Published in final edited form as:

J Magn Reson Imaging. 2014 July ; 40(1): 119–125. doi:10.1002/jmri.24340.

Left Atrial Late Gadolinium Enhancement with Water-Fat Separation: the Importance of Phase-encoding Order

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Abstract

Purpose—To compare two late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) methods: a Dixon LGE sequence with sequential phase-encoding order, reconstructed using water-fat separation, and standard fat-saturated LGE.

Materials and Methods—We have implemented a dual-echo Dixon LGE method for reconstructing water-only images, and compared it to fat-saturated LGE in twelve patients prior to their first pulmonary vein isolation (PVI) procedure. Images were analyzed for quality and fat-suppression. Regions of the left atrium were evaluated by a blinded observer (1=prominent enhancement, 0=mild or absent enhancement) on two sets of images (fat-saturated and water-only LGE), and agreement was assessed.

Results—Water-only LGE showed a trend toward better fat-suppression ($p=0.06$), with a significantly more homogeneous blood pool signal and reduced inflow artifacts (both $p<0.01$). Agreement between fat-saturated LGE and water-only methods was found in 84% of regions, significantly correlated by chi-squared test ($p<0.001$). The kappa value was 0.52 (moderate). The average number of enhancing segments was higher for fat-saturated LGE than water-only LGE (4.2 ± 2.7 vs. 3.2 ± 2.9 , $p=0.03$).

Conclusion—The two-point Dixon LGE technique reduces artifacts due to a centric k-space order. A similar enhancement pattern was observed irrespective of the LGE technique, with more enhancement detected by fat-saturated LGE.

Keywords

Late gadolinium enhancement; Dixon; atrial fibrillation; delayed enhancement; pulmonary vein isolation; fat-water separation; left atrium

INTRODUCTION

Left atrial (LA) scar imaging using late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) is important for the assessment of post-ablation therapy and pre-ablation arrhythmic substrate (1,2). Detection of scarring and fibrosis in the LA is challenging compared to left ventricular (LV) scar imaging (3,4), due to the thin LA wall (2–3mm), ubiquitous fat, and limited spatial resolution of the 3D navigator-gated (NAV) inversion recovery method. Pre-ablation LA remodeling is especially challenging for CMR imaging, because it is less intense than post-ablation scarring, representing a fibrosis only partially replacing the LA myocardium (5), and the enhancement is not yet histologically validated. Characterizing the LA myocardium ideally requires a sequence with high spatial resolution, good fat-suppression and cardiac and respiratory compensation, and excellent contrast based solely on T1 is preferred.

The LA is surrounded by fat (6), and fat-suppression is considered essential to reduce spurious enhancement and visualize LGE enhancement. MR fat suppression methods (7) include chemically selective fat suppression pulses, spatial-spectral pulses (water excitation); short inversion time (TI) inversion recovery (STIR) imaging and chemical shift based water-fat separation methods (8,9). Reported LGE pulse sequences attempt to suppress the fat surrounding the LA by employing fat selective saturation prepulses. This strategy requires centric phase-encoding ordering due to the significant regrowth of fat signal during the data acquisition window. This method is versatile and fast, but is sensitive to B0 and B1 inhomogeneities. More importantly, within a 100–200 ms acquisition window used in cardiac applications, fat signal regrowth causes imperfect suppression. Potentially most deleterious of all, the centric phase-encoding order required for fat-suppression causes high pass filtering of k-space (10) (11) (12), resulting in edge enhancement and a mottled blood pool appearance.

Finally, another disadvantage of combined chemical fat suppression and centric phase-encode ordering are inflow artifacts in the right pulmonary veins (13,14). For inversion recovery gradient echo, a NAV-restore (15) pulse is needed to re-invert the diaphragm, so that the diaphragm is not nulled at the time of NAV-gating, typically just before the acquisition segment. The NAV-restore generates inflow artifacts due to uninverted pulmonary vein blood. For centric encoding, these inflow artifacts are very bright, because the inflowing blood experiences very little saturation by RF pulses before acquisition of the center of k-space.

Image artifacts due to incomplete fat-suppression, filtering of k-space, and NAV inflow artifacts may create misleading LA enhancement which might be misidentified as scar, or reduce the confidence to identify true scar. Therefore, we have developed a high resolution water-fat separation LGE technique which permits sequential view-ordering. In this proof-

of-concept study, a high spatial resolution LGE method, similar to 2D LGE methods proposed for imaging LV scar (16) (17) and 3D LGE methods applied to pericarditis (18), was investigated for assessing the LA and pulmonary veins (PVs) in patients with atrial fibrillation (AF), using the dual-echo two-point Dixon LGE approach. We hypothesized that sequentially phase-encoded water-only LGE will provide images with reduced edge enhancement, better fat-suppression, and less mottled blood pool. We compared two LGE CMR methods, a Dixon LGE sequence with sequential phase-encoding order, reconstructed using water-fat separation and standard fat-saturated LGE, with respect to image quality and the LGE enhancement pattern.

METHODS

A phantom study was conducted with gadolinium doped water bottles (at T1s of 400ms, 300ms, and 250ms, representing myocardium, blood and scar respectively) and an oil phantom, using the conventional LGE sequence (described below), with sequential and centric k-space ordering. The line profiles in the phase-encoding direction were compared.

Twelve AF subjects (4 female, 59.8 ± 6.6 years) referred to our center for assessment of PV anatomy prior to undergoing their first PV isolation (PVI) procedure were prospectively recruited for this study. Written informed consent was obtained from the subjects and the study protocol was approved by our Institutional Review Board,. All scanning was performed on a commercial 1.5T MRI system (Achieva, Philips Healthcare, Best, the Netherlands), using a five-channel cardiac phased array coil.

LGE Sequences

For each subject, two free-breathing, ECG-triggered, 3D LGE acquisitions were obtained, 15–25 minutes after injection of 0.2mmol/kg Gd-DTPA (Magnevist, Bayer Healthcare, Wayne, NJ, USA). A Look-Locker sequence, performed prior to each LGE acquisition, was used to identify the best TI for nulling LV myocardium (19). Both sequences were 3D inversion recovery gradient echo (1RR between inversions) acquired axially to cover the entire left atrium, with phase-encoding direction right-left. For both LGE scans, the respiratory NAV was placed over the dome of the right hemi-diaphragm, with the NAV performed just prior to data acquisition, using a 5 mm acceptance window and no tracking, a 30 mm diameter cylindrical excitation, with a 36 mm diameter NAV-restore excitation. Parallel imaging was not used.

Conventional Fat-saturated LGE

The first LGE method was a previously described high spatial resolution 3D LGE sequence (2). Sequence parameters were: TR/TE/ θ =5.2ms/2.5ms/25°, a centric ky-order with a 146 ms window (28 TRs), 0.70 pixel water-fat shift, 400 × 320 mm FOV, matrix 286 × 228, spatial resolution $1.4 \times 1.4 \times 4$ mm³, and zero-filled to $0.625 \times 0.625 \times 2$ mm³. A chemically selective fat saturation preparation pulse (flip angle 110°--chosen to increase fat-nulling at the time of central k-space acquisition—which occurs about 10ms after the fat-saturation pulse, RF pulse 7.6 ms duration) was used to minimize the signal from pericardial fat. Fat-saturated LGE images were exported from the scanner.

Water-only LGE

Following the fat-saturated 3D LGE acquisition, a 3D inversion recovery gradient echo two-point Dixon LGE sequence was used. Sequence parameters were: TR/TE1/ TE/θ=6.3ms/2.3ms/2.3ms/25°, bipolar dual echo readout (without flyback), sequential ky-order with 176ms window (28 TRs), 0.28 pixel water-fat shift, 340 mm FOV, matrix 228 × 240, spatial resolution of 1.5 × 1.4 × 4 mm³, zero-filled to 0.625 × 0.625 × 2 mm³. Bipolar readouts were used, because for the spatial resolution required, a TE of 2.3 between echoes could not be achieved in conjunction with flyback. The high bandwidth (low water-fat shift) used was also necessary to achieve a 2.3 ms TE, and resulted in mitigation of any chemical shift artifacts in the echo images.

Water-fat Separation Image Reconstruction

The water-fat image separation reconstruction was performed off-line in Matlab, using a customized reconstruction (Mathworks, Natick, MA). The dual echo images with water and fat opposed-phase and in-phase, were combined algebraically after phase correction to reveal water-only and fat-only images, based on previously published methods (20), (21), as described in Figure 1. Briefly, the acquired data were Fourier-transformed into image space, generating two images, I_1 (TE=2.3ms, opposed phase), and I_0 (TE=4.6ms, in-phase) (Figure 1A):

$$I_1 = (W - F)e^{i(\phi_o - \phi)} \quad I_0 = (W + F)e^{i\phi_o} \quad \text{Eq. 1}$$

where W represents the water image, and F represents the fat image. The phases, ϕ and ϕ_o , represent the phase accrual due to off-resonance, gradient delays, and coil sensitivities etc. The phase ϕ_o is easily calculated as $\exp(i\phi_o) = I_0/|I_0|$ (Figure 1C). It is removed, from I_1 and I_0 , revealing a phase ϕ (Figure 1D).

$$I'_0 = I_0 e^{-i\phi_o} = (W + F) \quad I'_1 = I_1 e^{-i\phi_o} = (W - F)e^{-i\phi} = (W - F)e^{-i(\text{err} \cdot x + \phi_{\text{cor}})} \quad \text{Eq. 2}$$

The phase ϕ must still be removed, in order to generate fat and water only images, and cannot be calculated as above, unless it is known whether the pixel is fat or water dominated (i.e. the sign of $W-F$). First a correction was performed in which the linear phase error term due to gradient delays present in bipolar imaging is calculated and removed (Figure 1E), as described by Ma et al. i.e. $\phi = \text{err} \cdot x + \phi_{\text{Cor}}$ (20), and finally, the phase term ϕ_{Cor} , corrected for whether the pixel is dominated by water or fat (Figure 1G) is obtained using a region-growing algorithm (21), starting from a seed point placed in fat (Figure 1F).

Image Analysis

Analyses were performed using NIH ImageJ (v1.46r, NIH, Bethesda, MD). A single experienced blinded observer evaluated all images. Image quality was graded on a four point scale (0=poor 1=fair, 2=good, 3=excellent). Inflow artifacts and extent of blood pool mottling were graded on a 3 point scale (0=none, 1=mild, 2=prominent). Average fat signal intensity (measured around the right coronary artery ostium), blood signal intensity

(measured in the LA near the mitral valve) and a LA wall region that was visually enhanced (measured in a representative segment of the LA with LGE) were measured in each dataset. The contrast ratios (fat/blood and enhanced wall/blood) were calculated. LGE enhancement of the LA and pulmonary vein walls was visually determined and recorded using an 18 segment model: LA wall segments included the posterior wall, and inter-atrial septum; the four pulmonary veins (right inferior, right superior, left inferior and left superior) were each subdivided into 4 circumferential quadrants: superior, inferior, posterior, and anterior walls (Figure 2). For each patient, the number of enhancing segments was calculated, and compared using a two-sided paired student's t-test. Additionally, regions outside of the LA, including the aortic valve, mitral valve and the aorta, were assessed.

Intra-observer reproducibility was assessed by evaluating all images approximately 3 months later with results compared by Cohen's kappa, by a reader (DCP) with >5 years experience.

Statistical Analysis

Measured variables were analyzed for differences between methods. The relationship between in LGE enhancement was compared between methods on a segment basis using Pearson's chi-squared test. Cohen's kappa was also calculated. Qualitative measures of image quality were compared using the Wilcoxon sign rank test. Signal intensity contrast ratios were compared using the Student's paired t-test. A two-tailed p-value of <0.05 was considered to indicate significance. All statistical analyses were performed in Excel (Microsoft, Seattle, WA) or Stata IC 10 (College Station, PA).

RESULTS

Phantom Study

Figure 3 presents a phantom study, comparing the 3D LGE sequence with centric order, including fat-sat, to the identical sequence with sequential order (and no fat-sat). Bottles with T1s representative of blood, myocardium and scar were imaged. The TI (250 ms for centric, 275 ms for linear) was chosen to null the T1=400ms sample. A profile in the phase-encoding direction shows that there is edge-enhancement present, with a peak signal ratio of 1.4 (peak to mean signal) for the centric acquisition, while sequentially ordered LGE sequence has no edge-enhancement, indicating that it is a feature of the acquisition order.

Image quality

Overall image quality was not different between the fat-saturated and water-only LGE; with both methods images scoring 2.2 ± 0.7 , with 3=excellent. The ratio of fat to blood was 0.59 ± 0.25 for fat-saturated LGE vs. 0.42 ± 0.09 ($p=0.06$) for water-only LGE. The ratio of enhanced wall to blood was 1.5 ± 0.3 vs. 1.5 ± 0.5 for fat-saturated and water-only LGE, respectively. Average inflow artifact score was 0.8 ± 0.7 vs. 0.2 ± 0.4 ($p=0.009$), for fat-saturated and water-only LGE, respectively (0–2,3=prominent). Average blood pool inhomogeneity score was 1.25 ± 0.8 vs. 0.08 ± 0.3 ($p=0.004$), respectively. Less inflow artifacts and less blood pool signal mottling were observed on Dixon LGE with sequential acquisition order, with a trend towards better fat-suppression. Figures 2 and 4 illustrate these findings.

LA Enhancement Agreement between water-only LGE and Fat-saturated LGE

Agreement between water-only LGE and fat-saturated LGE images for all PV quadrants, the LA posterior wall and inter-atrial septum was investigated (Table 1). Agreement between fat-saturated and water-only LGE was found in 84% of regions. The enhancement on water-only LGE was significantly correlated with the enhancement on fat-saturated LGE by chi-squared test ($\chi^2(1) = 59.48$, $N = 216$, $p < 0.001$). Cohen's kappa was 0.52 (moderate agreement). Figure 2 and 4 compare the conventional fat-saturated LA LGE to the water-only LGE images. Figure 2E,F demonstrate that the left atrium is covered in fat. Fat-saturated 3D LGE found prominent scar in 23% of regions, while water-only LGE found 18% of regions prominently enhanced. Examples images with segments in agreement and disagreement are shown in Figure 4. Both methods represent a similar pattern of enhancement within each region (Figure 5A), with predominant enhancement of the LIPV and LA posterior wall. The total number of enhanced regions (with a maximum of 18) for each patient, obtained by water-only and Fat-saturated LGE methods, were linearly correlated ($R=0.87$) (Figure 5B). The average number of enhancing segments was higher for fat-saturated LGE than water-only LGE (4.2 ± 2.7 vs. 3.2 ± 2.9 , $p=0.03$). Of the 34 discordant segments, 23 showed enhancement on Fat-sat LGE not apparent on water-only LGE. Agreement on enhancement was 81% for left PVs, and 88% for right PVs ($p=0.09$). Intraobserver reproducibility for LGE Dixon showed agreement of 79% between repeat observations, with a kappa of 0.57 (moderate). For fat-saturated LGE, the agreement was 84%, with a kappa of 0.69 (substantial).

Agreement in Aortic Wall and Mitral and Aortic Valve Leaflets

The overall aortic wall enhancement pattern was graded as in agreement in 10/12 patients, with half of patients having prominent aortic enhancement by fat-saturated LGE. By fat-saturated LGE, 3/12 patients had prominent aortic valve enhancement, and 6/12 had prominent mitral valve enhancement. We found agreement about prominent enhancement in 7/12 aortic leaflets, and 8/12 mitral leaflets (62% total agreement).

DISCUSSION

We report an implementation of a water-fat separated two-point Dixon LGE method for LA wall imaging. The technique employed a slight increase in TR, which was accommodated in our protocol by increasing the acquisition window by 20%. The two-point Dixon LGE technique permits linear phase-encoding order and excellent fat-saturation, thereby removing artifacts produced by imperfect fat-saturation, and artifacts and edge enhancement due to the centric phase-encoding order.

Comparison of the two-point Dixon LGE and the fat-saturated LGE showed significantly correlated pattern of regional enhancement, aortic enhancement, and a linear correlation of number of enhancing regions per patient, based on a blinded subjective scoring of both techniques (Figure 5B). While there was less enhancement observed in water-only Dixon LGE, agreement was found in 84% of regions.

However, water-only LGE images failed to detect 48% of regions enhancing by fat-saturated LGE. This indicates that some LA wall enhancement is “real”, but other enhancement may be the result of artifacts. This has two possible interpretations: either the fat-saturated LGE overestimates LGE enhancement because of edge-enhancement due to strong weighting of high spatial frequencies; or Dixon LGE underestimates the LGE enhancement due to a reduced contrast afforded by a linear order. Our phantom study, showing an edge-enhancement effect with a maximum signal ratio (“scar” to “blood”) of 1.4, indicates that centrally-ordered LGE may generate some artifactual enhancement, since the signal ratio of visually enhanced wall to blood in patients was measured at 1.5. Other causes for disagreement are observer-error, and differences in delay post-injection, motion-compensation, inflow artifacts and myocardial nulling.

Reduced inflow-artifact and blood pool signal heterogeneity

The water-only images had reduced artifacts. The improvement in the mottled appearance of the blood pool is likely due to a smooth sequential phase-encode order used in Dixon LGE. Inflow artifact was significantly decreased by the use of the sequential phase-encoding order, as was blood pool signal heterogeneity (mottling). Since the NAV-gating methods were identical, we hypothesize that the suppression of in-flowing blood signal may be due to radiofrequency pulse saturation experienced by the inflowing blood before the acquisition of central k-space in the sequential phase-encode ordering technique. However, greater flow-artifacts on conventional LGE in the right PVs did not contribute greatly to discordance of the technique, since there was a trend towards greater agreement of the two techniques in the right PVs vs. the left PVs.

The reasons for prevalent and reproducible (among two methods) LA wall and aortic enhancement found in our study of pre-PVI patients are not known. LA wall enhancement is hypothesized to be the arrhythmic substrate of AF (1,22,23). The causes of aortic enhancement are beyond the scope of this study but might reflect an increased extra-cellular volume in the normal or remodeled aorta. The agreement in enhancement with different techniques suggests that the aortic enhancement is likely real. The mitral and aortic leaflets often enhance on high spatial resolution LGE—as they are partially composed of fibrous tissue (24). Therefore, the aortic and mitral leaflet enhancement was prevalent.

There are several limitations to our study. The true enhancement pattern is not known to serve as a reference standard. The imaging methods necessarily differed, including an acquisition window that was 30 ms longer with Dixon LGE, potentially causing some blurring, and a higher bandwidth for Dixon LGE, increasing noise. Also, the order of fat-saturated and Dixon LGE was not randomized, due to the imaging of clinical patients, and instead Dixon LGE images were acquired about 6 minutes later. These additional differences may have contributed to discordance in enhancement pattern. Finally, increased robustness of our implementation of this fat-water separation technique is important.

In conclusion, the two-point Dixon technique out-performs fat-saturated LGE in fat-suppression, inflow artifact reduction, and reduced blood pool signal heterogeneity, with a small increase in acquisition time and increased complexity of reconstruction. Irrespective of technique, there were similar enhancement patterns, indicating that the LGE enhancement

pattern observed in the thin-walled LA does at least partially reflect T1 differences in the LA myocardium.

Acknowledgements

Funding Sources: This work was supported by in part by grants from the NIH (NHLBI R21 HL 098573 & R21 HL103463)

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Figure 1.

Example of the fat-water separation technique (20), (21) which uses opposed-and in-phase images (A,B), described in Eq. 1 and 2. The phase (ϕ_0) of the in-phase image (shown in C) was calculated and removed from both images. The remaining phase (ϕ) (D) consisted of a linear phase term ($\text{err} \cdot x$) due to the bipolar readout, shown removed in (E), and an underlying phase ($\pm\phi_{\text{cor}}$) where $\pm$ corresponds to the $0^\circ/180^\circ$ phase due to water or fat-dominated pixels, and ϕ_{cor} is the underlying phase related to coils and off-resonance (shown in G). Note some possible flow-related sudden phase changes in the right PV (arrow, E), which do not affect the fat-water separation. The determination of water vs. fat-dominated pixels was performed using a region growing algorithm, with a seed pixel chosen in fat, as shown in (F). H) The resulting water image.

Figure 2.

Comparison in matched slices of fat-saturated LGE (A,C) and water-only LGE (B,D).

Regions chosen for analysis of enhancement were the left atrial (LA) posterior wall (PW), inter-atrial septum (IAS), and four quadrants around the left inferior pulmonary vein (PV) (LIPV), the left superior PV (LSPV), the right inferior PV (RIPV), and the right superior PV (RSPV), as labeled in (A,C). Additionally, enhancement of the aorta, aortic valve (AV), and mitral valve (MV) were also scored. Note the red arrows which point to regions of matched enhancement of the inferior quadrants of the LIPV (A,B), and the LA posterior wall of the LSPV (C,D). Finally, note the improved fat-suppression with water-only LGE, and the more homogeneous blood pool signal. E, F) Corresponding fat slices, exhibiting the extensive fat that surrounds the LA.

Figure 3.

A) Sequentially ordered LGE (TI=275ms), without fat-suppression, with bottles labeled with T1 (400ms = "myocardium", 300ms = "blood", 250ms = "scar"). B) Centrally ordered LGE (TI=250ms) with fat-suppression. C) Line profiles in the phase-encoding direction show edge-enhancement effects for centric LGE, with a maximal enhancement ratio of 1.4. No edge-enhancement was present in the frequency-encoding direction or on the sequentially ordered LGE.

Figure 4.

Fat-saturated LGE (A, C, E, F), and two-point Dixon LGE (B, D, F, H) compared in matched slices. (+) indicates a segment which was enhanced, (-) indicates no enhancement observed. Examples of regions in which blinded scoring showed disagreement (A-F) and agreement (G,H) are provided. Note also, better fat-suppression, more homogenous blood pool, and reduced inflow artifacts in the water-only LGE studies.

Figure 5.

A) Distribution of enhancement among regions by fat-saturated and water-only Dixon LGE. PV quadrants are labeled as Sup=superior, inf=inferior, ant=anterior, post=posterior. PW=posterior wall, IAS=inter-atrial septum. The distribution of enhancement demonstrates a similar pattern for both imaging methods, with enhancement most prominent in the LIPV regions and the posterior wall. B) Linear relation of number of enhancing regions, by water-only and fat-saturated LGE ($R=0.87$).

Table 1

Results of blinded assessment of LGE enhancement in an 18 segment model of the LA

	Fat-Sat LGE YES	Fat-sat LGE NO
Dixon YES	27	11
Dixon No	23	155