<table>
<thead>
<tr>
<th>Region</th>
<th>1^\text{st} 180^\circ</th>
<th>2^\text{nd} 180^\circ</th>
<th>Observable Magnetization</th>
</tr>
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<tr>
<td>1</td>
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<td>non-selective</td>
<td>S_1 \sim V_1 \cdot \cos(\pi \cdot J \cdot TE)</td>
</tr>
<tr>
<td>2</td>
<td>non-selective</td>
<td>selective</td>
<td>S_2 \sim V_2 \cdot \cos(\pi \cdot J \cdot 2t_1)</td>
</tr>
<tr>
<td>3</td>
<td>selective</td>
<td>non-selective</td>
<td>S_3 \sim V_3 \cdot \cos(\pi \cdot J \cdot (TE - 2t_1))</td>
</tr>
<tr>
<td>4</td>
<td>selective</td>
<td>selective</td>
<td>S_4 \sim V_4</td>
</tr>
</tbody>
</table>

Fig. 6)