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Diffusion-weighted double-echo steady-state with a three-dimensional cones trajectory for non-contrast-enhanced breast MRI

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Abstract

The image quality limitations of echo-planar diffusion-weighted imaging (DWI) are an obstacle to its widespread adoption in the breast. Steady-state DWI is an alternative DWI method with more robust image quality but its contrast for imaging breast cancer is not well-understood. The aim of this study was to develop and evaluate diffusion-weighted double-echo steady-state imaging with a three-dimensional cones trajectory (DW-DESS-Cones) as an alternative to conventional DWI for non-contrast-enhanced MRI in the breast. This prospective study included 28 women undergoing clinically indicated breast MRI and six asymptomatic volunteers. In vivo studies were performed at 3 T and included DW-DESS-Cones, DW-DESS-Cartesian, DWI, and CE-MRI acquisitions. Phantom experiments (diffusion phantom, High Precision Devices) and simulations were performed to establish framework for contrast of DW-DESS-Cones in comparison to DWI in the breast. Motion artifacts of DW-DESS-Cones were measured with artifact-to-noise ratio in volunteers and patients. Lesion-to-fibroglandular tissue signal ratios were measured, lesions were categorized as hyperintense or hypointense, and an image quality observer study was performed in DW-DESS-Cones and DWI in patients. Effect of DW-DESS-Cones method on motion artifacts was tested by mixed-effects generalized linear model. Effect of DW-DESS-Cones on signal in phantom was tested by quadratic regression. Correlation was calculated between DW-DESS-Cones and DWI lesion-to-fibroglandular tissue signal ratios. Inter-observer agreement was assessed with Gwet's AC. Simulations predicted hyperintensity of lesions with DW-DESS-Cones but at a 3% to 67% lower degree than with DWI. Motion artifacts were reduced with DW-DESS-Cones versus DW-DESS-Cartesian ($p < 0.05$). Lesion-to-fibroglandular tissue signal ratios were not correlated between DW-DESS-Cones and DWI ($r = 0.25$, $p = 0.38$). Concordant hyperintensity/hypointensity was observed between DW-DESS-Cones and DWI in 11/14 lesions. DW-DESS-Cones improved sharpness, distortion, and overall image quality versus DWI. DW-DESS-Cones may be able to eliminate motion artifacts in the breast allowing for investigation of

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higher degrees of steady-state diffusion weighting. Malignant breast lesions in DW-DESS-Cones demonstrated hyperintensity with respect to surrounding tissue without an injection of contrast.

Level of Evidence: 2.

Technical Efficacy Stage: 1.

INTRODUCTION

Diffusion-weighted imaging (DWI) has shown promise for non-contrast-enhanced magnetic resonance imaging (MRI) breast cancer screening.¹⁻⁴ However, while investigations of CE MRI continue to exemplify the strength of the modality for detecting breast cancers, broader establishment of DWI for screening has been challenging.⁵⁻⁸ DWI acquisitions have inherent image quality limitations, which can be particularly problematic for a screening examination where the goal is to detect small lesions and distinguish lesion morphology. The primary challenges of conventional DWI result from the dependency on an echo planar imaging (EPI) trajectory for motion robustness, which also induces distortion, blurring, and necessitates low resolution.⁹ To achieve acceptable image quality, most single-shot (ss)-DWI methods in the breast are limited to a much lower in-plane ($>2 \text{ mm} \times 2 \text{ mm}$) and through plane ($>3 \text{ mm}$) resolution than that of CE-MRI.⁵

DWI methods, which aim to improve image quality by breaking up the EPI trajectory into segments, have shown promising results in the breast. Readout-segmented EPI (rs-EPI) achieved improved overall image quality, improved anatomical structure distinction, and reduced distortion in comparison to ss-DWI in the breast, albeit without a significant increase in resolution.^{10,11} Multiplexed sensitivity-encoding DWI achieved an in-plane resolution of $1 \text{ mm} \times 1 \text{ mm}$ and improved overall image quality with respect to ss-DWI but with only a small improvement in the level of artifact.¹² While these results are encouraging, some degree of distortion and blurring will remain due to the EPI trajectory, even with segmentation. Further, each segmented method introduces new challenges such as extended scan time or motion-induced phase artifacts.^{13,14}

Steady-state DWI is an alternative to conventional DWI that does not require an EPI trajectory.¹⁵ Steady-state methods allow for efficient acquisition of a three-dimensional (3D) image volume through the use of a short repetition time (TR), and can achieve higher resolution than EPI DWI without distortion. As opposed to the preparation pulses used to impart diffusion-weighting in conventional DWI, the diffusion gradients in steady-state DWI are applied in each TR. This limits the size of the diffusion gradients while the steady-state signal formation introduces additional dependencies for the degree of diffusion-weighting including T1, T2, flip angle, and TR.¹⁵

In 2014, Granlund et al. investigated diffusion-weighted double-echo steady-state (DW-DESS) with a Cartesian trajectory for characterization of breast cancers in comparison to ss-DWI.¹⁶ The study reported higher resolution and lack of distortion of the DW-DESS images in comparison to conventional DWI in the breast. A high correlation of the lesion-to-fibroglandular tissue signal ratio (L/F) was also reported between DW-DESS and DWI, but a very low degree of diffusion-weighting was applied with the steady-state method.

The contrast and degree of diffusion-weighting of DW-DESS in the breast has not been extensively characterized, particularly at levels of diffusion-weighting typically necessary to distinguish breast cancers from surrounding normal tissue.

As with conventional DWI, steady-state DWI is susceptible to motion artifacts, which increase with increasing level of diffusion-weighting. This limitation was noted in Granlund et al.'s study and addressed with an elliptical-centric ordering of the Cartesian trajectory.¹⁶ While the typical motion effects in conventional DWI are strong ghosting artifacts, motion artifacts in steady-state DWI are a combination of ghosting and signal loss due to interruption of the steady state.¹⁷ A number of methods to reduce or correct motion artifacts with steady-state DWI acquired with Cartesian trajectories have been developed, including motion-compensated gradients and navigators.^{18,19}

Center-out, non-Cartesian trajectories are well suited for steady-state acquisitions, particularly when the goal is to achieve high-resolution images.^{20,21} Beginning the acquisition of data shortly after excitation allows for maximal time to get to the edge of k-space during the short TRs of the steady-state sequence. This has previously been demonstrated in the breast with a radial steady-state sequence that achieved 0.63-mm isotropic resolution within very short TRs (<5 ms).^{21,22} Non-Cartesian k-space trajectories that acquire the center of k-space of each TR are also inherently motion robust and have been investigated with steady-state DWI in the brain.^{17,23} Therefore, for steady-state DWI in the breast, center-out non-Cartesian trajectories have the potential to provide a number of advantages, including higher resolution and motion robustness. The ability to reduce motion artifact with steady-state DWI is particularly important as it may allow for the investigation of higher degrees of diffusion-weighting in the breast.

The aim of this work was to develop a non-Cartesian steady-state diffusion-weighted method, DW-DESS-Cones, for the imaging of breast cancer without a contrast injection and to investigate its motion robustness and contrast. Further, we sought to provide an initial characterization of the contrast expectation of DW-DESS-Cones in comparison to the contrast of conventional DWI in the breast.

MATERIALS AND METHODS

DW-DESS-Cones Acquisition

For DW-DESS-Cones, DW-DESS was implemented with a 3D cones trajectory and a water-only excitation (Figure 1). In a 3D cones trajectory, samples in k-space are acquired in spiraling paths along concentric conical surfaces.^{24,25} In this work, the trajectory was fully sampled with cones acquired sequentially from $-k_z$ to $+k_z$. Echo 1 was acquired with a cone-out starting from the center of k-space to the outer edge of k-space and echo 2 was acquired along the identical path starting at the edge of k-space back into the center. Echo 2, as the echo with diffusion-weighting, was the primary focus of this work. The diffusion gradient was applied along the z -axis. Per-axis gradient delays were determined empirically and applied through a combination of a bulk delay during the acquisition and axis-specific delay corrections during reconstruction. Regridding of data was performed with the Berkeley Advanced Reconstruction Toolbox (BART).²⁶ The resolution ($1.5 \text{ mm} \times 1.5$

mm in-plane) and slice thickness (3 mm) were chosen as a balance between the established optimal resolution for CE-MRI of the breast (1 mm × 1 mm × 2 mm) and the increased scan time of a center-out trajectory. TR and flip angle were chosen to provide a combination of near-maximum signal in the steady state and sufficient diffusion weighting based on the T1, T2, and apparent diffusion coefficient (ADC) literature values of breast cancers and fibroglandular breast tissue.²⁷⁻³² One of the advantages of the 3D cones trajectory versus a purely radial trajectory is the more efficient coverage of k-space resulting in a lower number of readouts required for a fully sampled trajectory.³³ In this study a fully sampled DW-DESS-Cones acquisition with the stated imaging parameters required 18,000 to 24,000 readouts with a total scan time of 3–5 min. Bandwidth of spectral-spatial pulse was 310 Hz.

DW-DESS-Cones Contrast

In conventional DWI, a b-value indicates the expected degree of diffusion-weighting based on diffusion gradient area and timing. In DW-DESS-Cones the relationship between applied diffusion gradient and contrast is not as direct as in conventional DWI and a conventional b-value cannot be used with this method. For the in vivo experiments in this work, all DW-DESS-Cones parameters were kept consistent except for the diffusion gradient amplitude. Experiments in a diffusion phantom (Model 128, High Precision Devices, Boulder, CO) were performed to align the degree of signal decay of DW-DESS-Cones with a range of diffusion gradient amplitudes to the signal decay with conventional DWI for a range of b-values. Based on these experiments, each DW-DESS-Cones gradient amplitude was assigned a b-value equivalent, breast (b_{eqbr}), based on the signal decay alignment with DWI. Conventional DWI was acquired with b-values of 0, 200, 400, 600, 800, and 1000 s/mm². DW-DESS-Cones was acquired with a TR of 12 ms, flip angle 20°, and diffusion gradient amplitudes of 5, 16, 26, 36, 47, 57, 68, and 78 mT/m with a 3 ms diffusion gradient pulse width. The range of diffusion gradient amplitudes for DW-DESS-Cones was chosen based on previous studies of DW-DESS acquired with a Cartesian trajectory.^{16,34} Diffusion gradient areas were chosen to ensure an integer number of phase cycles across each voxel to avoid shading artifacts.

The ADC of each of 13 vials in the phantom was calculated from the conventional DWI acquisition to delineate the range of b-values being tested. Correlation of the mean signal of a region of interest (ROI) in each vial was calculated. Scans were acquired with a 32-channel head coil on a 3 T GE MR750 scanner (General Electric Healthcare, Waukesha, WI). The b_{eqbr} descriptor was then used to indicate the degree of diffusion-weighting for the DW-DESS-Cones in vivo experiments.

As a second step in characterization of the contrast of DW-DESS-Cones, with specific regard to the detection of breast cancer, simulations were performed of the L/F of DW-DESS-Cones in comparison to conventional DWI. Signal ratio between malignant lesions (L) and fibroglandular tissue (F) for both DW-DESS-Cones and conventional DWI was simulated for three different levels of diffusion-weighting ($b = 200$ s/mm², 600 s/mm² and 1000 s/mm²) over a range of T2 values for both the lesions and the normal tissue. For DW-DESS-Cones a diffusion pulse width of 3 ms, TR of 15 ms, and 20° flip angle were used to reflect those of the in vivo acquisitions. ADCs of malignant lesions and

fibroglandular tissues were set to $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ and $2.0 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively.²⁷ A T1 of 1300 ms was used for both malignant lesions and fibroglandular tissue and the signal ratio was calculated for T2s from 30 to 100 ms.²⁸⁻³² Mean and standard deviation of L/F and percentage of lesions with lesion-to-fibroglandular ratios greater than one were measured and compared between the methods at each level of diffusion-weighting. The highest and lowest percent differences between L/F for DW-DESS-Cones and DWI were also calculated.

Volunteer Experiments for Assessment of Motion Artifact

Six asymptomatic volunteers were recruited to be scanned with both DW-DESS-Cones and DW-DESS-Cartesian. All recruitment followed institutional review board (IRB) policies and volunteers who agreed to participate signed written informed consent. The six volunteers were divided into three groups with different b_{eq} : Group 1: $b_{\text{eq}} = 200$; Group 2: $b_{\text{eq}} = 500$; and Group 3: $b_{\text{eq}} = 800$. Matrix size (256×256), number of slices (64), slice thickness (3.0 mm), field of view (360 mm), and flip angle 15° were the same for all cases. All scans utilized a 16-channel Sentinelle Breast Coil (In Vivo Corp, Orlando, FL) and were performed on a GE 3 T Signa Premier scanner (GE Healthcare, Waukesha, WI) with a dual-volume shim. TR and scan time were as follows: DW-DESS-Cones 8 ms/11 ms/13 ms, 3:07/4:13/4:58 min:s, and DW-DESS-Cartesian 10 ms/11 ms/13 ms, 2:45/3:03/3:31 min:s. The TRs increased slightly with increasing gradient amplitude and varied between cones and Cartesian k-space coverage because of the different imaging gradient structure. Readout with DW-DESS-Cones was kept to a minimum resulting in some degree of oversampling at the center of k-space and the consequently longer scan time of DW-DESS-Cones versus DW-DESS-Cartesian.

In bilateral breast MRI, the region of air between the breasts provides an ideal location in which to measure ghosting artifact.³⁵ To measure the level of motion artifact in DW-DESS-Cones versus DW-DESS-Cartesian, an artifact-to-noise ratio (A/N) was calculated as the ratio of mean signal in an ROI placed between the breasts (A) to that in an ROI in a region of noise (N) in the anterior edge of the image. For each DW-DESS-Cones/DW-DESS-Cartesian pair of scans A/N was calculated on every other slice of the central 32 slices of the acquisition, resulting in 16 A/N measurements across the breast in the superior-to-inferior direction.

Patient Experiments for Assessment of Motion Artifact, Lesion Contrast, and Image Quality

Patients undergoing clinically indicated breast CE-MRI at a single site were recruited consecutively from March to October 2019 to have a DW-DESS-Cones acquisition added to their examination. All recruitment followed IRB policies and patients who agreed to participate signed written informed consent. The MRI protocol also included ss-DWI and DCE-MRI. DW-DESS-Cones was acquired after the ss-DWI and both DW-DESS-Cones and DWI were acquired prior to the injection of contrast. DW-DESS-Cones was acquired with a 36 cm FOV and 256×256 in-plane matrix for an in-plane resolution of $1.4 \text{ mm} \times 1.4 \text{ mm}$. Slice thickness was 3.0 mm with 64 total slices, flip angle of 20° , and TR/TE2 9.6 ms/7.5 ms where TE2 is the TE of the second, diffusion-weighted, echo. Total scan time was 2 min and 54 s. Conventional DWI was acquired with the following parameters 160×160 matrix,

34 cm FOV, 46 slices with 5 mm slice thickness, 3× parallel imaging, TE of 60 ms, diffusion direction “3-in-1,” scan time of 1 min and 4 s. All scans utilized a 16-channel Sentinelle Breast Coil (In Vivo Corp, Orlando, FL) and were performed on a GE 3 T Discovery MR750 scanner (GE Healthcare, Waukesha, WI) with a dual-volume shim. A/N, as calculated in the volunteer studies, was measured in all 28 DW-DESS-Cones patient scans on a single central slice in the breast. While in the volunteer studies the level of motion artifact was compared between DW-DESS-Cones and DW-DESS-Cartesian, in patients only the DW-DESS-Cones sequence was acquired due to a limit on additional sequences that could be incorporated in the examination.

A blinded observer study was performed to rate image quality of DW-DESS-Cones in comparison to DWI. Three radiologists with 28 (Bruce L. Daniel), 3 (Sarah M. Pittman), and 20 (Eric L. Rosen) years of breast MRI expertise were presented DWI and DW-DESS-Cones axial image pairs from a patient, with the order of images left–right for each pair randomized. The radiologists were asked rate the image on the right in comparison to the image on the left for (1) sharpness, (2) distortion, (3) signal-to-noise ratio (SNR), and (4) overall image quality on the following scale: right image much better than left image, right image somewhat better than left image, right image equivalent to left image, right image somewhat worse than left image, right image much worse than left image. For each case three slices were chosen for analysis. The number of slices covering the breast in the DW-DESS-Cones acquisition was divided into thirds. A slice from each third of images was chosen for inclusion in the observer study. The paired DWI images were chosen to match the DW-DESS-Cones images based on closest slice location. The results of the observer study were then converted to a 5-point rating for each metric: 1, DW-DESS-Cones much worse than DWI; 2, DW-DESS-Cones somewhat worse than DWI; 3, DW-DESS-Cones equivalent to DWI; 4, DW-DESS-Cones somewhat better than DWI; and 5, DW-DESS-Cones much better than DWI. The percent of DW-DESS-Cones rated as better than DWI (4 and 5) for each metric was calculated along with inter-observer agreement.

For the in vivo lesion contrast assessment, a radiologist (Bruce L. Daniel) with 28 years of breast MRI experience identified lesions in the patient cases. Lesion identification was based on the current examination images in conjunction with previous imaging studies and pathology reports where available. Benign findings were included in analysis if they took up contrast on CE-MRI or were discernable on both DCE and conventional DWI. Lesion contrast was measured based on L/F. A central slice through the lesion was used for the measurement with one ROI placed in the lesion and one placed in a region of fibroglandular tissue within the same breast. If there was insufficient fibroglandular tissue in the chosen slice, the ROI was placed in fibroglandular tissue in an adjacent slice within the same breast. Correlation of the ratios was calculated between DW-DESS-Cones and DWI and each lesion was also categorized as hyperintense ($L/F > 1.0$) or hypointense ($L/F < 1.0$) and compared between the two methods.

Statistical Analysis

For motion artifact of DW-DESS-Cones and DW-DESS-Cartesian, the effect of method (Cones or Cartesian) and b_{eq} on A/N was assessed by a mixed-effects generalized linear

model with gamma family and log link, using fixed factors of method, b_{eqbr} , and their interaction, covariates of linear and quadratic effects of slice number, and random effect of subject. For phantom experiments correlation of signal with DW-DESS-Cones versus DWI was performed through a quadratic regression of signal based on gradient ADC and their interaction. The linear correlation and coefficient of determination between DW-DESS-Cones and DWI L/F ratios were calculated. Inter-observer agreement was assessed with Gwet's AC. All statistical analyses were done using Stata 16.1 (StataCorp LP, College Station, TX) and Matlab R2015b (MathWorks, Natick, MA). A significance level of 0.05 was used.

RESULTS

DW-DESS-Cones Contrast

ADCs in the diffusion phantom ranged from $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$ to $2.4 \times 10^{-3} \text{ mm}^2/\text{s}$. Signal decay in all vials was highly correlated with an adjusted $R^2 = 0.85$ between conventional DWI from b-values 0 s/mm^2 to 1000 s/mm^2 and DW-DESS-Cones from diffusion gradient amplitudes 16 mT/m to 68 mT/m (Figure 2). A starting point for b-value equivalency in the breast (b_{eqbr}) of the applied diffusion gradient amplitude with DW-DESS-Cones for this study was set based on signal in vials with a mid-range of ADC (Table 1). As DW-DESS-Cones contrast is dependent on other imaging parameters as well as the amplitude of the diffusion gradient, this b_{eqbr} is specific to the parameters of these experiments including TR of 15 ms, 20° flip angle, and gradient pulse width of 3 ms. The b_{eqbr} descriptor was then used in the in vivo experiments and contrast simulations to indicate the level of diffusion gradient amplitude applied as well as to indicate the potential level of contrast expected with respect to conventional DWI images.

The L/F simulations predicted the contrast for a range of lesions and fibroglandular tissues at three different levels of diffusion weighting for DW-DESS-Cones and conventional DWI (Figure 3). Mean ($\pm$ SD) L/F were 1.5 ± 0.4 (b_{eqbr} 200), 1.6 ± 0.4 (b_{eqbr} 600), and 1.7 ± 0.5 (b_{eqbr} 1000) for DW-DESS-Cones and 1.8 ± 0.7 ($b = 200 \text{ s/mm}^2$), 2.3 ± 1.1 ($b = 600 \text{ s/mm}^2$), and 3.2 ± 1.7 ($b = 1000 \text{ s/mm}^2$) for DWI. The percent of lesions with hyperintense signal ($L/F > 1.0$) with respect to the surrounding tissue was 63% (b_{eqbr} 200), 80% (b_{eqbr} 600), and 90% (b_{eqbr} 1000) for DW-DESS-Cones and was 67% ($b = 200 \text{ s/mm}^2$), 86% ($b = 600 \text{ s/mm}^2$), and 96% ($b = 1000 \text{ s/mm}^2$) for conventional DWI. L/F for DW-DESS-Cones was 3% to 40% lower at $b = 200 \text{ s/mm}^2$, 14% to 55% lower at $b = 600 \text{ s/mm}^2$ and 22% to 67% lower at $b = 1000 \text{ s/mm}^2$. These results indicate that the percentage of lesions with signal higher than the surrounding tissue increases similarly between DW-DESS-Cones and conventional DWI with increasing diffusion gradient strength, but that the signal ratio itself between lesion and the surrounding fibroglandular tissue is larger with conventional DWI than with DW-DESS-Cones.

Volunteer Experiments for Assessment of Motion Artifact

Representative examples of the motion artifacts in DW-DESS-Cones versus DW-DESS-Cartesian at the three levels of diffusion gradient amplitude from the volunteer study are shown in Figure 4. DW-DESS-Cones and DW-DESS-Cartesian in the volunteer experiments

were run with $b_{eq}br = 200, 500, \text{ and } 800$. Mean ($\pm SD$) A/N were 1.9 ± 0.4 ($b_{eq}br 200$), 2.0 ± 0.6 ($b_{eq}br 500$), and 1.4 ± 0.2 ($b_{eq}br 800$) for DW-DESS-Cartesian and 1.1 ± 0.03 ($b_{eq}br 200$), 1.0 ± 0.02 ($b_{eq}br 500$), and 1.0 ± 0.03 ($b_{eq}br 800$) for DW-DESS-Cones. The mean A/N of close to 1.0 for all levels of diffusion-weighting with DW-DESS-Cones indicated little to no motion artifact in the images. At all three levels of diffusion gradient amplitude DW-DESS-Cones had significantly lower A/N than DW-DESS-Cartesian (all $p < 0.05$) (Figure 5). The experiments at $b_{eq}br 800$ had significantly less artifact than both $b_{eq}br 200$ and $b_{eq}br 500$ ($p < 0.05$) but $b_{eq}br 200$ and $b_{eq}br 500$ were not different from each other ($p = 0.51$). The difference in A/N between DW-DESS-Cones and DW-DESS-Cartesian was also significantly lower at $b_{eq}br 800$ in comparison to $b_{eq}br 200$ and $b_{eq}br 500$ ($p < 0.05$).

Patient Experiments for Assessment of Motion Artifact, Lesion Contrast, and Image Quality

Clinical indications for the 28 patients were: screening—high-risk 16, screening—other 1, diagnosis—evaluation of breast abnormality 5, short-term follow-up 1, staging—evaluation of extent of known tumor 5. DW-DESS-Cones diffusion gradient amplitude for the in vivo experiments was set to achieve a $b_{eq}br = 500$ based on the results of the phantom and volunteer experiments while also taking into consideration the increased motion and variation in positioning of lateral immobilization paddles possible in the clinic. The general image quality of DW-DESS-Cones with respect to the conventional DWI image is demonstrated in a set of representative cases (Figure 6). The lack of motion artifact in DW-DESS-Cones is demonstrated in these examples as are two instances of the reduced distortion with DW-DESS-Cones versus DWI. The mean A/N was 0.97 ± 0.02 for all cases indicating minimal motion artifact at $b_{eq}br 500$ with DW-DESS-Cones.

Seventy total slices were included in the observer study. In eight cases one or two of the three sections of slices contained only fat so no slice was chosen from that section. The percentage of slices with ratings indicating better performance with DW-DESS-Cones versus DWI (ratings 4/5) for each of the three observers for each metric were as follows: sharpness: 93%, 97%, and 96%; distortion: 90%, 94%, and 91%; SNR: 11%, 46%, and 0%; overall image quality: 76%, 77%, and 96% (Figure 7). Inter-observer agreement for each metric was 0.80 (95% confidence interval: 0.75–0.84) for sharpness, 0.86 (0.81–0.91) for distortion, 0.59 (0.49–0.70) for SNR, and 0.64 (0.52–0.76) for overall image quality.

Fifteen lesions (five malignant and 10 benign) were identified in 15 of the 28 cases. Types of lesions were triple negative breast cancer (TNBC) (1), invasive ductal carcinoma (IDC) (1), IDC + ductal carcinoma in situ (DCIS) (2), invasive lobular carcinoma (ILC) (1), mucinous IDC + DCIS (1), fibroadenoma (5), benign enhancing mass (1), lymph node (1), cyst (1), and fluid collection (1). One lesion, the ILC, was not discernable relative to the surrounding tissue on DWI or DW-DESS-Cones so was not included in contrast measurement. L/F was not correlated between DW-DESS-Cones and DWI ($r = 0.25$, $p = 0.38$). Eleven of the 14 lesions had concordant designation of hyperintensity or hypointensity with DW-DESS-Cones and DWI (Figure 8). On both DW-DESS-Cones and DWI, five of five malignant lesions were hyperintense with respect to fibroglandular tissue. For the benign lesions, six of nine lesions had concordant designation of hyperintensity or hypointensity on DW-DESS-

Cones and DWI images (five cases hyperintense and one case hypointense). Representative lesion examples are shown in Figure 9.

DISCUSSION

In this study, the DW-DESS-Cones method reduced motion artifacts with respect to DW-DESS-Cartesian allowing for the investigation of higher levels of diffusion-weighting in volunteers ($b_{eq}br$ 800) and patients ($b_{eq}br$ 500) with steady-state DWI in the breast. Image sharpness, distortion, and overall image quality were highly rated with DW-DESS-Cones versus DWI. The L/F ratios were not correlated between DW-DESS-Cones and conventional DWI in patients but in 11/14 cases the hyperintensity/hypointensity of the lesion versus the fibroglandular tissue were concordant between the methods. Finally, simulations of DW-DESS-Cones contrast between malignant lesions and surrounding fibroglandular tissue provided a broader representation of the potential contrast of steady-state DWI in comparison to conventional DWI.

The primary goal of implementing DW-DESS with 3D cones was to take advantage of the inherent motion robustness of the trajectory. Some method of motion correction is necessary to investigate high levels of steady-state diffusion contrast in the breast. Reduced motion artifact with DW-DESS-Cones was achieved in both asymptomatic volunteers up to a $b_{eq}br$ 800 and in 28 patients at $b_{eq}br$ 500 undergoing clinically indicated breast MRI. In the volunteer studies there was also a significant main effect of the $b_{eq}br$ on the level of artifact with the cases at $b_{eq}br$ 800 having significantly less artifact than those acquired at $b_{eq}br$ 200 or $b_{eq}br$ 500. The reduction of artifact level at the higher level of diffusion-weighting may be the result of the lower SNR in these images. Measuring the artifact in the region between the breasts provided a means to separate the artifact signal from the underlying tissue, therefore facilitating an “artifact-only” measurement. However, this determination of artifact does not capture diagnostic impact as the depiction of tissues will be affected by both artifact level and signal properties like SNR of the tissue itself. Contrast-to-noise studies of breast lesions at different levels of diffusion-weighting would help to further delineate the optimal protocol. Finally, while DW-DESS-Cones was successful at eliminating the coherent ghosting artifacts due to motion, there are likely additional effects due to motion interrupting consistency of the steady-state.¹⁷ Prospective real-time methods which have been developed for correction of motion effects on formation of the steady-state should be investigated in future work.³⁶

As the motion robustness of DW-DESS-Cones was sought to facilitate a wider investigation of DW-DESS for non-contrast-enhanced MRI, we also performed simulations of the contrast of DW-DESS-Cones in comparison to that of conventional DWI in the breast over a wide range of lesions. These simulations were performed as an independent component of the study to provide a higher level framework of the contrast expectations of DW-DESS-Cones with increasing diffusion gradient strength versus conventional DWI. Noise was not included in the simulations as they were not intended to translate directly to detection of lesions in vivo. This was due to the number of parameters (TR, flip angle) yet to be optimized, and the dependence of this optimization on improved characterization of the T1 and T2 of breast tissues.¹⁵ For example, T2s of breast lesions as well as normal fibroglandular

tissue can vary widely and are minimally characterized in the literature. Recent studies of quantitative T2-weighting in the breast report T2 of breast cancers to be greater than 60 ms and T2 of fibroglandular tissue to be less than 60 ms.²⁹⁻³² Referencing these T2s within the simulations in this work, DW-DESS-Cones would produce a promising signal ratio of greater than 2.0 between the lesion and fibroglandular tissue; imaging parameters (diffusion gradient strength, TR, flip angle) could then be more specifically chosen to maximize contrast of these tissues.

The results of the observer study demonstrated the potential for robust image quality with DW-DESS-Cones with increased sharpness, reduced distortion, and improved overall image quality versus conventional DWI with high inter-observer agreement. Two of the three observers strongly preferred the SNR of DWI over DW-DESS-Cones, with the third observer rating the SNR of DW-DESS-Cones as higher in just under half the images. SNR limitations of DW-DESS may be expected because of the lower baseline signal of steady-state sequences. The SNR in DW-DESS-Cones can be further affected by increased diffusion-weighting, motion corruption of the steady-state signal, and apparent SNR loss from incoherent artifact of the non-Cartesian trajectory. Therefore, additional motion correction and trajectory optimization may be impactful for improving SNR. We also expect a more consistent SNR performance with better positioning of the patients, as signal drop-off across the breasts in some cases indicate that lateral immobilization paddles were not flush to the breast tissue, which may affect signal of the steady-state sequence more than that of DWI. Finally, structured artifacts from chemical shift of fat and parallel imaging were not individually assessed in this work but were considered as part of the overall image quality metric.

In the in vivo assessment of lesion contrast, 11 of 14 lesions demonstrated concordant hyperintensity or hypointensity with respect to the surrounding tissue on DW-DESS-Cones and conventional DWI. All five malignant lesions included in the signal measurements demonstrated hyperintensity with respect to the surrounding tissue on both DWI and DW-DESS-Cones although signal ratio values were not highly correlated between the methods. This lack of correlation of L/F is in contradiction to a previous investigation of DW-DESS-Cartesian in the breast which reported a high correlation between DW-DESS-Cartesian and conventional DWI in 35 lesions.¹⁶ One possible explanation for the contradiction is that the level of diffusion-weighting applied in the previous study was less than $b = 200 \text{ s/mm}^2$ and therefore the high correlation may instead have been due to T2-weighting. A single malignant lesion, an ILC, was not included in the analysis as it was not discernable on either DWI or DW-DESS-Cones images. Further studies will help to elucidate if signal behavior of the ILC is due to pathology or specific only to this case.

In this work, phantom experiments were performed to establish a starting point for b-value equivalency (b_{eqbr}) of DW-DESS-Cones in the breast. The b-value equivalency was not meant to be generalizable across future studies but to reflect the potential level of DW-DESS-Cones diffusion-weighting for the specific imaging parameters chosen in this work. Here the b_{eqbr} indicated a change in the diffusion gradient amplitude of the DW-DESS-Cones sequence keeping all other imaging parameters constant. Determining true b-value equivalency of DW-DESS is very challenging due the dependency not only

on the characteristics of the diffusion gradient pulses but also on the imaging and tissue parameters (TR, flip angle, T1, T2).^{15,37} Similarly, the more complex signal dependencies of DW-DESS also affect determination of ADC with these methods. One limitation of DW-DESS-Cones is that it does not provide quantitative diffusion information. There are a few reports of calculation of ADCs with steady-state DWI in anatomies with limited motion and well-characterized tissue T1, T2, and ADC such as cartilage.^{34,38} There is also potential for DW-DESS-Cones to be used in conjunction with conventional DWI methods for a non-contrast-enhanced screening protocol. Such a protocol would draw on the strengths of both methods: DW-DESS-Cones for lesion identification and depiction of morphology and DWI for quantification.

While calculation of ADCs with DW-DESS-Cones may eventually be possible, the current method without quantitative diffusion information could still be effective at screening for breast cancer, particularly with continued improvement in the depiction of lesion morphology. The resolution of DW-DESS-Cones in this study was lower than that which is standard for CE MRI in the breast. With the elimination of coherent motion artifacts of DW-DESS-Cones established, a primary focus of future work will be on increasing the resolution to better match that achieved with CE-MRI. Center-out trajectories are well-suited to achieve high-spatial resolution within the short TRs of steady-state sequences as demonstrated in previous studies of 3D radial balanced steady-state free-precession (bSSFP) in the breast.^{21,22} With respect to a purely radial 3D trajectory, cones is more efficient as each readout covers a more independent region of k-space and the ability to extend the readout in cones can be used to further reduce the degree of oversampling of the central portion of k-space.²⁴ However, the trade-off to the extension of the readout may be increased blurring in the image which could also negatively impact depiction of lesion morphology. Therefore, while the cones trajectory provides the opportunity to achieve clinically feasible scan times with minimal undersampling with a center-out trajectory, the development of DW-DESS-Cones with higher resolution will also necessitate incorporation of methods for blurring correction.^{39,40}

Limitations

One of the primary limitations of this study is that DW-DESS-Cones was acquired in patients with a $b_{eq}br$ of 500 which is below the range of b-values (600 s/mm^2 to 800 s/mm^2) generally recommended to detect breast cancers with conventional DWI.²⁷ This conservative choice of $b_{eq}br$ was based on the expectation of higher variability in motion artifact in the clinical setting. However, $b_{eq}br$ 800 images were acquired in the volunteer studies and we expect that DW-DESS-Cones with this degree of diffusion-weighting can be achieved in future clinical studies. Further, it is promising that even at this slightly lower than ideal $b_{eq}br$, signal contrast between lesions and surrounding tissue with DW-DESS-Cones was still achieved. The small number of lesions in this study for contrast analysis was also a limitation. While an observer-based assessment with a higher number of lesions was beyond the scope of this study, such a study will be necessary to continue to characterize the contrast of DW-DESS-Cones for the detection of breast cancers without a contrast injection. The contrast simulations in this study did not include noise as these were intended to present a broad picture of contrast expectations for DW-DESS-Cones

using a specific set of parameters. Therefore, the simulations are limited as they do not explicitly represent level of tumor detection in vivo. A final limitation of this work was that in patients, DW-DESS-Cones was compared to conventional ss-DWI with parallel imaging. More advanced conventional DWI methods (such as rs-DWI) which provide improved resolution and reduced blurring and distortion are available clinically and will be utilized in future studies to assess the performance of DW-DESS-Cones.^{13,14}

CONCLUSION

The DW-DESS-Cones method achieved robust elimination of motion artifact both in volunteers and in a clinical setting, allowing for higher degrees of steady-state diffusion-weighting to be investigated in the breast. On DW-DESS-Cones images, malignant lesions demonstrated hyperintensity with respect to surrounding tissue without an injection of a contrast agent. Simulations of DW-DESS-Cones contrast for a range of lesions provided a broader perspective for the contrast expectations of DW-DESS-Cones with respect to conventional DWI for the detection of breast cancer. Observer study results demonstrate the potential for improved image quality with DW-DESS-Cones. Future in vivo studies of DW-DESS-Cones in more lesions will be pursued to continue to characterize the contrast and refine the method, particularly in terms of the potential for high resolution with the cones trajectory.

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FIGURE 1:

DW-DESS-Cones pulse sequence (a) and subset of readouts from full trajectory (b). A cone-out is acquired in echo 1 with the same cone-in acquired in echo 2, which is the echo that exhibits diffusion-weighting. The imaging gradients G_x , G_y , and G_z reflect the specific imaging parameters (256×256 matrix, 360 mm field of view, 64 slices, 3 mm thickness) utilized in this implementation (a). The cones trajectory provides a more efficient coverage of k-space in comparison to a purely radial trajectory. The primary advantage of cones (b) for this work is the averaging of motion effects due to the sampling of the center of k-space for each readout

FIGURE 2:

Signal of diffusion-weighted imaging (DWI) with increasing b-values from $b = 0$ s/mm² to $b = 1000$ s/mm² (a) and signal of DW-DESS-Cones with increasing diffusion gradient amplitudes from 5 mT/m to 78 mT/m (b) for a range apparent diffusion coefficients (ADCs). Representative phantom images from DWI $b = 600$ s/mm², $b = 1000$ s/mm² and DW-DESS-Cones 47 mT/m, 68 mT/m. Signal decay with the two methods is highly correlated between DWI $b = 0$ s/mm² and $b = 1000$ s/mm² and DW-DESS-Cones diffusion gradient amplitudes 16 mT/m and 68 mT/m. Based on these experiments a b-value equivalent breast (b_{eqbr}) is defined (Table 1) to indicate expected level of diffusion-weighting for DW-DESS-Cones in this work

FIGURE 3:

Simulations to relate potential malignant lesion-to-fibroglular tissue signal ratio (L/F) of DW-DWSS-Cones (a) to that of conventional diffusion-weighted imaging (DWI) (b) for a range of tumor and fibroglandular tissue T2s. Scale for signal ratio on right with hyperintensity indicated with $L/F > 1.0$ and hypointensity indicated with $L/F < 1.0$. For both DW-DESS-Cones and conventional DWI the percentage of lesions with signal hyperintense to that of surrounding tissue increases with increasing diffusion gradient area. However, the mean L/F is greater for all diffusion gradient areas for conventional DWI in comparison to DW-DESS-Cones

FIGURE 4:

Image examples from asymptomatic volunteers in which motion artifact (arrows) is greatly reduced with DW-DESS-Cones (b,d,f—dashed arrows) versus DW-DESS-Cartesian (a,c,e—solid arrows) at all three diffusion gradient strengths ($b_{eq}br$ 200, 500, 800)

FIGURE 5:

At all three levels of diffusion-weighting (a, b, c) artifact-to-noise ratio (A/N) is significantly lower with DW-DESS-Cones (blue markers) than with DW-DESS-Cartesian (gray markers). For all diffusion gradient amplitudes with DW-DESS-Cones, A/N is close to 1.0 indicating minimal additional motion artifact above background noise. The smaller difference in A/N between the two techniques at $b_{eq}br$ 800 may be due to the lower signal-to-noise ratio (SNR) at this level of diffusion-weighting

FIGURE 6:

Three representative cases of DW-DESS-Cones with b_{eq} of 500 acquired in patients (a,c,e) demonstrate the robust elimination of motion artifacts (solid arrows). The general image quality of DW-DESS-Cones is also demonstrated in comparison to the respective conventional diffusion-weighted imaging (DWI) images acquired at $b = 600 \text{ s/mm}^2$ (b,d,f). The DW-DESS-Cones images have reduced distortion in two areas near the nipple (c—dotted arrow) and a biopsy clip (e—dotted arrow) where distortion is apparent in the corresponding DWI images (d,f—dotted arrows)

FIGURE 7:

Rating of sharpness, distortion, SNR, and overall image quality for blinded observer study of DW-DESS-Cones versus diffusion-weighted imaging (DWI). Ratings 1: DW-DESS-Cones much worse than DWI; 2: DW-DESS-Cones somewhat worse than DWI; 3: DW-DESS-Cones equivalent to DWI; 4: DW-DESS-Cones somewhat better than DWI; 5: DW-DESS-Cones much better than DWI

FIGURE 8:

In 11/14 lesions DW-DESS-Cones (black bars) and conventional diffusion-weighted imaging (DWI) (gray bars) had concordant hyperintensity (lesion-to-fibroglandular tissue ratio $[L/F] > 1.0$) or hypointensity ($L/F < 1.0$) of lesion with respect to the surrounding tissue. Abbreviations: b. mass, benign enhancing mass; DCIS, ductal carcinoma in situ; FA, fibroadenoma; IDC, invasive ductal carcinoma; LN, lymph node; Mu. IDC, mucinous IDC; TNBC, triple negative breast cancer

FIGURE 9:

Four malignant lesions (a–d, TNBC, triple negative breast cancer; IDC, invasive ductal carcinoma) and two benign fibroadenomas (e,f, FA) on CE-MRI (Column 1). All lesions are visible on conventional diffusion-weighted imaging (DWI) (Column 2) and on DW-DESS-Cones (Column 3) with hyperintense signal with respect to surrounding tissue. Respective lesion-to-fibroglandular tissue ratios (L/F) are shown on each DWI and DW-DESS-Cones image

TABLE 1.b-Value equivalent (b_{eqbr}) for DW-DESS-Cones in this study

Conventional DWI b-value (b) (s/mm ²)	DW-DESS- Cones diffusion gradient amplitude (mT/m)	DW-DESS- Cones b-value equivalent— breast (b_{eqbr})
0	16	0
200	26	200
400	36	400
600	47	600
800	57	800
1000	68	1000

Note: b-Value equivalency—breast (b_{eqbr}) metric established for DW-DESS-Cones based on phantom experiments (Figure 2).