Improvement of Gadoxetate Arterial Phase Capture With a High Spatio-Temporal Resolution Multiphase Three-Dimensional SPGR-Dixon Sequence

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Purpose: To determine whether a multiphase method with high spatiotemporal resolution (STR) by means of a combination of parallel imaging, pseudorandom sampling and temporal view sharing improves the capture and intensity of gadoxetate arterial phase images as well as lesion enhancement.

Materials and Methods: Thirty-seven patients were imaged with a conventional spoiled gradient echo acquisition and 48 with a high STR multiphase acquisition after the administration of gadoxetate. Arterial phase capture, image quality, and quality of fat suppression were qualitatively graded. Fourteen lesions in the conventional group and 28 in the high STR multiphase group were imaged, including 34 focal nodular hyperplasias. The ratio of lesion to parenchyma enhancement as well as relative hepatic artery enhancement were calculated. Chi-squared, Mann-Whitney U and student t-tests were used to compare differences.

Results: The high STR multiphase acquisition included the arterial phase more frequently than conventional acquisitions (P < 0.001), with the arterial phase missed in 17% (95% CI of 4–28%) of patients with conventional acquisition compared with 2% (95% CI of 0–6%) with the high STR multiphase acquisition. There was no loss of image quality or degree of fat saturation. Additionally, there was increased relative intensity of the hepatic arteries (P = 0.01) as well as lesion enhancement (P < 0.001) as well as lesion enhancement.

Conclusion: The high STR multiphase acquisition resulted in more reliable gadoxetate arterial phase capture compared with a conventional acquisition while preserving image quality with robust fat saturation.

Key Words: gadoxetate; arterial phase; view sharing; FNH

artifactual. A two-point Dixon based fat–water separation technique has been proposed, which is somewhat insensitive to field inhomogeneities, and provides very robust fat saturation in short breathhold times (15,16). A DCEMRI technique that combined TRICKS with a Dixon-based fat–water separation scheme was proposed for hepatic imaging (17). This method relied on consistent breathholding due to the larger temporal footprint of the TRICKS acquisition, which forced view sharing across breathholds. Recently, a high spatio-temporal resolution (STR) DCEMRI technique which combined nearest neighbor view sharing of pseudo-randomly under-sampled peripheral \( k \)-space with parallel imaging (DIfferential Sub-sampling with Cartesian Ordering or DISCO) was proposed (18). This technique restricted view sharing to within a breathhold while minimizing motion artifacts due to its pseudo-random traversal of peripheral \( k \)-space.

No clinical study to our knowledge has evaluated the effect of improving the temporal resolution of the MR acquisition to match the more compact bolus of gadoxetate. In this study, we sought to determine whether a high STR imaging method that uses a combination of parallel imaging and view sharing (DISCO) improves capture of the gadoxetate arterial phase.

**MATERIALS AND METHODS**

**High STR Multiphase Pulse Sequence**

The Differential Sub-sampling with Cartesian Ordering (DISCO) sequence has been previously described [high STR multiphase acquisition] (18). In short, the sequence is based on a three dimensional (3D) fast SPGR-Dixon sequence with an elliptically ordered \( k_x-k_z \) that is segmented into four regions: the first representing the center of \( k \)-space (labeled A) and the remaining three representing equally distributed pseudo-random sub-samples of the periphery of \( k \)-space (labeled \( B_1 \), \( B_2 \), and \( B_3 \)) (Fig. 1). During each breathhold, the three peripheral \( k \)-space segments are alternated with the central portion of \( k \)-space (e.g., acquisition order of \( AB_1AB_2AB_3AB_1A \)). View sharing is restricted to nearest temporal neighbors and to \( k \)-space segments acquired within the same breathhold to minimize temporal blurring and motion misregistration. Additionally, two dimensional (in \( k_y \) and \( k_z \)) self-calibrated hybrid space parallel imaging (following view-sharing) was incorporated to further accelerate the acquisition. A typical acquisition takes 30 s, with a temporal phase reconstructed every 5.4 s (SD = 1.4 s) depending on the volume acquired. The temporal footprint, or the time taken to acquire all three peripheral \( k \)-space segments, was 16.2 s. A 2-point Dixon reconstruction algorithm with a region growing fat–water separation method is used to create separate fat and water images (16).

**Patient Groups**

Informed consent was waived for this retrospective study by our local institutional review board. For both acquisitions, all imaging was performed on a 3T MR750 system (GE Healthcare, Waukesha, WI) using the upper 20 elements of a 32-channel torso phased array coil (NeoCoil, Pewaukee, WI). In each patient, 0.025 mmol/kg of gadoxetate (Eovist, Bayer Healthcare) was administered at a rate of 2.5 mL per second, followed by 20 mL saline at the same rate. A standard
15-s delay was used for all patients without using bolus tracking. The patients were instructed to hold their breath just before the end of the 15-s delay. Patients with an estimated GFR < 30 mL/min/1.73 m² were excluded.

The first group of patients, which included 37 consecutive patients imaged between September 2009 and June 2011, were imaged using a routine clinical 3D SPGR-Dixon (conventional, LAVA-FLEX) sequence with the following parameters: 340 × 256 matrix, ±167 kHz bandwidth, 12° flip angle, TR/TE1/TE2 4.1/1.2/2.4, 3.6 mm section thickness reconstructed to 1.8 mm sections, and 2 × 2 ARC (Autocalibrating Reconstruction for Cartesian imaging) acceleration (19). This conventional sequence takes 25 s to acquire, with acquisition time varying slightly based on the number of slices required to cover the liver. For each of these subjects, a separate breathhold was used for the arterial, portal venous, and delayed phases. Identical parameters were used for the precontrast sequence was acquired before the administration of contrast.

The second group included 48 consecutive patients imaged between July 2011 and July 2012, and were imaged using the high STR multiphase sequence described above. The following parameters were used: 320 × 224 matrix, ±167 kHz bandwidth, 15° flip angle, 3.0- to 4.4-mm section thickness reconstructed to 1.5–2.2 mm sections, TR/TE1/TE2 4.1/1.2/2.4, typical number of slices acquired per volume 60, 2 × 2 outer acceleration, and five time points reconstructed during each arterial breath hold. For the precontrast sequence, a single time point, which included all four segments of k-space, was acquired with identical parameters before the administration of contrast.

**Qualitative Image Quality Analysis**

The percent of studies with adequate arterial phase capture was calculated for each patient group. For each exam, all phases imaged were classified as one of the following: angiographic referring to hepatic artery enhancement without any portal venous enhancement, early arterial referring to hepatic artery enhancement with early filling of the portal vein, late arterial referring to complete opacification of the portal vein without enhancement of the hepatic veins, and portal venous referring to opacification of both the portal and hepatic veins. The percentage of patients where imaging included an early arterial, late arterial or both early and late arterial phase were calculated for each group.

Image quality was graded by a board-certified radiologist on a 5-point scale for overall quality (0: Nondiagnostic; 1: Only large and intensely enhancing lesions would be detectable; 2: Only large or intensely enhancing lesions would be detectable; 3: Image quality for detection of small subtly enhancing lesions; 4: No artifacts and minimal image noise) and the quality of fat saturation (0: Complete failure of fat suppression; 1: Large regional fat–water swaps due to failure of the Dixon algorithm; 2: Regional fat–water failures but still interpretable; 3: Minimal failures in image periphery; 4: Perfect fat–water separation). We additionally tabulated the number of phases for the high STR multiphase and conventional acquisitions that demonstrated any evidence fat–water swapping. For high STR multiphase sequences, the highest quality grading for either an early or late arterial phase was also calculated. Additionally, for each phase imaged in the high STR multiphase and conventional acquisitions respiratory artifact was graded (0: no respiratory artifact; 1: minimal respiratory artifact allowing for detection of small enhancing lesions; 2: respiratory artifact was significant enough to allow detection of only large lesions; 3: severe respiratory artifact rendering study nondiagnostic). The grading was grouped as minimal respiratory artifact (grades 0 and 1) and significant respiratory artifact (grades 2 and 3).

**Quantitative Arterial Enhancement Analysis**

All quantitative analysis was performed using OsiriX software (20). Regions of interests (ROIs) were placed over the hepatic artery and the closest adjacent hepatic parenchyma that did not include any major vessels. For the high STR multiphase acquisitions, ROIs were propagated between phases so that the size of each ROI remained identical, although each ROI had to be repositioned depending on patient motion between phases. The ratio of hepatic artery intensity to precontrast intensity within the hepatic artery as well as to adjacent hepatic parenchyma was determined using both average and maximum intensities within the ROIs. For the high STR multiphase acquisitions, the results from the phase with the peak enhancement ratio were selected for analysis.

**Lesion Analysis**

Only lesions greater than 1 cm were included for analysis, and a maximum of three lesions were included per patient. Within the patients imaged with the conventional acquisition, there were 14 hypervascular lesions in 12 patients, which included 9 focal nodular hyperplasias (FNH). In the patients imaged with the high STR multiphase acquisition, there were 28 hypervascular lesions in 19 patients, which included 25 FNHs. The diagnosis of FNH was based on typical imaging findings, including relative hyperintensity with respect to adjacent liver on the hepatobiliary phase. At each time point imaged, an ROI was placed within the hypervascular lesion without inclusion of scar and an ROI was placed in directly adjacent hepatic parenchyma, taking care to not include any vascular structures. Lesion enhancement relative to precontrast images (lesioncone) and relative to adjacent parenchyma (lesionadj) were calculated. For the high STR multiphase acquisitions, the maximum lesioncone and lesionadj were selected for analysis. Additionally, for the high STR multiphase acquisitions, the temporal phase at which lesionadj occurred was recorded.

**Statistical Analysis**

A chi-squared test was used to compare the percentage of conventional versus high STR multiphase studies that contained either an early or late arterial phase, and 95% confidence intervals (CI) were calculated.
chi-squared test was also used to compare the number of phases in each group that had significant respiratory artifact and fat–water swapping. A Mann-Whitney U test was used to compare image quality and quality of fat saturation between the two groups. A Student t-test was used for comparison of means of lesion intensity and relative hepatic artery intensity between conventional and high STR multiphase acquisitions. A Wilcoxon signed rank test was used to determine if there was a difference in the timing of lesion pre and lesion adj phases within the high STR multiphase group. Excel 12.1.0 (Microsoft, Redmond, WA) and SPSS Statistics 17.0 (SPSS, Chicago, IL) were used for statistical analysis. A P-value of < 0.05 was used to determine significance for all tests.

RESULTS
Reliability of Arterial Phase Capture
The use of the high STR multiphase acquisition resulted in a higher rate of arterial phase capture. Of the 37 patients imaged with the conventional acquisition, 4 were imaged during the angiographic phase, 10 during the early arterial phase, 21 during the late arterial phase, and the bolus was missed in two cases. Overall 31/37 or 84% (95% CI: 72–96%) of patients imaged with the conventional acquisition had an early or late arterial phase image. Of the 48 patients imaged with the high STR multiphase acquisition, 25 had an angiographic phase, 43 an early arterial phase, and 42 a late arterial phase. Overall 47/48 or 98% (95% CI: 94–100%) of patients had an early or late arterial phase using high STR multiphase acquisitions (Fig. 2 and 3: P < 0.001 for comparing conventional versus high STR multiphase acquisitions for percent of patients with either early or late arterial phase images). On average, high STR multiphase acquisitions provided 1.88 ± 0.81 early arterial phases and 2.08 ± 1.20 late arterial phases per study. 83% of patients imaged with high STR multiphase acquisitions had both early and late arterial phase images.

Image Quality
Image quality was not significantly different between the conventional and high STR multiphase groups. When including all phases from the high STR
multiphase arterial breathhold compared with the conventional arterial phase, image quality and fat saturation did not differ (average image quality score of 3.72 ± 0.59 for high STR multiphase versus 3.59 ± 0.72 for conventional, Z = -1.00 and P = 0.32; average score of quality of fat saturation of 3.84 ± 0.41 for high STR multiphase versus 3.76 ± 0.43 for conventional, Z = -1.55 and P = 0.12). Additionally, when comparing the best quality arterial phases from the high STR multiphase acquisitions there was no significant difference between the groups (average image quality of 3.71 ± 0.87 for high STR multiphase versus 3.58 ± 0.72 for conventional, Z = -1.57 and P = 0.12), and the overall quality of fat saturation was not significantly different in either group (average quality of fat saturation of 3.73 for high STR multiphase ± 0.84 versus 3.76 ± 0.43 for conventional, Z = -1.012 and P = 0.31). The percentage of phases with fat-water swapping did not differ between the high STR multiphase and the conventional acquisitions (percent of imaged phases in the conventional group with fat-water swapping was 14% with a 95% CI of 3–25%, and for the high STR multiphase group the percentage of phases imaged with fat-water swapping was 13% with a 95% confidence interval of 9–18%; P = 0.95). The rate of significant respiratory artifact did not differ between the two groups (percent of imaged phases in the conventional group with significant respiratory artifact was 16% with a 95% CI of 4–28%, and for the high STR multiphase group the percentage of phases imaged with significant respiratory artifact was 13% with a 95% confidence interval of 8–17%; P = 0.55).

Quantitative Arterial Enhancement

The high STR multiphase acquisition resulted in increased relative intensity of the hepatic arteries. The ratio of hepatic artery intensity to precontrast hepatic artery intensity was greater with high STR multiphase compared with conventional acquisitions (Fig. 4: average intensity ratio: 4.22 ± 1.54 for high STR multiphase versus 2.94 ± 1.04 for conventional, P < 0.001; maximum intensity: 6.18 ± 2.44 for high STR multiphase versus 4.03 ± 1.64 for conventional, P < 0.001). When comparing the ratio of hepatic artery intensity to adjacent parenchyma, there was only a significant increase for average intensities likely reflecting focal vessel enhancement within the selected parenchymal ROIs that affected only maximum intensity values (Fig. 4: average intensity: 1.77 ± 0.62 for high STR multiphase versus 1.32 ± 0.54 for conventional, P < 0.001; maximum intensity: 1.99 ± 0.67 for high STR multiphase versus 1.80 ± 0.78 for conventional, P = 0.22).

Lesion Analysis

The maximum relative enhancement of lesions with respect to adjacent parenchyma was greater in lesions...
imaged with high STR multiphase compared with conventional acquisitions (lesion\textsubscript{adj} of 2.16 ± 0.67 for high STR multiphase versus 1.62 ± 0.46 for conventional, \( P = 0.01 \)). There was no significant difference in the precontrast intensity of lesion relative to adjacent parenchyma (lesion\textsubscript{adj} of 0.96 ± 0.33 for high STR multiphase versus 0.90 ± 0.17 for conventional, \( P = 0.55 \)). There was a trend toward a greater maximum relative enhancement in lesions with respect to precontrast images with the high STR multiphase acquisition, but this did not reach statistical significance (lesion\textsubscript{pre} of 2.85 ± 0.66 for high STR multiphase versus 2.50 ± 0.42 for conventional, \( P = 0.07 \)).

Of note, the time point at which lesion\textsubscript{adj} occurred was earlier than lesion\textsubscript{pre} in high STR multiphase lesions (mean phase of lesion\textsubscript{adj} 2.0 ± 1.1 and mean phase of lesion\textsubscript{pre} 3.4 ± 1.8, \( Z = -4.24 \) and \( P < 0.001 \)). Additionally within the high STR multiphase group, lesion\textsubscript{adj} occurred during the early arterial phase in 20 lesions, the late arterial phase in 6 lesions and the angiographic phase in two lesions (Fig. 5). Four of the 6 lesions where the lesion\textsubscript{adj} occurred in the late arterial phase did not have early arterial phase images due to early bolus timing. Although not qualitatively analyzed, spatial resolution was preserved allowing delineation of small sub-centimeter arterial hyperenhancing lesions (Fig. 6).

**DISCUSSION**

The incorporation of temporal view sharing and parallel imaging to allow the acquisition of multiple arterial phases within one breathhold resulted in more reliable gadoxetate arterial phase capture compared with a conventional acquisition while preserving image quality with robust fat saturation. Additionally, relative hepatic artery enhancement and lesion enhancement improved significantly. In our study, 17% of patients imaged with the conventional acquisition missed both the early and late arterial phases while only 2% of patients imaged with the high STR multiphase acquisition missed both phases.

Proper arterial phase timing is difficult with gadoxetate due to its brief bolus duration, and capturing the arterial phase is critical for many hypervascular hepatic lesions such as hepatocellular carcinoma, adenoma, FNH, and hypervascular neuroendocrine metastasis. Typical extracellular agents, such as gadopentetate dimeglumine (Magnevist, Bayer Healthcare), have a larger bolus size and broader peak arterial enhancement; therefore the chance that the central k-space acquisition coincides with the arterial bolus is more likely. Further work is being performed to analyze the effect on arterial timing with typical extracellular contrast agents. One additional reason that arterial phase capture may be limited with gadoxetate administration is secondary to a recently reported association with acute transient dyspnea (21).

The reason that arterial phase capture and relative enhancement is improved with the high STR multiphase acquisition is likely due to the oversampling of the center of k-space. Other techniques, such as keyhole, result in significant blurring artifact which limits the diagnostic accuracy of the image (6). One unique benefit of the DISCO implementation of the multiphase acquisition is that due to the pseudo-random selection of the periphery of k-space, motion artifacts
are dispersed resulting in preserved image quality. With the high STR multiphase acquisition, the center of \( k \)-space is sampled roughly every 5 s, increasing the probability that the center of \( k \)-space is acquired during peak arterial enhancement.

Bolus tracking software is often used to optimize the timing of the arterial phase (22) and fluoroscopic triggering has previously been shown to aid in arterial phase capture with gadoxetate (23). By incorporating triggering or using slower injections rates, the arterial capture rates likely would have been improved with the conventional technique (2). What is remarkable is that using the high STR multiphase acquisition resulted in arterial phase capture in nearly all patients without the use of bolus tracking or changing the dose or injection rate. This could allow for improved workflow without the need for bolus tracking. Of note, bolus tracking with gadoxetate can be problematic as the bolus is short and getting patients to suspend their respiration between aortic arrival and hepatic arrival can be difficult. Additionally, the use of a separate test bolus can confound arterial phase images due to hepatobiliary retention of gadoxetate. Nonetheless bolus tracking techniques are another method of acquiring the appropriate arterial phase.

The optimal hepatic arterial phase depends on the pathology being imaged. For example, with hepatocellular carcinoma, the late arterial phase has the highest sensitivity for detecting lesions (24,25). Comparison of lesion conspicuity on different arterial phases for FNH has not previously been performed, but it has been noted that lesion to adjacent parenchyma ratios are greatest during the arterial phase as compared with the portal venous phase (26). In our series, 71% of lesions had a maximum enhancement ratio \( \text{lesion}_{\text{adj}} \) during the early arterial phase, suggesting that early arterial phases might provide the greatest lesion conspicuity for FNH. Additionally, there likely is variability within each disease entity as to which phase has the highest sensitivity; therefore, the usage of a technique which acquires numerous phases during the arterial phase breathhold may be preferred. For the evaluation of FNH in the setting of gadoxetate, the arterial phase is less critical than with conventional extracellular agents as the hepatobiliary phase provides additional diagnostic information (27,28). As gadoxetate becomes used more frequently in the evaluation of hepatocellular carcinoma and hypervascular metastasis, accurate arterial phase timing will become critical (29,30).

One main limitation of this study is the lack of intra-patient and intra-lesion comparisons. To perform intra-patient and intra-lesion comparisons, patients would have to be injected and imaged twice, which was not possible in this retrospective study. Additionally, the lesion analysis included a small number of lesions within the conventional group, and it is possible that the differences in lesion-to-

Figure 6. Multiple subcentimeter arterial enhancing lesions in a patient with numerous FNHs imaged using the high STR multiphase acquisition. First row demonstrates a 6 mm arterial enhancing FNH an axial images near the liver tip (white arrow). The second row demonstrates a 5 mm FNH in segment 8 near the dome of the liver (white circle). The third row demonstrates a third lesion on coronal reformations measuring 3 mm along the inferior surface of the liver (white arrow head), which is presumed to represent a small FNH. Note the robust fat saturation throughout the imaged volume.
Parenchymal enhancement may reflect differences in lesion pathology between the two groups rather than differences in technique. Also the high injection rate used (2.5 mL/s) and the lack of bolus tracking limited the conventional technique. The quantitative analysis is also limited as image noise is not taken into account in the analysis. It has been well demonstrated that noise calculations in sequences accelerated with parallel imaging are difficult to measure (31), although numerous previous articles have taken approaches similar to ours in analyzing relative enhancement data (5).

In conclusion, the high spatiotemporal resolution multiphase DISCO acquisition provides clinically acceptable arterial phase capture without the use of bolus timing techniques or compromising spatial resolution or coverage.

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REFERENCES


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