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Z-spectrum appearance and interpretation in the presence of fat: influence of acquisition parameters

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Abstract

Purpose—CEST-MRI is increasingly evolving from brain to body applications. One of the known problems in the body imaging is the presence of strong lipid signals. Although their influence on the CEST effect is acknowledged, there was no study focusing on the interplay among echo time (TE), fat fraction (FF) and Z-spectrum. This study strives to address these points, with the emphasis on the application in the breast.

Methods—Z-spectra were simulated at in-phase (IP) and out-of-phase (OP) of the main fat peak at -3.4 ppm with FF varying from 0 to 100%. MTR_{asym} in two ranges centering at the exchanging pool and at 3.5 ppm approximately opposite the non-exchanging fat pool were calculated and were plotted against FF. The results were verified in phantoms and in vivo.

Results—The results demonstrate the combined influence of FF and TE on the Z-spectrum for gradient echo based CEST acquisitions. The influence is straightforward in the IP images, while it is more complicated in the OP images, potentially leading to erroneous CEST contrast.

Conclusion—The study provides a basis for understanding of the origin and appearance of lipid artifacts in CEST imaging and lays the foundations for their efficient removal.

Keywords

CEST; Lipid artifact; IP; OP; Breast imaging; Body imaging

Introduction

Chemical exchange saturation transfer (CEST) is a novel contrast mechanism (1), which is based on the chemical exchange processes between the protons in water and solutes (2–5). CEST can indirectly detect the low concentrated solutes which are not observable with

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conventional MRI (6). Moreover, due to the dependence on exchange rate, CEST is sensitive to the environmental parameters, such as pH and temperature (7–9). Therefore, CEST methodology is a focus of increased research interest and may have a significant clinical impact.

Often, CEST effect is measured using the Magnetization Transfer Ratio Asymmetry (MTR_{asym}) analysis, $MTR_{\text{asym}} = [M_{\text{ZW}}(-\omega_s) - M_{\text{ZW}}(\omega_s)] / M_{\text{Z0}}$, where $M_{\text{ZW}}(-\omega_s)$ and $M_{\text{ZW}}(\omega_s)$ are the signal intensities acquired with the RF irradiation applied at a frequency offset ω_s or $-\omega_s$, and M_{Z0} is the reference signal without the saturation.

Most human applications of CEST focused on the brain, utilizing solute amides resonating at 3.5 ppm, the so-called Amide Proton Transfer (APT) (8,10–12). Recently, promising applications were reported outside the brain, such as in prostate cancer (13), breast cancer (14–17) and renal ailments (18). One of the problems in body imaging is the presence of a large fat signal. Fat appears bright in both T_1 - and T_2 -weighted images, confounding image interpretation (19). The problem is very acute in breast, where fibroglandular tissue and fat are interleaved. The influence and the suppression of fat signals have been investigated long before CEST. However, the influence of fat in CEST imaging is relatively new and underexplored, although its confounding influence is acknowledged (20). ^1H -NMR spectrum of fat displays multiple peaks with the main peak at -3.4 ppm from water (21). As a result, the MTR_{asym} analysis becomes inaccurate in the presence of fat, affecting APT most. Moreover, fat overlaps with the Nuclear Overhauser Enhancement (NOE) (22–25).

Although methods to remove lipid artifacts in CEST imaging were reported (22,26,27), there was no study focusing on the interplay between image acquisition parameters, fat fraction (FF) and the Z-spectrum.

The goal of this paper is to discuss how the fat influences the Z-spectrum taking echo time (TE) into account in the gradient echo based sequences. The interplay is studied in simulations and verified in phantom and in vivo experiments. We predominantly focus on the CEST at 1 ppm, since previous studies indicated that it might be the most sensitive to the malignant alternations in breast (14,17,28–30). However, other offsets, exchange regimes and experimental parameters are briefly addressed. This study demonstrates and explains the abnormal appearance of Z-spectra when fat is present and emphasizes the importance of a correct choice of the imaging parameters. The goals are to help in recognizing lipid artifacts in CEST images, to provide suggestions on the selection of imaging parameters and to build a foundation for the most efficient removal of these artifacts in the future studies.

Methods

Simulation

Simulations (Matlab, The Mathworks, Natick, MA) used a three-pool Bloch-McConnell model including a bulk water pool (subscript w), a solute pool (s) and a fat pool (f). The water and solute pools are in chemical exchange and the solute/water ratio was kept constant. There is no exchange between fat and the other pools. To simulate different intravoxel FF, the pool sizes for water (M_{0w}) and fat (M_{0f}) varied between 0 and 1, with FF

$= M_{0f}/(M_{0w}+M_{0f})$ increasing from 0 to 100% while satisfying $M_{0w}+M_{0f}=1$. Other parameters included $T_{1w} = 1.5$ s, $T_{2w} = 0.8$ s, $M_{0s}/M_{0w} = 0.005$, $T_{1s} = 1$ s, $T_{2s} = 1$ s, $\omega_s = 1$ ppm, $k_{sw} = 100$ Hz, $T_{1f} = 0.8$ s, $T_{2f} = 0.5$ s, $\omega_f = -3.4$ ppm, where $\omega_{s/f}$ is the chemical shift between water and the solute/fat pool, and k_{sw} is the exchange rate from solute to the water pool. A CW pulse with length $t_{sat} = 5$ s and $B_1 \sim 0.97$ μ T was used for all simulations. To study the influence of TE while avoiding the influence of other imaging parameters, the water and fat Z-magnetizations after the saturation pulse were tipped to the XY-plane assuming a perfect 90° pulse. Then, the signal was simulated assuming two conditions: in-phase (IP, 360° phase difference between water and fat) and out-of-phase (OP, 180° phase difference). The simulated MTR_{asym} was averaged in two ranges: 0.8–1.2 ppm centering at the solute pool (hydroxyl- MTR_{asym}) and 3.3–3.7 ppm centering at 3.5 ppm (amide- MTR_{asym} , opposite to fat resonance, to monitor fat influence on the Z-spectra in the absence of an exchanging moiety). Additional simulations were performed to gauge the influence of different solute properties ($\omega_s = 1, 2, 3.5$ and 5.1 ppm in slow, intermediate and fast regime) as well as under different experimental conditions ($B_1 = 0.5$ – 5 μ T and $t_{sat} = 0.5$ – 7.5 s), and the results are presented in the Supporting Information.

Phantom

Three phantoms containing water solutions of exchanging molecules and oil (Vegetable Oil, Crisco) were prepared. Phantom I contained 100 mM choline at pH=5.9 (24°C, no additional buffers). Phantoms II and III contained 194 mM iopamidol (Isovue-370, Bracco Diagnostics Inc.) with the pH adjusted by titration to 7.5 and 6.0 respectively. Since the water solutions and oil are immiscible, an interface between them builds up automatically (Fig. 1).

In vivo study

Three female volunteers without known breast ailments were recruited. The human studies were approved by the local Institutional Review Board (IRB) and performed in accordance with the guidelines.

MRI

All MRI scans were performed on a 3T whole-body scanner (Ingenia, Philips Healthcare). The phantom studies employed a 15-channel head-spine coil at room temperature ($\sim 22^\circ$ C). CEST images were acquired using a 2D single-shot T_1 -weighted turbo field echo (TFE) sequence. Two scans were used to acquire CEST images with different TEs: i) IP at 2.30 ms and ii) OP at 3.45 ms, with the same TFE acquisition inter-pulse delay TR of 5 ms. The saturation pulse train was 4900 ms in length and consisted of 98 hyperbolic secant (HS) pulses, each 50 ms long, flip angle (FA) = 900° and no inter-pulse delay, equivalent to $B_{1,CW} = 1.17$ μ T (31). The total saturation and acquisition length was 5.1 s. Alternated parallel transmission is used to achieve an RF duty cycle of 100% (32). 41 points in the Z-spectrum in the range ± 6 ppm for phantom I or ± 10 ppm for phantoms II and III were acquired. Other imaging parameters were: centric k-space ordering, voxel size 2×2 mm², slice thickness 8 mm and excitation FA = 45° . To obtain an image with varying FF, the image plane was placed oblique at the interface of oil and choline/iopamidol water solution (Fig. 1). Thus, the resulting image had a FF decreasing from 100% down to 0% from left to right (33).

The in vivo study employed a 16-channel bilateral breast coil. CEST images were acquired using the same TFE sequence with the same TEs (IP/OP) and inter-pulse TR as in the phantom study. The saturation pulse train (2 s) consisted of 40 HS pulses. Different saturation length was used in vivo to adhere to the stricter SAR limitations (<90% body) and to utilize shorter T_1 in tissue (less time needed to reach the saturation steady-state). Total saturation and acquisition length was 2.6 s. 33 points in the Z-spectrum in the range ± 6 ppm were acquired. Other imaging parameters were: centric k-space ordering, voxel size 2×2 mm², slice thickness 5 mm and excitation FA = 10°.

In all studies, a separate B_0 mapping sequence (dual echo FE with TE₁/ TE=2.3/2.3 ms for two IP images) immediately followed the CEST imaging, without B_0 re-adjustment between the scans.

Data processing

The data were processed using custom MATLAB codes on a pixel-by-pixel basis. The field inhomogeneity was corrected using the separate B_0 map. The ROIs were placed manually on regions with different FFs to generate ROI-averaged Z-spectra and MTR_{asym}. The exact FF in the experiments was not determined. The ROIs were selected qualitatively based on the position in the image. The IP and OP MTR_{asym} were averaged in different ranges to generate CEST maps: i) 3.3–3.7 ppm for the influence of fat (no exchanging pool present) in all the phantoms; ii) 0.8–1.2 ppm or 4.0–4.4 ppm and 5.3–5.7 ppm for choline or iopamidol, respectively. For the image plane position (Fig. 1) used in the phantom study, increasing row number corresponds to the increasing FF. The MTR_{asym} for each frequency range was averaged row-by-row and plotted against the row number (Fig. 4a).

Results

Simulation

Figure 2 shows the representative simulated IP and OP Z-spectra and MTR_{asym} with different intravoxel FFs. Here both the Z-spectra and MTR_{asym} are normalized to the sum of the water and fat pool sizes. Importantly, in the experiment, the results are normalized by the reference signal, which is also affected by the presence of fat and choice of TE. The influence of fat is further studied in two particular ranges, hydroxyl and amide, using continuously increasing FF (Fig. 3). Here, the MTR_{asym} was normalized to the reference signal (for comparison, normalization by the sum of the pool sizes is shown in Supporting Fig. S1).

As expected, if only water or fat is present, the IP and OP Z-spectra are identical (Fig. 2a vs. f and e vs. j). In-phase the water and fat signals overlap and the IP Z-spectra (Fig. 2a–e, blue line) are straightforward to understand: the water dip shrinks while the fat dip increases as the FF increases. Linear monotonic decrease of both hydroxyl- and amide-MTR_{asym} are observed in Figure 2a–e (red line) and Figure 3a,b.

The OP Z-spectra and MTR_{asym} are more complicated than the IP, since water and fat have a phase difference of $(2n+1)\pi$ ($n \in \mathbb{Z}$). As shown in Figure 2f–j, both water and fat could form ‘dips’ and ‘ascends’ in the Z-spectra depending on the FF. The reference signal approaches

zero as FF approaching 50% (Fig. 2g–i). As a result, close to $W \sim F$ the MTR_{asym} normalized to the reference signal may become a very large positive or negative number, depending on the sign of the MTR_{asym} before normalization. As shown in Figure 3c, the hydroxyl- MTR_{asym} as a function of FF increases at first, indicating that the decrease of the reference signal is faster than the decrease of the hydroxyl- MTR_{asym} before normalization. As FF approaches 50%, the hydroxyl- MTR_{asym} rapidly drops to a large negative value and gradually increases back to approximately zero for $FF > 50\%$. Conversely, the amide- MTR_{asym} increases from 0 to a very large value as FF increases from 0 to 50% and then decreases as FF further increases to 100% (Fig. 3d). The MTR_{asym} normalized to the sum of the water and fat pool sizes (Fig. 2, red line) shows similar trend to the MTR_{asym} normalized to the reference (Fig. 3) except for the decreasing OP hydroxyl- MTR_{asym} at low to mid FF (Supporting Fig. S1).

Additional simulations (Supporting Figs. S2–S9) demonstrate that while the details change, the overall behavior remains consistent with the Figure 3 for a variety of experimental and solute parameters.

Phantom Experiments

Figure 4 and Supporting Figure S8 show the results of the phantom I. The normalized IP and OP Z-spectra and MTR_{asym} were averaged in four ROIs: W only, $W > F$, $W < F$ and F only. The choline peak is relatively far from the direct fat influence, especially at the low power levels used here. Comparing Figure 2 and Supporting Figure S8, the experimental Z-spectra and MTR_{asym} maps display the same trends as the simulation. For the IP case, both the hydroxyl- (Fig. 4b) and amide- (Fig. 4d) MTR_{asym} decrease as FF increases, similar to the simulation (Fig. 3a,b). The hydroxyl- MTR_{asym} decreases from ~15% to ~0% (Fig. 4b) while the amide- MTR_{asym} decreases approximately linearly from 0% to about –45% (Figure. 4d). As shown in Figure 4e–h, the OP MTR_{asym} maps display very large negative or positive values in the middle where $W \sim F$ due to normalization by the reference values close to zero. In the regions $W > F$ and $W < F$, the behavior of both the hydroxyl- and amide- MTR_{asym} (Fig. 4f,h) are also in exact agreement with the trend observed in the simulation (Fig. 3c,d).

Supporting Figures S11–S14 show the results of the phantoms II and III. The 4.2 ppm peak of iopamidol is close to direct influence of fat, while the 5.5 ppm peak is further away and thus is less influenced by fat. Moreover, there are two exchanging pools and exchange-mediated T_2 shortening (34). Despite these differences from the simple model systems above, the IP and OP CEST maps and MTR_{asym} (Supporting Figs. S11–S14) show similar behavior as phantom I and simulations (Figs. 3 and 4).

In vivo study

The representative in vivo IP and OP Z-spectra are shown in Figure 5. The Z-spectra were not normalized. The pixels were chosen on a straight line going from pure fat into pure fibroglandular tissue (Fig. 5k). Comparing Figures 2, 4 and 5, it is evident that the in vivo Z-spectra display exactly the same behavior as was predicted in simulations and phantoms.

Discussion

In the simulations, the MTR_{asym} of the solute is only weakly influenced by fat, because the two pools are relatively far from each other ($|2.4|$ ppm). The linear decrease of IP MTR_{asym} at both frequency ranges (Fig. 3a,b) is due to the monotonic decrease of the relative size of the water pool.

The intensity of the OP Z-spectrum at any frequency can be quantitatively explained by the equation: $\text{intensity} = |\text{Z-Intensity}(\text{water}) - \text{Z-Intensity}(\text{fat})|$. Consider the reference signal: it is equal to the absolute value of fraction difference between water and fat; e.g. resulting in 0.4 in the cases of $W > F$ ($|0.7 - 0.3| = 0.4$) and $W < F$ ($|0.3 - 0.7| = 0.4$) and 0 in the case of $W = F$ ($|0.5 - 0.5| = 0$). The reference signal may become lower than the rest of the Z-spectrum. For example, consider $W > F$ and the saturation is at -3.4 ppm (labeled by in Fig. 2g). Assuming that fat is fully saturated at this frequency while water is unperturbed, the OP Z-spectrum value becomes $|0.7 - 0| = 0.7$ which is larger than the reference signal value of 0.4.

In practice, the reference signal is always nonnegative since magnitude images are used most of the time. Thus, the sign of MTR_{asym} before normalization determines the sign of the MTR_{asym} after normalization by the reference signal. The hydroxyl- MTR_{asym} becomes negative when the water “dip” at 0 ppm in the Z-spectrum changes to an “ascent” due to the increasing FF (Fig. 2f-i). At low FF, the amide- MTR_{asym} is positive because there is an “ascent” at the lipid frequency in the Z-spectrum (Fig. 2g-h); at larger FF, amide- MTR_{asym} becomes negative as Z-spectrum intensities form a “dip” around -3.4 ppm.

The oil used in the phantom study has multiple peaks (35). The main peak is at about -3.4 ppm, followed by the peaks of decreasing sizes at -3.8 ppm and 0.6 ppm. The experimental IP and OP images refer to the main peak of the oil. The other peaks may introduce additional asymmetry of the Z-spectrum as reflected in Supporting Figures S10–S11.

The field inhomogeneity was corrected using the B_0 maps generated by a sequence with two IP echoes. This method may not be as accurate as WASSR (36) in pixels without fat and underperforms in pixels with large FF. However, WASSR is suboptimal for B_0 correction in the images containing pixels with FF in the broad range, from 0 to 100%, since WASSR fails in voxels with little or no water (36).

Saturation parameters and the solute properties influence the Z-spectrum and the MTR_{asym} . However, as the simulations included in the Supporting Information demonstrate, these parameters did not largely alter the overall behavior of the IP and OP MTR_{asym} against FF (Supporting Figs. S2–S7). While these parameters influenced the specific values of the MTR_{asym} , the overall trends (i.e. decreases with FF and singularity areas) remained the same. Thus, the explanation suggested above is largely valid.

Other experimental parameters including T_1 , T_2 , T_2^* , excitation FA, and TR together determine the acquired signal (including the reference) and thus will further influence the Z-spectrum appearance. Moreover, presence of multiple fat peaks or multiple exchanging sites at high concentration may potentially lead to a non-zero reference signal at FF=50% and

smoothing of the singularities. However, the detailed exploration of the influence of these factors is beyond the scope of this note.

Two well-defined acquisition conditions, IP and OP, were investigated here. Other TEs will lead to complicated behavior consisting of a mix of the effects. Moreover, while quantification methods other than MTR_{asym} may be used successfully in IP Z-spectra to eliminated lipid/NOE peak (15), these methods would fail in the OP Z-spectra.

Conclusions

We demonstrate that the TE and FF together determine the appearance of the Z-spectrum for gradient echo based sequences. Phantom and in vivo studies agree with the simulation. Although several lipid artifact removal methods were reported in CEST (3,15–17,37), additional studies are needed to examine the efficiency of various fat removal methods and their influence on the CEST contrast.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Schematic of the phantom and the imaging plane.

Figure 2.

Simulated (a–e) IP and (f–j) OP Z-spectra (blue line) and MTR_{asymp} (red line) with fat fraction of 0% (W), 30% (W>F), 50% (W=F), 70% (W<F) and 100% (F). The Z-spectra were normalized to the sum of the water and fat pool size for display convenience. (* in g and i) mark the “fold-back” of the negative values in the Z-spectra when magnitude is taken. (Δ in g) labels a fat related peak (see text for further discussion).

Figure 3.

The simulated MTR_{asym} averaged in two ranges: 0.8–1.2 ppm (a,c) and 3.3–3.7 ppm (b,d) for IP (a,b) and OP (c,d) respectively. The MTR_{asym} were normalized to the reference signal, which is the sum of the water and fat signals with their relative phase taken into account. Part of the MTR_{asym} (very large negative and positive values due to normalized to a reference signal close to 0) are not shown in (c) and (d) for display convenience.

Figure 4.

The MTR_{asym} maps of choline-oil phantom (Phantom I) were generated by averaging the MTR_{asym} in two frequency ranges: 0.8–1.2 ppm (a,e) and 3.3–3.7 ppm (c,g) for both IP (a,c) and OP (e,g). The MTR_{asym} in each case are then averaged in the middle part of the CEST maps (vertical dashed line in a, omitted in other images) row-by-row (horizontal dashed line in a, omitted in other images) and plotted against the image row number (b,d,f,h). Part of the MTR_{asym} (very large negative and positive values due to normalization to a reference signal close to 0) are not shown in (f) and (h) for display convenience.

Figure 5.

Representative IP (a–e) and OP (f–j) Z-spectra without normalization and B_0 correction for different fat fractions from a healthy volunteer. The Z-spectra were from separate pixels shown as dots in the OP image acquired at $TE = 3.45$ ms (k).