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Characterizing and Eliminating Errors in Enhancement and Subtraction Artifacts in Dynamic Contrast-Enhanced Breast MRI: Chemical Shift Artifact of the Third Kind

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Abstract

Purpose—To characterize errors in enhancement in breast DCE MRI studies as a function of echo time and determine the source of dark band artifacts in clinical subtraction images.

Methods—Computer simulations, oil and water substitute (methylene chloride) as well as an ACR quality control phantom were tested. Routine clinical DCE breast MRI study was bracketed with (accelerated) in-phase DCE acquisitions in 5 patients.

Results—Simulation results demonstrated up to –160% suppression of the expected enhancement caused by differential enhancement of fat and water. 2D gradient-recalled echo (GRE) and fat-suppressed 3D GRE phantom imaging confirmed the simulation results and showed that fat suppression does not eliminate the artifact. In-vivo in-phase DCE images showed increased enhancement consistent with predictions and also confirmed increased spatial blurring on in-phase 3D GRE images. Combined multi-dimensional partial Fourier and parallel imaging provided a time-equivalent in-phase DCE MRI acquisition.

Conclusion—Errors in expected enhancement occur in DCE breast MRI subtraction images due to differential enhancement of fat and water and incomplete fat signal suppression. These errors can lead to artificial suppression of enhancement as well as dark band artifacts on subtraction images. These artifacts can be eliminated with a time-equivalent in-phase fat-suppressed 3D GRE sequence. Understanding chemical shift artifact of the third kind, a unique artifact of artificial enhancement suppression in the presence of intravoxel fat and water signal, will aid DCE breast MRI image interpretation. In-phase acquisitions (combined with simultaneous min TE or opposed-phase echoes) may facilitate qualitative, quantitative and longitudinal analysis of contrast enhancement.

Keywords

Dynamic contrast-enhanced (DCE) MRI; subtraction artifact; chemical shift artifact; paradoxical enhancement; breast MRI; enhancement errors

INTRODUCTION

Breast tissue contains a unique interdigitation of planes of fat and fibroglandular tissue (Fig. 1), leading to voxels with variable concentrations of fat. The American College of Radiology (ACR) requires either chemical shift fat-suppressed dynamic contrast-enhanced (DCE) images or post- from pre- contrast subtraction images in the breast MRI protocol for accreditation(1). Subtraction artifacts reduce the diagnostic utility of these critical sequences. A common cause is patient motion (Fig. 2). However, centers across the country have struggled for years with subtraction artifacts on breast MRI of unknown cause. Most are using short and wide bore scanners, for patient comfort. These unexplained artifacts consist of hypointense bands consistently observed in the subtraction images (Fig. 3), despite the lack of motion between the acquisitions (supporting Fig. S1). The artifacts reduce reader confidence by introducing inhomogeneity and perceived misregistration as well as by confounding enhancement heterogeneity analysis. The artifacts persisted despite attempts over several years at protocol optimization by site physicists and vendor technicians (including using multiple types of fat suppression, e.g. chemical shift selective (CHESS) and spectral attenuated inversion recovery (SPAIR), modifying signal-to-noise ratio (SNR), changing resolution, and switching from sagittal to axial plane imaging). These artifacts could not be explained by well-known chemical shift artifacts(2) of the first kind (fat signal shift in readout direction) or second kind (intravoxel phase cancellation at fat-water interfaces)(3), since they were present on the subtraction images only.

Contrast-enhanced breast MRI is performed with a fat-suppressed 3D gradient-echo (GRE) technique with a minimum echo-time (TE) and pulse repetition time (TR), which minimizes effective transverse relaxation time (T_2^*)-induced signal loss and minimizes total scan time using a Volumetric Interpolated Breath-hold Examination (VIBE) sequence(4). The minimum TE varies based on scanner hardware, resolution and other acquisition parameters but is typically 1.5–2ms, which is close to the opposed-phase condition for fat and water at 1.5T ($TE_{opp}=2.3ms$, $\delta_{fw}=3.4ppm$ (5)) and therefore fat and water are partially opposed (shortest in-phase echo-time at 1.5T is 4.6ms). At 3T, fat and water are opposed-phase at 1.2ms and in-phase at 2.3ms and therefore fat and water are again partially opposed. We hypothesized that these artifacts were related to reduction of signal in voxels containing more fat than water after contrast (Fig. 4). This phenomenon has previously been reported on nonsubtraction images in the opposed-phase condition in abdominal imaging and termed “paradoxical suppression of fat”(6,7). There has been speculation on the potential for a fat containing tumor or a small tumor surrounded by fat to be missed on subtraction of opposed-phase images due to this artifact(7,8).

The purpose of this study was to characterize errors in contrast enhancement at all off-resonance phase angles between fat and fibroglandular tissue (angle between fat and water magnetization vectors; to fully characterize the phenomenon previously reported in the opposed-phase condition) and to determine whether the subtraction artifacts could be removed by imaging with an in-phase time-equivalent sequence. This was preliminarily presented at the ISMRM(9).

METHODS

Computer Simulations

Simulations of voxels containing 0–100% mixtures (1% increments) of fat and water were performed using Matlab (Mathworks, Natick, MA). The lipid magnetization vector was simulated with an off-resonance phase angle of -180° to 180° compared to water magnetization vector in 1.8° steps. 50% enhancement was assumed for the water (i.e. fibroglandular) component and 10% enhancement for fat (values obtained from patient DCE MRI measurements and correspond with previously reported values(6)). Complex addition of fat and water components was performed ($\mathbf{M}=\mathbf{M}_w+\mathbf{M}_f$; a vector addition of the two components as happens physically) before and after contrast enhancement, followed by subtraction of magnitude values [$|\mathbf{M}_{\text{post}}| - |\mathbf{M}_{\text{pre}}|$] (as performed automatically on the scanner for subtraction images). Magnetization relaxation was ignored.

Phantom Experiments

Water and fat are not miscible; therefore, methylene chloride CH_2Cl_2 (Carolina Biological Supply Company, Burlington, NC) was chosen to simulate water due to its similar proton chemical shift ($\delta_{\text{CH}_2\text{Cl}_2}=5.3$ ppm(10) vs. 4.7 for water) and miscibility with oil(11). Due to the different chemical shift from water, fat and methylene chloride are opposed-phase at 1.96ms and in-phase at 3.91ms at 1.5T. Similar to prior work, chromium acetylacetonate (CrAcAc) (Sigma-Aldrich, Milwaukee, WI) served as the doping agent. Safflower oil (LouAna, Brea, CA) was used to simulate adipose fat(12). Four stock solutions were created. Solution 1 was pure safflower oil, simulating breast adipose tissue ($T_1/T_2\sim 330/53\text{ms}$ (13)). Solution 2 contained methylene chloride + 1mM CrAcAc, simulating unenhanced fibroglandular breast tissue ($T_1/T_2\sim 1200/58\text{ms}$ (13)). Solution 3 contained safflower oil + 1.4mM CrAcAc to simulate enhanced adipose tissue. Solution 4 contained methylene chloride + 2.1mM CrAcAc to simulate contrast-enhanced glandular tissue. One set of glass vials were filled with 10 mL liquid total each: 0–10mL from solution 1, in 1mL increments, and 10–0mL in –1mL increments of solution 2 to simulate 0–100% lipid fractions (in 10% increments, 11 vials) prior to enhancement. A second set of vials was prepared similarly with 10 mL total volume using solutions 3 and 4 to simulate 0–100% lipid fractions (in 10% increments) of glandular breast tissue and adipose fat after contrast enhancement. The relaxivity of CrAcAc was calculated to be 0.64/(mMs) based on data from Hillaire, et al.(11). The concentration of CrAcAc was determined using the desired T_1 of fat and fibroglandular tissue provided above and the unenhanced T_1 of safflower oil and methylene chloride measured experimentally. The T_1/T_2 values of the solutions were determined to be: CH_2Cl_2 (5948/3426ms), solution 1 (185/79ms), solution 2 (1226/954ms), solution 3 (89/47ms) and solution 4 (646/527ms). No attempt was made to shorten T_2 of the phantoms mimicking fibroglandular tissue since: the longest TE (6ms) was short compared to T_2 (58ms) the theoretical maximal signal reduction was $1-\exp(-6/58)=10\%$ (5); assuming relatively small change in T_2 before and after contrast, the effect of T_2 relaxation cancels in the % change calculations; finally, the spoiled GRE signal is modulated by T_2^* which is scanner and patient dependent, making achieving a specific value for T_2 less useful.

The vials in a plastic holder, were submerged in a water bath to minimize susceptibility effects, and placed in a single-channel head coil in a 1.5T scanner (Siemens Avanto, Erlangen, Germany). Care was taken to align similar lipid-concentration vials in the receive coil along its longitudinal axis of symmetry and the pre-scan normalize filter was used to minimize receive coil inhomogeneity on the subtraction. The T1 of the solutions were measured using a fit to an exponential in Matlab to spin-echo experiments; TR was varied from 20ms-10s with TE=12.6ms. T2 was calculated using a fit to exponential decay using multi-echo spin-echo sequence (TE=50–1600ms in 32 steps), TR=10,000ms. An initial experiment was performed using a single-slice 2D GRE sequence, varying TE=2.0–6.0ms in steps of 0.2ms, with slice thickness=10mm, TR=8.1ms, 32 averages, matrix=256×256, receiver bandwidth (BW)=675Hz/pixel (px), flip angle (FA)=10°, field-of-view (FOV)=300×300mm. A second experiment was performed using a fat-suppressed 3D VIBE sequence similar to those used clinically, but modified for use with the single-channel coil (generalized autocalibrating partially parallel acquisition (GRAPPA) parallel imaging factor of 2 removed and slices reduced from 196 to 120, assume dominant fat flag turned off). Acquisition parameters included: TE=1.5–5.9ms in steps of 0.2ms, TR=4.5ms (TE=1.5–2.7ms) and then increased every TE thereafter using the minimize TR flag (longest TR=7.67ms for TE=5.9ms), number of phase encoding lines=538, BW=450Hz/px, FA=10°, image matrix=384×384, FOV=320×320mm, slice thickness = 1mm. The default clinical sequence has SPAIR fat suppression(14) and 6/8 partial Fourier (PF) in the partition-encode direction. The data were analyzed using OsiriX Lite (Bernex, Switzerland). A circular region-of-interest was drawn and the mean (magnitude) signal recorded for each vial. Subtraction and % error calculations were performed on the magnitude data, as is done clinically on subtraction DCE images.

To maintain the temporal resolution of the DCE study, the in-phase acquisition was accelerated to compensate for the longer TR. A time-equivalent acquisition was designed with increased PF in both partition and phase-encode dimensions. Prior studies have successfully combined PF in two dimensions(15) as well as PF and parallel imaging(16). It was therefore felt that this acceleration method could be used to reduce acquisition time while not affecting image contrast. Furthermore, SNR calculations revealed the SNR gained by imaging at a longer TR required at the in-phase echo-time matched the SNR lost by increased PF imaging; therefore, there was no SNR penalty.

Additional phantom experiments were performed to investigate high-contrast spatial resolution and low-contrast object detectability using the standard minimum TE/TR clinical VIBE sequence as well as modified versions leading to the time-equivalent in-phase version. The large ACR quality control phantom was used containing standard inserts for these measurements(17). High-contrast spatial resolution was measured by determining the smallest set of holes that could be independently resolved in horizontal and vertical dimensions. For low-contrast detectability, the number of rungs on which all three discs could be seen were counted. Four versions of the sequence were tested: standard clinical SPAIR fat-suppressed VIBE sequence (TE/TR=1.5/4.5ms, PF=6/8 in partition-encode direction only, 50% slice resolution, resolution=0.8×0.8×1mm, GRAPPA=2, acquisition time (T_{acq})=2min 17s), in-phase VIBE sequence (TE/TR=4.8/7.0ms, partition-encode PF=6/8, T_{acq} =3min 19s), in-phase with increased partition-encode PF (TE/TR=4.8/7.0ms,

partition-encode PF=5/8, T_{acq} =2min 59s) and in-phase with increased PF in both phase and partition-encode dimensions (TE/TR=4.8/7.0ms, partition-encode PF=5/8 and phase-encode PF=6/8, T_{acq} =2min 16s). The accelerated in-phase acquisition had 1s improved temporal resolution compared to the standard clinical min TE sequence.

Human Imaging

Clinical DCE MRIs are performed on a short and wide-bore 1.5T scanner (Siemens Espree). This is done to use the same system for MR-guided needle biopsy when needed and for patient comfort. Images were obtained in the sagittal plane for planning of an image-guided biopsy using a fat-suppressed VIBE sequence. Acquisition parameters included: slice thickness=2.5mm, TE=3.8ms, TR=8.4ms, BW=200Hz/px, matrix=384×384, FOV=240×240mm, FA=15°. Subtraction DCE images are computed by the scanner automatically by subtracting magnitude data. Images were analyzed in Matlab by drawing horizontal and vertical profiles through the images to measure translation.

In-vivo testing was performed to assess the ability to improve the image quality of the clinical DCE protocol. The project was reviewed and determined to qualify as Quality Improvement by the University of Pennsylvania's Institutional Review Board. Testing was done on 5 patients undergoing routine clinical breast DCE MRI studies. On all patients, verbal informed consent was obtained prior to the study. In order not to alter the standard DCE clinical images, the routine breast MRI protocol was performed, with the addition of in-phase fat-suppressed 3D GRE acquisitions bracketing (before and after) the standard minimum TE DCE study (the standard DCE study includes one fat-suppressed 3D GRE acquisition before and three acquisitions after intravenous administration of gadolinium contrast agent). For three patients, the only change in the modified bracketing DCE acquisition was changing the TE from the minimum TE to the in-phase echo-time (with a corresponding increase in TR), resulting in a TE=4.8ms and scan time increase of approximately 1.5 minutes for each 3D acquisition (only one in-phase post contrast acquisition was performed to limit additional scan time to ~8 min total for patient comfort). For two patients, the time-equivalent in-phase acquisition was used, having increased PF from 6/8 to 5/8 in partition and from 8/8 (off) to 6/8 in phase-encoding dimensions. In the accelerated in-phase bracketed studies, multiple in-phase post-contrast datasets were acquired while limiting total scan time increase to ~10min. The standard clinical DCE MRI acquisition time for each volumetric study was approximately 2.5min, for the in-phase scan was approximately 4min and for the time-equivalent in-phase acquisition was several seconds shorter than the routine minimum TE study. Due to bracketing the clinical study, there was an increased delay between the pre and post-contrast in-phase images as well as an increased delay between contrast injection and in-phase post-contrast images. The modified in-phase sequence used the in-phase echo-time flag available on the scanner, which used TE=4.8ms at 1.5T (slightly longer than the predicted in-phase echo time of fat and water at 1.5T of 4.6ms, due to B_0 slightly lower than 1.5T). Manual subtraction of magnitude images as well as magnitude profile analysis was performed in Matlab.

RESULTS

Figure 5 shows the simulation results. Fig. 5a shows the simulated total voxel magnitude as a function fat fraction (0–100% fat; and hence 100–0% water). Note phase cancellation for a 50–50 fat-water voxel in the opposed-phase condition. Fig. 5b shows a similar plot after contrast enhancement. The water voxel enhances by 50% and the pure fat voxel by 10%. The phase cancellation now occurs at a higher proportion of fat, since the fat component enhances less than water. Fig. 5c shows the subtraction ($|M_{\text{enhanced}}| - |M_{\text{unenanced}}|$). Enhancement (subtraction) is a linear function of water content while in-phase, but has non-linearity when out of phase. There is negative enhancement (below dotted line) when fat and water are near the opposed-phase condition (i.e. paradoxical enhancement for 160° and 180° curves). Fig. 5d plots the normalized % error in enhancement from in-phase [$100 \cdot (\text{sub}(\phi) - \text{sub}(\phi=0)) / \text{sub}(\phi=0)$]. Changes in enhancement are negative and increase when the fat-water phase angle increases. Enhancement suppression is up to -160% of the expected enhancement. Error increases when there is more fat than water signal. Fig. 5e shows the normalized subtraction error (from in-phase condition), re-plotted as a function of fat-water phase angle. When imaged in-phase there is no error in enhancement, regardless of fat signal; error increases as fat-water phase angle increases. Fig. 5f is a contour plot of subtraction error as a function of both fat signal fraction and fat-water phase angle. There is $<20\%$ error within $\pm 60^\circ$ fat-water phase angle, for all fat signal fractions. The largest errors occur at the opposed-phase condition ($\pm 180^\circ$) with 60% fat signal fraction.

Figure 6 plots the 2D gradient-echo phantom results (without fat suppression). In Fig. 6a, fat has $4\text{--}5\times$ higher signal magnitude than water due its shorter T1. Signal cancellation occurs at a lower oil fraction ($\sim 30\%$) due to the higher lipid signal. Phase cancellation increases as the echo-time approaches the out-of-phase condition ($TE=2.0\text{ms}$). Fig. 6b shows the signal magnitude from vials doped with additional CrAcAc simulating enhanced tissue (note both methylene chloride and fat vials have increased in intensity, as expected). Fig. 6c plots the subtraction of vials ($|M_{\text{enhanced}}| - |M_{\text{unenanced}}|$), which shows near uniform enhancement of the vials regardless of oil content when imaging near the in-phase condition ($TE=3.8$ and 4.0ms). As predicted in simulations, there is enhancement suppression as TE is shortened to the opposed-phase condition ($TE=2.0\text{ms}$), with paradoxical enhancement observed at three echo times ($TE = 2.0, 2.2$ and 2.4ms), the TEs closest to the opposed-phase condition. Fig. 6d shows the % error in subtraction from the in-phase condition. There is enhancement suppression which is a function of echo-time (fat-water phase angle); the maximal reduction occurs at $TE=2.0\text{ms}$ (opposed-phase condition), with 159% enhancement suppression. Fig. 6e plots subtraction error from in-phase as a function of echo time. There is no error in enhancement at the in-phase condition (dotted line, $TE=3.9\text{ms}$) regardless of fat signal, with exponential error increase as phase angle increases to the opposed-phase condition ($TE=2.0$ or 5.9ms , 1st and 2nd opposed-phase conditions, respectively). Fig. 6f shows a contour plot of % error from in-phase. The maximal errors occur at $TE=2.0$ and 6.0ms (opposed-phase conditions) and 40% oil fraction. Substantial reductions in observed enhancement occur over a large range of echo times ($TE=2.0\text{--}3.3\text{ms}$ and $4.5\text{--}6\text{ms}$) and over a large range of fat signal content, including oil fractions as low as 15%. Low ($<10\%$) errors in enhancement occur

from TE=3.5–4.5ms, centered on the in-phase condition (TE = 3.9ms) for all fat signal fractions.

Figure 7 depicts the fat-suppressed 3D GRE phantom results. Fig. 7a shows the signal magnitude from vials simulating unenhanced tissue. The signal from the 100% lipid vial has been reduced due to the applied fat suppression, to below the level of pure methylene chloride vial (e.g. at TE=2.5ms, signal magnitude is 110 vs. 150 for methylene chloride). Compared to the fat unsuppressed experiment, there is ~85% relative fat signal attenuation due to the SPAIR fat suppression; however, the suppressed lipid signal is now ~75% of the methylene chloride signal at this TE. There is increased lipid signal as TE increases, due to obligatory TR increase; demonstrating rapid lipid signal regrowth (e.g. 145% fat signal increase at TE=3.9ms). Voxel signal cancellation occurs at a higher lipid fraction (90%), since the lipid signal has been suppressed. Fig. 7b plots the magnitude of the vials simulating enhanced tissue; both methylene chloride and lipid signals have increased, as expected. Fig. 7c shows the subtraction ($|M_{\text{enhanced}}| - |M_{\text{unenhanced}}|$), again demonstrating reduction in subtraction signal from in-phase condition as a function of TE, with paradoxical enhancement for TE values of 1.9–2.5ms, near the opposed-phase condition (TE=2.0ms). Fig. 7d plots % subtraction error from the in-phase condition; the suppression again increases as TE is shortened and is greater in voxels with more lipid than methylene chloride. The maximal reduction in enhancement is 141%. Fig. 7e plots subtraction error as a function of echo-time. Again, no error is observed regardless of oil fraction near the in-phase condition (TE = 3.9ms, dotted line). Error exponentially increases as TE is shortened or lengthened, thereby increasing the methylene chloride-lipid phase angle. The maximal error or reduction occurs at TE = 2.3ms, near the opposed-phase condition. Fig. 7f shows the contour plot of the normalized error as a function of echo-time and fat signal fraction. There are negligible errors in enhancement near the in-phase condition (TE=3.9ms, dotted line) and substantial errors (>20%) from TE = 1.6–3.5ms and 4.8–6ms). An oil fraction of 40% is required to create >10% errors in enhancement, due to the use of fat-suppression.

Figure 8 depicts DCE MRI images obtained using the standard clinical minimum TE/TR and the modified in-phase acquisitions. The minimum TE/TR images demonstrate high spatial resolution in the nonsubtraction images (Figs. 8a–b); however, there are many areas with little or no enhancement throughout the breast on the subtraction image (Fig. 8c), with areas of signal below the fat enhancement level. These give an impression of dark serpiginous band artifacts throughout the breast, which are better appreciated when scrolling through the 3D volume. There was no motion between pre and post-contrast images as shown in supporting figure S1 (available online). On the in-phase images, there is resolution degradation (spatial blurring) in nonsubtraction images (Figs. 8d–e). There are also subtle linear hypointense structures radiating from nipple to chest wall (arrow in Figs. 8d). In the in-phase subtraction image (Fig. 8f), there are multiple areas of increased enhancement (arrows), most notably in the skin and peripheral right breast as well as both peripherally and centrally in the left breast. Of note, there is a horseshoe shaped enhancing lesion in the posterolateral left breast that appears more uniform on the in-phase images compared to minimum TE image (Fig. 8c).

Figure 9 shows quantitative differences between the minimum TE and in-phase subtraction images (Figs. 8c and 8f). Fig. 9a plots the % difference from minimum TE to in-phase subtraction images (i.e. $100 * [\text{sub}(\text{in-phase}) - \text{sub}(\text{minTE})] / \text{sub}(\text{minTE})$). Note the widespread areas of low-spatial-frequency increase in enhancement in the 100–200% range. Note that the increases are non-uniform throughout each breast and different between the breasts, indicating the difference is not simply due to the slightly longer delay from injection to in-phase image acquisition. There are narrower (high spatial frequency) areas of signal increase/decrease, which may represent edge effects due to the differences in image resolution from the blurring observed in the in-phase acquisition. Comparison profiles drawn through the subtraction images (Figs. 9b–d) show multiple areas of substantial increased signal in the in-phase subtraction compared to minimum TE subtraction images; the increases are non-uniform throughout each breast and different between the breasts, representing true increases in enhancement signal in both breasts in the in-phase acquisition. These are not high spatial frequency, but rather match the spatial extent of enhancement in the minimum TE subtraction profile; therefore, the increased intensity do not represent edge effects but rather true geographic areas of increased breast DCE signal.

Figure 10 depicts horizontal and vertical profiles through the right breast at another slice location in the mid breast (same patient as Figs. 8–9). These profiles show there was no translation of the breast in the imaging plane (circles denote edges of breast) on the non-subtraction images. Despite the lack of motion, there are multiple areas of subtraction signal below zero in the minimum TE subtraction (dotted lines, arrows) that are not present on the in-phase subtraction. These correspond to the dark band artifacts observed in the clinical minimum TE subtraction images, caused by paradoxical contrast enhancement, which have been removed with in-phase imaging.

Images from a time-equivalent in-phase DCE study is provided online (supporting Fig. S2). The resulting images are similar to the less accelerated in-phase data. Specifically, the minimum TE data have high spatial resolution; however, there is less enhancement and more serpiginous dark band artifacts in the subtraction image. In-phase images have decreased spatial resolution as well as subtle linear dark signal representing Cooper's ligaments in the breast. The in-phase subtraction image shows greater enhancement in the skin and breast; and the central serpiginous dark bands have been removed. The field-of-view was changed while optimizing the clinical DCE study at the scanner causing a small mismatch between pre and post contrast in-phase images, corrupting subtraction data from the first two in-phase subtractions; therefore, data from the 3rd post-contrast in-phase DCE study is shown.

Supporting Table S1 (available online) summarizes results of the ACR quality control phantom imaging (images also available online as Supporting Figs. S3–S7). The standard clinical VIBE sequence with imaging time of 2min 17s had a spatial resolution of 1.1mm and a score of 26 on the low-contrast detectability test. Both the in-phase as well as the time-equivalent in-phase VIBE sequences had a high contrast spatial resolution of 1.0mm and low contrast detectability score of 31. Therefore, the modified in-phase sequence performed better on these objective tests, indicating that the loss of spatial resolution observed in-vivo was not related to loss of spatial resolution in the sequence itself (e.g. from acceleration

using multi-dimensional PF combined with parallel imaging and/or reconstruction algorithm errors).

DISCUSSION

Unexplained hypointense band artifacts present on breast DCE MRI subtraction images without motion are caused by increased phase cancellation between fat and fibroglandular tissues after contrast administration when not imaged in-phase and also result in artificial suppression of enhancement in subtraction images. This phenomenon was previously described on non-subtraction images in the abdomen on opposed-phase imaging only. In this paper, this artifact was studied at all out-of-phase conditions and specifically with respect to the effect on subtraction images, with emphasis on breast DCE MRI. Simulation results and phantom experiments confirm enhancement suppression by up to -160%. Therefore, the expected enhancement can be altered anywhere from the expected physiological or full enhancement to null (complete masking of enhancement) and even negative (paradoxical enhancement). The simulation and phantom results have characterized this phenomenon, termed chemical shift artifact of the third kind (as it does not always lead to paradoxical enhancement), over all fat-water phase angles (echo times) and all fat signal concentrations. A time-equivalent in-phase sequence was tested in-vivo, which eliminated this artifact.

Breast MRI is used to screen high risk women for breast cancer(18,19), as a problem solving tool for complex cases screened using mammography and ultrasound, to stage local disease, to assess response to chemotherapy and to differentiate postsurgical changes from cancer recurrence(19,20). Studies are assessed and reported using the Breast Imaging and Reporting Data System (BIRADS). The intensity of contrast enhancement, the enhancement dynamics (persistent, plateau and washout) as well as homogeneity of enhancement are assessed(20).

The amount and pattern of enhancement have diagnostic and prognostic significance. Tumor enhancement is due to angiogenesis as well as tumor grade(21,22) and correlates with lymph node status at surgery and tumor grade at pathology(23). DCE metrics (area under the enhancement curve, enhancement index at 30sec) have a higher hazard ratio for determining disease-free survival and overall survival than both tumor size and pathological grade(24). Higher enhancement ratio (both % increase and post/pre ratio) predicts favorable response to chemotherapy(25). Changes in enhancement can be used to monitor effectiveness of neoadjuvant chemotherapy and predict residual disease(25,26). Enhancement is a surrogate marker for aggressive disease phenotypes (higher tumor grade, estrogen receptor (ER)/progesterone receptor (PR)-, high Ki-67 score)(27–29). Contrast washout correlates with metabolic activity at 18F-fluorodeoxy glucose (FDG)-positron emission tomography (PET) (30) and enhancement of background tissue around a tumor correlates with ipsilateral breast cancer recurrence risk(31,32). Enhancement heterogeneity is a marker of malignancy(33–35). Peak enhancement may correlate with grade of pre-malignant entities such as ductal carcinoma in situ (DCIS)(36). Lesion enhancement is critical for conspicuity and correlates inversely with interpretation time and missed cases(37). More complex spatio-temporal analyses of the pharmacokinetics of contrast uptake during DCE MRI using wavelets has shown that quantitation of intratumoral heterogeneity of the dynamics allows improved prediction of breast cancer recurrence risk(38). Data from multi-site trials have shown that

functional tumor volumes measured using enhancement thresholds from DCE data predict recurrence free survival(39).

Therefore, equally if not more important than the desire to understand and eliminate the subtraction dark band artifacts, is the need to avoid artificially suppressing enhancement in order to accurately detect, judge and quantitate contrast enhancement. There are limitations with the current method of minimizing TE/TR to minimize scan time and T2* effects. For example, the effectiveness and/or method of fat signal suppression may change from scan to scan based on magnetic field homogeneity and shimming, which will lead to variable amount of enhancement suppression. Also, scan parameter choice such as field-of-view, resolution, phase oversampling, scan plane selection, etc. will all affect the minimum achievable TE and therefore the degree of enhancement suppression. Finally, several hardware constraints such as field strength (B_0) as well as gradient strength and slew rate will affect the in-phase condition and minimum TE, respectively. Therefore, these changes will lead to variable levels of enhancement suppression from scan to scan which will impact the perceived enhancement, potentially leading to difficulty or erroneous judgments about the presence of disease or response to treatment. Performing DCE MRI in-phase using the time-equivalent sequence proposed here would eliminate much of this variability, which is important not only for longitudinal analysis of the patient but also for multi-site clinical trials to avoid a potentially confounding variable.

Linear hypointense bands radiating from the nipple to chest wall on in-phase nonsubtraction images are felt to represent Cooper's ligaments or collagen suspensory ligaments of the breast (40). Due to the short T2*, they appear hypointense at the longer TE. The in-phase nonsubtraction images demonstrate spatial resolution degradation (spatial blurring). Other authors (41) documented moderate spatial blurring in 3D GRE abdominal imaging, which was worse in-phase compared to opposed-phase; the authors noted that this artifact is not well documented in the literature. This study corroborates the finding of increased spatial blurring in in-phase imaging; we believe the effect is accentuated here due to the larger difference in echo time between minimum TE to in-phase imaging (e.g. $4.8-1.6\text{ms} = 3.2\text{ms}$) compared to opposed-phase to in-phase imaging ($4.8-2.4\text{ms} = 2.4\text{ms}$). This likely implies that the blurring is T2* dependent and is likely worse in the breast than abdomen due to closer proximity to air-tissue interfaces. ACR quality control phantom experiments showed the modified in-phase sequence had improved high-contrast spatial resolution and low-contrast detectability. Therefore, the spatial blurring is due to T2* blurring of breast in-vivo in the clinical Espree (short and wide bore) scanner at the longer TE, as opposed to a problem with the image acquisition or reconstruction (as was confirmed on in-phase non-accelerated imaging). At 3T, the in-phase condition occurs at a shorter TE (2.3ms) and may reduce the T2* blurring effect, as might scanning in a magnet with higher magnetic field homogeneity and/or with improved shimming. As was shown in (41) there is significantly less blurring using 2D instead of 3D GRE images, which could be used. It is important to note that while the nonsubtraction images are referenced during image interpretation, the subtraction images are the key images due to the subtlety of the changes on the nonsubtraction images. Therefore, having improved contrast enhancement on the subtraction may outweigh some loss of resolution on nonsubtraction images. Furthermore, high-resolution volumetric T2-weighted images ($1.0 \times 1.0 \times 3.0\text{mm}$ STIR) are acquired during

the standard clinical DCE exam, mitigating loss of spatial resolution on the nonsubtraction T1-weighted images. Some spatial blurring in the nonsubtraction DCE images also protects against motion-induced dark band artifacts in the subtraction images, which are frequently observed clinically and have proven challenging to eliminate.

The in-phase acquisition acquired a single echo centered at the in-phase echo time ($TE=4.8\text{ms}$ at 1.5T). Without any increase in scan time, a second earlier echo could be obtained at the minimum TE in order to provide the high resolution T1-weighted images to use in conjunction with the in-phase subtraction, thereby eliminating the spatial resolution degradation on in-phase non-subtraction images. Alternatively, a second echo could be centered on the opposed-phase echo time ($TE=2.4\text{ms}$) in order to obtain two-point Dixon data, which would also allow fat and water signal to be separated. This study may provide further rationale for performing Dixon/IDEAL fat-water decomposition in the breast.

Gradient-echo T1-weighted pre and post-contrast imaging is performed routinely in all subspecialties of clinical radiology. It is important to understand the chemical shift artifact of the third kind, as there are significant clinical implications for contrast-enhanced imaging of any structure or tumor that is composed of or juxtaposed with fat and non-fatty tissues (whose presence is often unknown prior to imaging).

Conclusion

Currently, clinical contrast-enhanced imaging is performed with minimum TE/TR in order to minimize scan time and T2* effects. However, this can create significant limitations regarding suppression of contrast enhancement (up to -160%) in voxels containing a mixture of fat and water signal. Here we document resulting dark band artifacts in clinical subtraction breast DCE MRI, which interfere with interpretation of images and show the elimination with a time-equivalent in-phase sequence. In order to eliminate both the subtraction artifact as well as errors and variability in contrast enhancement, consideration should be given to performing gradient-echo contrast enhanced imaging in-phase.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Breast anatomy in a 65-year-old woman. (a) Standard craniocaudal (CC) view of the left breast in a mammogram demonstrating scattered fibroglandular tissue (25–50% of breast is fibroglandular tissue). The higher attenuating tissue is fibroglandular and the lower attenuation tissue is fat. Vertically oriented thin curvilinear hyperattenuating structure in the midbreast (*) is a blood vessel. (b) Breast ultrasound obtained in the same patient with a 13 MHz linear transducer. The skin surface is oriented superiorly and the chest wall is inferior (3.5cm depth). The hyperechoic material at mid depth is fibroglandular tissue and the isoechoic material surrounding and interdigitating is fat tissue. There is a complex structural mixture of fat and fibroglandular tissue in the breast, unique in the body, with many fat-water interfaces and voxels containing varying concentrations of fat.

Figure 2.

Motion-induced subtraction artifacts in clinical DCE Breast MRI. Images obtained in the sagittal plane at 1.5T (TE/TR=3.8ms/8.4ms) in a 51-year-old patient: (a) Unenhanced and (b) contrast-enhanced fat-suppressed T1-weighted VIBE images, (c) standard (unsigned integer) subtraction image. White arrows denote motion induced subtraction artifacts. The images have been overlaid on a grid for profile analysis. (d) Horizontal profiles at the level of the nipple and (e) vertical profiles through the anterior breast: upper solid and dashed profiles are before and after contrast, respectively; lower solid and dotted lines depict the unsigned integer and real subtraction profiles, respectively. Note there has been horizontal translation and vertical deformation of the breast (circles) resulting in the dark/negative subtraction artifacts (black arrows). The profile axis labels correspond to the grid locations in the images.

Figure 3.

Hypointense subtraction artifacts in standard clinical DCE MR images without motion. Fat-suppressed 3D T1 weighted VIBE images acquired in the axial plane in a 35-year-old woman (a) before and (b) after intravenous contrast administration (minimum TE/TR = 1.6ms/4.1ms); (c) resulting unsigned integer subtraction image. Note the hypointense artifacts with signal level below the suppressed fat in the subtraction image (white arrows). Profiles drawn through the breasts confirm no bulk motion, available online as supplementary figure S1.

Figure 4.

Paradoxical contrast enhancement. Schematic depicting water, fat and total voxel signal in the opposed-phase condition for a voxel containing 75% fat and 25% water before and after contrast administration as well as the subtraction of voxel magnitudes. 50% enhancement of fibroglandular tissue and 10% enhancement of fat signal have been depicted. Before contrast, there is partial phase cancellation of fat and water signals (chemical shift artifact of second kind, intravoxel phase cancellation). After contrast administration there is a larger increase in water signal than fat due to its greater perfusion resulting in increased phase cancellation of the fat and water signals. The overall voxel signal is reduced and the subtraction is negative (star).

Figure 5.

Simulation results. Total voxel signal for fat fractions from 0–100%, each line represents a different fat-water phase angle (legend, degrees). Voxel signal is calculated (a) before and (b) after contrast administration and (c) shows the subtraction of magnitude values. (d) Subtraction % error from the in-phase case. (e) % error in enhancement plotted as a function of the fat-water phase angle (Φ_{fw}), with each curve representing a different fat fraction (FF, provided in the legend). (f) Contour plot of the % normalized subtraction error in enhancement as a function of both voxel fat fraction and fat-water phase angle.

Figure 6.

2D GRE phantom results. Signal in each vial plotted as a function of lipid fraction; each curve represents a different echo time (provided in legend) for (a) vials simulating unenhanced breast tissue, (b) vials doped with additional CrAcAc simulating enhancement and (c) the subtraction ($|M_{enhanced}| - |M_{unenanced}|$). Subtraction signal below the dotted line represents paradoxical enhancement. (d) Subtraction % error in enhancement from the in-phase condition $100 \cdot [\text{Sub}(\text{TE}) - \text{Sub}(\text{TE}=4\text{ms})] / \text{Sub}(\text{TE}=4\text{ms})$ plotted as a function of lipid fraction, each curve representing a different TE. (e) Subtraction % error from in-phase plotted a function of echo time, each curve representing a different oil fraction (provided in the legend, FF). (f) Contour plot characterizing the subtraction % normalized error from in-phase as a function of both TE and oil fraction. Vertical dotted line denotes the in-phase condition for oil and methylene chloride at 1.5T (TE=3.9ms).

Figure 7.

Fat-suppressed 3D VIBE phantom results. Signal from each vial plotted as a function of oil fraction for (a) vials simulating unenhanced breast tissue, each curve represents a difference echo time (provided in the legend). (b) Signal from vials with additional CrAcAc simulating enhanced breast tissue and (c) subtraction ($|M_{\text{enhanced}}| - |M_{\text{unenhanced}}|$) result; subtraction signal below the dashed line represents paradoxical enhancement. (d) Subtraction signal % error from in-phase condition plotted as a function of oil fraction, each curve again represents a different echo time. (e) Subtraction errors from in-phase plotted now as a function of echo time, each curve now represents a different oil fraction (provided in the legend, FF). (f) Contour plot characterizing % normalized subtraction error from in-phase as a function of echo time and oil fraction. The vertical dotted lines represent the in-phase condition for oil and methylene chloride at 1.5T (TE=3.9ms).

Figure 8.

Comparison in-vivo breast DCE MRI images in 44-year-old patient. Left column are clinical DCE images obtained with minimum TE/TR (1.7ms/4.1ms, T_{acq} =2min:19s) and right column were obtained using a in-phase VIBE sequence (TE/TR = 4.8ms/7.2ms, T_{acq} =3min:47s) that bracketed the clinical exam. Routine clinical sequence (a) before, (b) 4.6 minutes after intravenous contrast administration (3rd post) and (c) subtraction ($|M_{enhanced}| - |M_{unenanced}|$). (d–f) represent images at the same slice position obtained using the in-phase VIBE sequence, (d) before contrast, (e) 4th post contrast scan (7.0min delay after injection) and (f) the in-phase subtraction (9.3 minutes between in-phase pre and 4th post). Closed arrows depict Cooper's ligament that is hypointense at the longer echo time. Note the areas of increased enhancement (arrows) in the in-phase subtraction image (f) compared to minimum TE subtraction (c).

Figure 9.

Analysis of magnitude differences in subtraction images obtained using minTE and in-phase techniques. (a) % difference map between in-phase (IP) and minimum TE (minTE) subtraction images ($100 \times [\text{sub}(\text{IP}) - \text{sub}(\text{minTE})] / \text{sub}(\text{minTE})$), images provided in figure 8. (b) Horizontal profiles through both subtraction images in the anterior breasts, circles denote areas of increased enhancement in the in-phase technique in the medial right breast and mid left breast. (c) Vertical profiles through the medial right breast in the subtraction images, showing substantial increases in enhancement in the skin and peripheral breast tissue (arrows). (d) Vertical profiles through the mid left breast subtraction images, showing increased enhancement in the posterior left breast, corresponding to the horseshoe lesion in figure 8f.

Figure 10.

(a) Horizontal and (b) vertical profiles through the minimum TE (min TE) as well as (c–d) in-phase DCE images, obtained at a different location in the mid breast in the same patient as figures 8 and 9. Note the good alignment of the breast edges (circled for comparison) before (pre) and after (post) contrast administration, indicating there has been no bulk translation of the breast during either acquisition period. The unsigned integer (csup U) as well as real (csup R) subtraction profiles are plotted with a -300 offset for clarity. Note the areas of real subtraction signal below the offset (dotted lines, arrows) denoting paradoxical enhancement present on the minimum TE subtractions, which are not present on the in-phase subtractions.