Feasibility of Internally Referenced Brain Temperature Imaging with a Metabolite Signal

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The feasibility of using a metabolite signal as an internal reference for self-referenced temperature distribution measurement was examined. Line scan echo-planar spectroscopic imaging (LSEPSI) was applied to obtain quick multi-voxel spectroscopic measurements and to avoid possible spectral degradation from motion. Temperature distribution in a rabbit brain in vivo was successfully visualized by means of the chemical shift of water, which was measured by using naturally abundant (up to 10 mM) N-acetyl-aspartate (NAA) as the reference signal. Unlike the phase-mapping approach, this technique does not require a pixel-by-pixel subtraction. Therefore, in theory, it is more resistant to inter-scan motion or changes in susceptibility. The spatial and temporal resolutions of this technique are 1.5 cm³ and 4.5 min. A higher signal-to-noise ratio and optimization of the water and outer-volume suppression capabilities will be required to further enhance the temperature-mapping capabilities.

Keywords: temperature, chemical shift, water, line scan echo-planar spectroscopic imaging (LSEPSI), internal reference

Introduction

Following initial feasibility reports,1–5 non-invasive temperature imaging techniques employing the temperature dependence of the water proton chemical shift have rapidly emerged as a practical means of monitoring various kinds of thermal therapies.6–9 Since the standard approach utilizes voxel-by-voxel subtraction of phase images, which are directly related to the water proton resonance frequency, tissue susceptibility changes and inter-scan body motion are inherent and significant sources of error. A spectroscopic technique that also detects a temperature-insensitive proton component as an internal reference from which to measure the water proton chemical shift is a simple and reasonable approach to avoiding these errors. In fact, the internally referenced measurement of temperature has been widely investigated on various samples with the use of spectrometers,1,10,11 single-voxel magnetic resonance spectroscopy (MRS),12,13 and magnetic resonance spectroscopic imaging (MRSI).14,15

With the MRSI method, the internal reference is a spectral component observed along with the water resonance within a voxel. The conventional MRSI approach requires acquisition times that are generally too long for temperature applications. To extend the internal-reference method, a faster method with echo-planar spectroscopic imaging (EPSI)16,17 has been examined to measure liver temperature with lipid used as the internal reference.18
With this approach, however, the spectra can be severely degraded because of motion and field instability occurring during the phase encoding process for the entire duration of acquisition. It therefore seems necessary to examine other fast EPSI methods to determine the feasibility and viability of the internal-reference method.

The line scan echo-planar spectroscopic imaging (LSEPSI) method was adopted to allow for quick multi-voxel spectroscopy and to avoid the spectra degradation that arises due to motion and field instability by eliminating the phase encoding process. To date, tissue lipid has been adopted as the source of the internal reference signal because of its abundance in tissues such as the breast. In this work, a metabolite signal of much smaller content (up to 7 mM) will be considered for imaging temperature. As a specific goal, brain temperature imaging in vivo with the water proton chemical shift measured from NAA (N-acetyl-aspartate) was investigated.

**Materials and Methods**

The LSEPSI sequence is depicted in Fig. 1. The column was selected by $\pi$ and $\pi/2$ pulses with $y$ and $z$ axis gradients simultaneously applied to avoid signal saturation among the columns lying at different $y$ positions as the columns are sequentially sampled. First- and higher-order shimming was carried out manually in a conventional manner over the area covered by the columns.

The two-dimensional spatial distribution of proton spectra was obtained for a 20 mM NAA phantom in a 3.0T MRI (Signa LX 8.3M4, GE Medical Systems, Milwaukee, WI, U.S.A.). Two separate scans, with and without water suppression, were performed to obtain the NAA and water spectra, respectively. Four columns were swept with the following parameters: TR: 2000 ms, TE: 144 ms, number of echoes per train: 256, echo spacing: 1.184 ms (spectral band width, 845 Hz or 6.6 ppm), number of shots per column: 1, number of acquisitions: 32 (for water-suppressed, taking 4 min 16 s) or 1 (for non-water-suppressed, taking 8 s), read-out bandwidth: 32 kHz, spatial matrix along the read-out direction: 32, field of view (FOV): $24 \times 24$ cm$^2$, and column thickness: 10 mm. The phantom was heated to 70°C by a 2.45 GHz microwave. Scans were performed at 16 temperature points during the cooling process. The phantom temperature was monitored by T-type (Copper-Constantan) thermocouples (handmade, 0.1 mm in bare-wire diameter). The resonance frequencies of the NAA and water signals were estimated by means of complex Lorentzian fitting (CLF) software. A single peak Lorentzian curve was fit to each spectral component after an appropriate frequency band was defined around the spectral position. The water proton chemical shift measured from NAA was then converted into a temperature according to the calibration coefficient obtained between the chemical shift and the thermocouple temperature.

To assess the feasibility of the method in vivo, temperature distribution mapping of a rabbit brain under laser heating was performed. The experimental procedures were carried out with the approval of the Institutional Review Board (IRB). An optical fiber fed from an Nd: YAG laser (CW 60, Spectron Laser Systems Ltd., UK) was inserted into the left lobe of the brain of a New Zealand white rabbit (female, 4 kg in weight) under general anesthesia. The brain temperature was monitored on both sides.
of the brain with an optical fiber thermometric system (Model 3100, Luxtron Corp., Santa Clara, CA; Fig. 2). The imaging methods and conditions were identical to those of the phantom experiment, except that the number of acquisitions was 128 and two columns were imaged at 32 locations along each column, taking 8 min 32 s for the water-suppressed spectra.

Results

As Fig. 3 shows, the correlation coefficients between the chemical shift ($\delta_{\text{H}_2\text{O-NAA}}$) and the thermometer temperature ($T$) were quite high for both phantom ($r = 0.999$) and rabbit brain ($r = 0.932$). The regression coefficients were 0.0097 ppm/°C in both samples, which agreed well with results reported in the literature.$^{12,13}$ The calibration result for the phantom was sufficient for making the temperature images shown in Fig. 4. The animal’s condition was stable throughout the heating process. As shown in Fig. 2, three adjacent voxels along one column were interrogated within the brain. Figure 5 shows a typical spectrum for one voxel. Figure 6 shows the temperature elevation distributions over the three voxels. The water proton chemical shifts measured from NAA (i.e., the chemical shift difference between water and NAA) in the three voxels before heating were, from left to right, 2.585 ppm, 2.696 ppm, and 2.661 ppm, respectively, a spread of approximately 0.1 ppm. Figure 2 shows the cross-sectional (axial) view of the rabbit brain slice after fixation by formalin and clearly shows destructive tissue damage from the laser heating.
Fig. 4. Temperature distribution (absolute values) along a column in the NAA phantom.

Fig. 5. LSEPSI spectra at the central voxel in the rabbit brain (voxel ‘‘2’’ in Fig. 2) obtained at 3.0T. (a) The water peak in the non-water-suppressed spectrum and (b) NAA peak in the water-suppressed spectrum are clearly shown.

Fig. 6. The temperature change distribution along the column in the rabbit brain in vivo under laser heating is shown with the corresponding temperature elevation (°C) obtained by the optical thermometer in the central voxel. The time passage (min) after the start of laser heating is shown in brackets.

Discussion

For imaging temperatures with the internal reference technique, it is essential to precisely detect the peak positions of the water and the reference signal. Both in the phantom and in the animal, the NAA signals appeared as sharp peaks in the LSEPSI spectra. In the 20 mM phantom spectra, the signal-to-noise ratio obtained with 32 acquisitions was approximately 10; in the brain, with 128 acquisitions, this ratio was 5. As reported in other literature in which the single-voxel spectroscopy technique\textsuperscript{14,15} was used, the water and NAA peaks were not markedly degraded with heating up to 50°C in either the phantom or animal tissue. Curve fitting was successful for estimating the peak frequency of the NAA resonance in the brain as well as in the phantom.
The correlation of the water-NAA chemical shift with the temperature (Fig. 3) agreed well with the values reported in the literature. The temperature maps shown in Figs. 4 and 6 quite clearly reflected the temperature distributions in the phantom and the animal brain.

These results, together with the single-voxel results reported by others, demonstrate that the water proton chemical shift measured from the small peak of the metabolite obtained within multiple voxels of LSEPSI can be an appropriate indicator of mapping temperature. The correlation between the chemical shift and temperature obtained in the animal brain was, however, with some contingency, because the chemical shift was the average value over the voxel volume (1.5 cm³), which was far larger than the probing volume of the thermometer. Further examinations with multiple temperature probes per voxel may be useful in assessing the true precision of the procedure. It may be necessary to undertake more animal experiments in order to further examine the reproducibility and stability of the proposed method.

The spatial deviation of the absolute values of the water-NAA chemical shift obtained before heating was as great as 0.1 ppm, which is equivalent to a temperature difference of 10°C. Although the reason for this deviation in the chemical shift is not clear, it may be due to a spatial distribution of water and NAA protons, residual water baseline variation from voxel to voxel, and susceptibility within a voxel. This fact implies that the absolute value of the chemical shift can deviate markedly, independent of the temperature. The extent and the factor of this deviation make absolute temperature measurement problematic and are under investigation.

Conclusions

The experimental results shown here demonstrate the feasibility of imaging of temperature change distribution with the internal-reference method and the use of a small metabolite signal. However, the feasibility of absolute temperature imaging has not yet been proven. The following items must be examined as further technical improvements of the method: sampling of more columns per TR to allow for higher temporal resolution to reduce the effect of intra-scan motion artifacts, and investigation of the spatial variation of the chemical shift difference, which we observed and which complicates absolute temperature measurement.

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