Highly accelerated subtractive femoral non-contrast-enhanced MRA using compressed sensing with k-space subtraction, phase and intensity correction

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Purpose: To develop an improved reconstruction method, k-space subtraction with phase and intensity correction (KSPIC), for highly accelerated, subtractive, non-contrast-enhanced MRA.

Methods: The KSPIC method is based on k-space subtraction of complex raw data. It applies a phase-correction procedure to restore the polarity of negative signals caused by subtraction and an intensity-correction procedure to improve background suppression and thereby sparsity. Ten retrospectively undersampled data sets and 10 groups of prospectively undersampled data sets were acquired in 12 healthy volunteers. The performance of KSPIC was compared with another improved reconstruction based on combined magnitude subtraction, as well as with conventional k-space subtraction reconstruction and magnitude subtraction reconstruction, both using quantitative metrics and using subjective quality scoring.

Results: In the quantitative evaluation, KSPIC had the best performance in terms of peak SNR, structural similarity index measure, contrast-to-noise ratio of artery-to-background, and sharpness, especially at high acceleration factors. The KSPIC method also had the highest subjective scores for all acceleration factors in terms of vessel delineation, image noise and artifact, and background contamination. The acquisition can be accelerated by a factor of 20 without significant decreases of subjective scores. The optimal size of the phase-correction region was found to be 12-20 pixels in this study.

Conclusion: Compared with combined magnitude subtraction and conventional reconstructions, KSPIC has the best performance in all of the quantitative and qualitative measurements, permitting good image quality to be maintained up to higher accelerations. The KSPIC method has the potential to further reduce the acquisition time of subtractive MRA for clinical examinations.

Keywords: background suppression, compressed sensing, fresh-blood imaging, magnetic resonance angiography, non-contrast-enhanced
INTRODUCTION

Although contrast-enhanced MRA (CE-MRA) is widely established in the clinical routine for the diagnosis of vascular diseases, non-contrast-enhanced MRA (NCE-MRA) techniques have drawn increasing attention in recent years because of the safety concerns about gadolinium-based contrast agents.2,3 Subtractive NCE-MRA is a class of techniques that displays vasculature by subtracting dark-blood (DB) images from bright-blood (BB) images. Typical subtractive NCE-MRA techniques include cardiac-gated 3D fast spin echo (FSE) (also called fresh-blood imaging),4,5 flow-sensitive dephasing,6,9 and arterial spin labeling.10,11

Most NCE-MRA methods have a much longer acquisition time than CE-MRA, which not only limits the clinical acceptance of these techniques, but also renders them sensitive to artifacts from patient motion. The problem of low time efficiency is worse for subtractive NCE-MRA techniques, as it requires multiple acquisitions. Any motion between the different acquisitions can lead to misregistration, which causes artifacts and impairs vessel signal.12 Several efforts have been made to reduce the acquisition time, such as partial Fourier (PF) sampling, parallel imaging (PI), and compressed sensing (CS).

Signal sparsity is an important factor for both CS and PI reconstruction. With increasing sparsity, fewer samples are needed to accurately reconstruct the signal, and a better reconstruction quality can be achieved from a given number of samples.12,13 The MR angiograms are especially sparse, ideally with signal only from blood vessels, and minimal background signals. However, performing CS reconstruction on BB and DB data sets separately, followed by magnitude subtraction, does not take advantage of the sparsity of the subtracted angiogram. Rapacchi et al proposed a CS algorithm that combines BB and DB reconstruction together and adds a magnitude subtraction term in the cost function to exploit the sparsity of angiograms.14 This method was reported to improve CS reconstruction in both thoracic DCE-MRA and NCE dynamic intracranial MRA.14,15 To distinguish it from the traditional magnitude-subtraction method, this method will be called “combined magnitude subtraction” (CMS) in this paper.

Complex subtraction of raw data before reconstruction is an alternative approach to promote sparsity. The subtracted k-space data are inherently sparse in its image-domain representation. Although having drawbacks in terms of increased sensitivity to phase error and imposed SNR penalty,14,15 complex subtraction in k-space has shown superior performance in both peripheral CE-MRA and NCE-MRA with PI, especially at large acceleration factors (AFs).12,16

Another problem with subtractive NCE-MRA is that some background tissues have different intensity levels in BB and DB images, resulting in residual signal in the subtracted images.17-21 The reasons for this include different schemes applied in BB and DB acquisitions,19 R-R variations caused by the irregular heartbeats,20 and the variation in TRs between consecutive readouts.21 Our previous work proposed an intensity correction (IC) method to correct the intensity difference of background tissues and improves background suppression.19 Basically, it uses a weighted subtraction (\(I_{\text{Subtracted}} = I_{\text{Bright}} - \beta I_{\text{Dark}}\)) instead of simple subtraction. The weighting factor \(\beta\) is determined by robust regression, which calculates the regression coefficient of background tissues from a scatter plot showing the voxel intensity of BB images versus DB images. This weighted-subtraction approach can give background signals close to zero in the subtracted images. Previously this approach has only been applied to magnitude images that have been separately reconstructed.

In this study, we propose applying the weighted-subtraction approach to k-space data (instead of to image data, as used in Li et al19). This approach aims to reduce the background levels in the subtraction images, which is expected to increase sparsity and improve the performance of CS at high acceleration factors. However, weighted complex subtraction is expected to cause an increase in negative signals after subtraction, which would appear as background artifacts because of the loss of polarity in the reconstructed magnitude image.22,23 Moreover, the weighting factor cannot be obtained directly from complex data sets.

In this paper, we develop an improved reconstruction method based on k-space subtraction, termed as k-space subtraction with phase and intensity correction (KSPIC). A phase-correction procedure is used to preserve the polarity of the negative signal and remove background artifacts. This procedure requires a background reference for phase corrections, which can be provided by the BB or DB data set in subtractive NCE-MRA. Moreover, an IC procedure is applied, with the weighting factors calculated from the DB images and BB images generated by a fast and incomplete CS reconstruction. Second, for comparison, the CMS method14,15 is implemented for subtractive NCE-MRA. The reconstructions are based on the L1-iterative self-consistent PI reconstruction algorithm,24 with the split Bregman algorithm25 used for CS reconstruction. The performance of KSPIC and CMS is compared with conventional k-space subtraction reconstruction (KS) and magnitude subtraction reconstruction (MS) in both retrospectively and prospectively undersampled peripheral cardiac-gated 3D FSE data sets.
2 | THEORY

2.1 | Independent reconstruction with magnitude subtraction afterward (MS)

One conventional strategy is to reconstruct BB and DB data sets (denoted by subscripts $b$ and $d$, respectively) independently, and then do MS. The reconstruction can be written as an unconstrained optimization problem as follows:

$$u_b = \arg \min_{u_b} \left\{ \|RFu_b - f_b\|^2 + \lambda \|\Phi u_b\|^2_{1,2} + \gamma \| (G - I) Fu_b \|^2 \right\}$$

(1)

$$u_d = \arg \min_{u_d} \left\{ \|RFu_d - f_d\|^2 + \lambda \|\Phi u_d\|^2_{1,2} + \gamma \| (G - I) Fu_d \|^2 \right\}$$

(2)

where $f_b$ and $f_d$ are the acquired data; $u_b$ and $u_d$ are the estimated images; $G$ denotes the self-consistent PI reconstruction (SPIRiT) kernels computed from autocalibration signals; $F$ is the Fourier operator; $R$ is a k-space sampling operator; $\Phi$ is the sparsifying transform operator that is finite differences in the Fourier operator; $I$ is the identity operator; $\| \cdot \|^2$ is the L2-norm; $\| \cdot \|^2_{1,2}$ is the joint norm combining both the L1-norm along the voxel dimension and L2-norm along the coil dimension; and $\lambda$ and $\gamma$ are two regularization parameters that determine the balance among the data consistency, calibration consistency, and the promotion of sparsity. Following the reconstruction, the IC method based on robust regression can optionally be applied to the reconstructed BB and DB images to suppress residual signals from background tissues (MS-IC) by performing a weighted subtraction

$$I_{\text{Subtracted}} = I_{\text{Bright}} - \beta I_{\text{Dark}}$$

The model of robust regression using deviation angle (with the radius influence factor of 0.5) was used in all cases in this study.

2.2 | k-Space subtraction before reconstruction (KS)

Subtracting the raw data in KS can take advantage of the sparsity more directly. The reconstruction can then be formulated as

$$u_i = \arg \min_{u_i} \left\{ \|RFu_i - (f_b - f_d)\|^2 + \lambda \|\Phi u_i\|^2_{1,2} + \gamma \| (G - I) Fu_i \|^2 \right\}$$

(3)

2.3 | Combined reconstruction with magnitude subtraction

The combined reconstruction adds magnitude subtraction terms between BB and DB data sets, which can exploit the sparsity of subtracted images. The values of $u_b$ and $u_d$ are iteratively minimized in a single algorithm:

$$u_i = \arg \min_{(u_b, u_d)} \left\{ \|RFu_b - f_b\|^2 + \lambda \|\Phi u_b\|^2_{1,2} + \mu \|u_b - u_d\|^2_{1,2} + \gamma \| (G - I) Fu_b \|^2 \right\}$$

(4)

where $\mu$ is the parameter controlling the weight of the subtraction terms. Intensity correction can also be used after the CMS reconstruction (CMS-IC).

2.4 | k-Space subtraction with phase correction

For cardiac-gated 3D FSE, the signal intensity of some background tissues, such as muscle and fat, may appear slightly higher on the DB images. Its representation in the image domain should become negative after subtraction. However, when using k-space-subtraction methods, the negative signal loses its polarity when taking the magnitude of the reconstructed image, and appears as background artifacts on the subtracted angiograms (Figure 1A).

Phase-sensitive detection can be used to correct this background phase variation so that the real part of the image can be used, and the polarity can be preserved. (Figure 1A). This method normally requires an additional acquisition of a background phase reference, which should adequately represent the background phase variation but not be corrupted by polarity shifts. Fortunately, in subtractive NCE-MRA, this reference can be provided by the BB or DB data, which has the same background phase variation as the subtracted data set and all positive values in the image domain. Moreover, when the background signal has different phases in the BB and DB data, phase errors are created but can be reduced when taking the real values instead of the magnitudes (Figure 1B).

In KS with phase correction (KSPC), a homodyne low-pass filter is applied to the BB or DB data to obtain a low-resolution image as a background phase reference. The phase of the reference image $\phi_r$ is then removed from the reconstructed subtracted image $I_s$ on a pixel-by-pixel basis, so that the polarity of the negative signal is preserved in the real part of the resultant image ($I_{PC}$):

$$I_{PC} = \text{Real} \left\{ I_s e^{-i\phi} \right\}.$$  

(5)

Finally, the corresponding background artifacts can be removed by nulling the negative values.

2.5 | k-Space subtraction with phase and intensity correction

Intensity correction can also be used in k-space subtraction approaches. To calculate the weighting factor before the full
CS reconstruction, a fast CS reconstruction is first performed to acquire a partially reconstructed image set. Weighted subtraction in k-space can lead to additional negative signals after subtraction, but these can be removed by the phase-correction procedure.

The image reconstruction process of KSPIC is as shown in Figure 2. First, a fast CS reconstruction with only two iterations and without PI reconstruction is performed on 10% of the k-space data. The 10% subsampled data were obtained by performing a one-dimensional fast Fourier transform in the x-direction to form a hybrid $x-k_y-k_z$ space, and then selecting equally spaced axial slices along the x-direction. Next, IC is performed on the subsampled data to calculate the weighting factor, and a weighted complex subtraction is performed on the k-space data. A full CS reconstruction, in combination with SPIRiT for PI and homodyne detection for PF sampling, is then performed on the full subtracted data set. The background artifacts caused by negative signals can be more serious when IC is applied. Therefore, a background phase reference is reconstructed from the symmetric central region of the DB data set and is used to correct the background phase variation (as described previously for KSPC).

2.6 Summary of reconstruction strategies

The reconstruction strategies included in this study are listed in Table 1. The KS-IC images will not be assessed because they are corrupted by background artifacts caused by inverted negative signals. All other methods will be evaluated in the retrospective study using quantitative metrics. The MS, KS, CMS-IC, and KSPIC methods will be evaluated in the prospective acceleration study using subjective quality scores.

3 METHODS

3.1 Subjects and data acquisition

The femoral arteries of 12 healthy subjects (8 men and 4 women; age range 24–45 years) were imaged using the cardiac-gated 3D-FSE sequence. Examinations were performed using a 1.5T system (Discovery MR450; GE Healthcare, Waukesha, WI) and a 32-channel or 8-channel cardiac array coil. Studies were approved by the local research ethics committee, and all participants gave informed consent.
Before the 3D acquisition, multiple 2D echocardiogram-gated FSE fresh-blood images with a single thick slice and increasing cardiac trigger delays were used to determine the appropriate diastolic echocardiogram delay times.5

The “adaptive refocus” technique, which is used for the MR system vendor product sequence, was applied to all the cardiac-gated 3D-FSE acquisitions. It uses variable refocusing flip angles in the systolic acquisitions, which start from an initial flip angle of 105° and end with constant flip angles of 180°, thus increasing the flow sensitivity.31 The diastolic acquisitions use constant 180° refocusing flip angles with the same echo spacing as the systolic acquisitions. For retrospective acquisitions, flow-spoiling gradients4 (10% of one-half the area of the readout gradient) were applied in fully sampled acquisitions with a smaller matrix size (224 × 224 × 80). No flow-spoiling gradients were used for prospective acquisitions with the image matrix size of 320 × 320 × 80.

For the retrospective simulated study, 10 fully sampled cardiac-gated 3D FSE data sets were acquired from 10 subjects and accelerated using AFs from 4 to 20. Simulated undersampling was then performed on fully sampled data sets. The CS, PI, and PF sampling were combined together to accelerate the acquisitions using Poisson disk-sampling patterns.32,33
For the prospective acceleration, a CS-accelerated cardiac-gated 3D-FSE pulse sequence was developed. Ten groups of prospectively accelerated images were acquired from 10 subjects, each with four data sets accelerated by 10x, 15x, 20x and 25x, respectively. Additional details of the sequences are listed in Supporting Information Table S1.

### 3.2 Compressed-sensing reconstruction

All data sets were first compressed into four virtual channels to reduce computational burden before the image reconstruction. Following CS reconstruction, the reconstructed individual channel images are combined into a single composite image by using an adaptive combination method instead of the conventional root-sum-of-squares technique. The performance of coil compression and channel combination was assessed on three fully sampled data sets with 32 channels, and the optimal number of virtual channels was therefore determined. The results are shown in Supporting Information Figure S1.

All of the reconstructions were based on the split Bregman algorithm, together with projection over convex sets iterations for the L1-iterative self-consistent PI reconstruction. The details of the CS reconstruction algorithm are found in Supporting Information Table S2. Finite differences were used as the sparsifying transform. The split Bregman algorithm has a rapid convergence, allowing CS reconstruction in a small iteration number. In this study, the full CS reconstruction had 10 iterations in total, with five inner iterations and two outer iterations. The fast partial CS reconstruction for IC had only two iterations with no inner iterations. The regularization parameters in Equations (1)-(4) were optimized in a separate pilot study. Because the calibration consistency term was solved by the projection over convex sets iterations without using its weighting parameter $\gamma$, only $\lambda$ and $\mu$ (only for CMS) needed to be optimized; this optimization was performed by retrospectively undersampling k-space using a range of parameter values, and then maximizing the peak SNR (PSNR) between CS-reconstructed images and the fully sampled reference images. All raw k-space data were normalized by their maximum image intensity before reconstruction, which allows the same weighting parameters to be used for a large range of MRA data sets.

### 3.3 Central region of k-space

The central region of k-space acquired from BB or DB data has three purposes, which are (1) calculating the linear combination weights for SPIRiT, (2) estimating the background phase reference for phase correction, and (3) calculating the weights for adaptive channel combination. In this study, the central region for SPIRiT reconstruction and adaptive combination of coil elements was obtained from BB data, whereas the central region for phase correction was obtained from DB data. The performance of reconstructions using the central regions selected from different data and with different sizes was evaluated and compared.

### 3.4 Image assessment

For the retrospective study, simulated accelerated images were evaluated using several objective quantitative metrics. The PSNR and structural similarity index measure (SSIM) were calculated to evaluate reconstruction accuracy. The PSNR is used widely to measure the cumulative squared error between the target images and the reference images, and provides similar information to normalized RMS error. Instead of measuring errors, SSIM measures the structural similarity between two images, which is modeled as a combination of three factors including loss of correlation, luminance distortion, and contrast distortion.

Fully sampled images were used as the reference in PSNR and SSIM calculation. Using any one method for the reference image reconstruction would likely bias the comparisons toward that method, so instead the reference images were defined as an average of all appropriate methods: The reconstruction methods were categorized into two groups: those with IC and those without. The reference images were defined as the average of the fully sampled images reconstructed by different methods (ie, for the evaluation of KSPIC, MS-IC, and CMS-IC, the reference images were the average of images reconstructed by KSPIC, MS-IC and CMS-IC, whereas for the evaluation of KSPC, KS, MS and CMS, the reference images were the average of images reconstructed by KSPC, KS, MS, and CMS).

Contrast-to-noise ratio (CNR) of artery-to-background was used to evaluate the arterial signal intensity level. Arterial and background signal was calculated by applying arterial and background tissue masks obtained from subtracted images and BB images, respectively. The SD of the difference image (subtraction images of the reconstructed angiograms from the reference fully sampled angiograms) was used for noise estimation. The CNR of artery-to-background, together with SSIM, have been reported to show a good concordance with radiologists’ qualitative evaluation.

An automatic method was implemented to assess the sharpness of the vessel edges. Arterial regions were detected on the individual axial reformats by the circular Hough transform. The sharpness was then evaluated on the profiles of the arterial edges in two directions using a least-squares curve fit based on the sigmoid function.

To evaluate the background-suppression effect, signal ratios of background tissues (veins, bladder, and testis) to arteries were measured on retrospectively accelerated images reconstructed by the different methods. Signal intensities of different tissues were measured from matched regions of
interest drawn in representative regions in the target tissues on the maximum intensity projections of subtracted images.

For the prospective acceleration study, maximum intensity projections of the images reconstructed by four different methods were assessed by two experienced radiologists (N.S. with 10 years of experience and A.P. with 3 years of experience) in a randomized order, and their scores were averaged. The radiologists were blinded to reconstruction methods and AFs. Three separate aspects of the images were graded: vessel delineation; image noise and artifacts; and background and venous contamination. The criteria for scoring are listed in Table 2.

### 3.5 Statistics analysis

Statistical analysis evaluated differences between KSPIC/KSPC and the other reconstruction methods. For subjective image-quality scores, Wilcoxon signed-rank tests were performed to identify pairwise differences between KSPIC and each of MS, KS and CMS-IC, respectively. For quantitative metrics results, paired Student’s t-tests were performed to assess pairwise differences between KSPIC/KSPC and the other reconstructions at 4×, 12×, and 20×. Pairwise comparisons include KSPIC versus MS-IC, KSPIC versus CMS-IC, KSPC versus MS, KSPC versus KS, and KSPC versus CMS. Statistical significance was defined at $p < .05$ in all tests.

### 4 RESULTS

#### 4.1 Retrospective simulation

Figure 3 shows example images of KS, MS, CMS-IC, and KSPIC in fully sampled and retrospectively accelerated data sets using AFs from 4 to 20. The KSPIC method has good and consistent image quality over the range of different AFs. Noticeable image degradation in terms of increased artifacts, residual background tissue, and impaired vessel delineations can be observed in KS, MS and CMS-IC, especially when the AF is large.

Figures 4 and 5 show quantitative evaluation results of the seven different methods. The corresponding values and statistical evaluations are summarized in Supporting Information Tables S3-S5 (shown only at 4×, 12×, and 20×).

#### 4.1.1 The PSNR, SSIM, and CNR of artery-to-background

Reconstruction methods with and without IC are shown separately in Figure 4, because their evaluations used different reference images and therefore cannot be compared. The KS method with phase correction has the best performance in terms of SSIM and CNR of artery-to-background, both with IC (KSPIC) and without IC (KSPC). The PSNR values of CMS/CMS-IC and MS/MS-IC are higher when the AF $< 8$, but decrease rapidly with increasing AF. Compared with MS/MS-IC, CMS/CMS-IC has larger CNR but lower SSIM values. The PSNR of CMS/CMS-IC is between that of KSPC/KSPIC and MS/MS-IC—higher than MS/MS-IC but lower than KSPC/KSPIC when the AF $< 8$, and lower than MS/MS-IC but higher than KSPC/KSPIC when the AF $> 8$. The KS method has low PSNR and CNR. In comparisons between KSPC/KSPIC and other reconstructions, significant differences existed in all cases except the PSNR of CMS at 4×, SSIM of KS at 20×, CNR of CMS at 4×, and PSNR of CMS-IC at 12×.

#### 4.1.2 Sharpness

The k-space-subtraction methods (KSPC/KSPIC and KS) have significantly better sharpness than magnitude-subtraction methods (MS/MS-IC and CMS/CMS-IC) at all of the AFs. No significant differences were found between KS and KSPC.

### Table 2 Criteria for subjective scoring

| Score | Vessel delineation | Image artifacts | Background and venous contamination |
|-------|-------------------|-----------------|------------------------------------|
| 1     | Nondiagnostic delineation, poor delineation of all-sized arteries | Severe artifact and/or noise leading to nondiagnostic images | Severe background or venous contamination affecting diagnosis |
| 2     | Acceptable delineation of main/large arteries but impaired delineation of intermediate and small arteries | Moderate artifact and/or noise, impairing the definition of the fine structures of vessels | Moderate background or venous contamination |
| 3     | Good display of main/large arteries but impaired delineation of small branches | Mild artifact and/or noise, but not impairing the delineation of vessels | Minimal background or venous contamination but not affecting diagnosis |
| 4     | Excellent arterial display with good delineation of all-size arteries | Excellent artifact and noise suppression | Excellent background and signal suppression |
4.1.3 | Signal ratios of background tissue to arteries

As shown in Figure 5, the methods with IC show lower values than the methods without IC (MS-IC vs MS, CMS-IC vs CMS, and KSPIC vs KSPC/KS). The measurements of magnitude-subtraction methods (MS/MS-IC and CMS/CM-IC) increase with increasing AFs, whereas the measurements of k-space subtraction methods (KSPIC, KSPC, and KS) do not increase or even decrease with increasing AFs. The KSPIC method has the lowest measurements at all AFs and for all measured background tissues. This difference between KSPIC and other reconstructions was significant in every case except for the vein-to-background ratios with MS-IC and CMS-IC at 4× (Supporting Information Table S5).

**FIGURE 3** Example images of retrospective simulated accelerations using different reconstructions. A, Sampling patterns with the acceleration factors (AFs) from 4 to 20. B-E, Maximum intensity projections (MIPs) (left femoral arteries) of images reconstructed by k-space subtraction reconstruction (KS), magnitude subtraction reconstruction (MS), combined magnitude subtraction with intensity correction (CMS-IC), and KSPIC, respectively. Image degradation in terms of residual venous signal (blue arrowheads), image blurring or artifacts (yellow arrowheads), and impaired vessel delineations (red arrowheads) can be observed in KS, MS, and CMS-IC.
FIGURE 4  Plots summarizing the quantitative evaluation of simulated acceleration. Peak SNR (PSNR), structural similarity measure (SSIM), contrast-to-noise ratio (CNR) of artery-to-background, and sharpness versus the AF were calculated for the different reconstructions. Top row: reconstructions with intensity correction (IC) including KSPIC, MS with postprocessing IC, and CMS with postprocessing IC. Bottom row: Reconstructions without IC including KS with phase correction, CMS, conventional MS, and conventional KS. The values are the mean and SD calculated over 10 volunteer data sets.

FIGURE 5  Signal ratios of background tissue to arteries of different reconstruction methods with different AFs. A, Signal ratios of veins to arteries. B, Signal ratios of bladder to arteries. C, Signal ratios of testis to arteries. The values are the mean and SD calculated over 10 volunteer data sets.
4.2 | Prospective acceleration

The average scan times of 10×, 15×, 20×, and 25× accelerated acquisitions were 272, 193, 138, and 112 seconds, respectively.

Example maximum intensity projections from 2 healthy volunteers are demonstrated in Figure 6. All four methods have good image quality at 10× acceleration, but image blurring and artifacts appear on MS and CMS-IC at 25× acceleration. Compared with magnitude-subtraction methods, KS has good noise suppression and less venous contamination, but impaired delineations of small branches can be observed on the KS images. Residual background tissues, such as veins and bladder, can be observed on the MS and KS images. The CMS-IC method has improved background suppression by using IC, while KSPIC has the best suppression.

Subjective image quality scores are summarized in Figure 7 and Supporting Information Table S6. Subjective scores show good agreement with the objective evaluation results using quantitative metrics in the retrospective study. The KSPIC method has the highest scores in all three scores, including vessel delineation, image artifacts, and background and venous contamination. The high scores are maintained at large AFs. No significant differences were observed between 10× acceleration and other larger AFs, except the vessel delineation score at 25×.

The MS and CMS-IC methods have lower scores, and their performance degrades rapidly with increasing AF. The KS method has good suppression of noise, artifacts and background signals, but shows poor vessel delineation. Significant differences were found in all cases between KSPIC and the other reconstructions, except the image artifacts and background contamination scores of CMS-IC at 10×, and the background contamination scores of KS at 20× and 25×.

4.3 | Phase correction

The phase-reference correction can be performed based on either BB or DB data, but in many cases using DB data led to reduced incoherent artifacts, especially on the axial slices that contain high signal intensity tissues with large areas, such as the testis (Figure 8A). The effect of the size of the central k-space region used for phase estimation (phase-correction region) was evaluated on all of the data. The quantitative evaluation shows that 12-20 was the optimal range of the region length (width = 1/2 length) in this study (Figure 8B). Larger phase-correction regions led to rapid decreases of all three measurements. In particular, excessively detailed phase estimation led to arterial phase change in the DB images (Figure 8C), leading to central signal loss in the arteries (Figure 8D). The phase
map obtained from the subtracted data contained inverted polarity and was corrupted by phase singularities; thus, it cannot be used as background phase reference (bottom row in Figure 8C).

4.4 | Computation time

The KSPIC method only needs to reconstruct one subtracted data set, and therefore has lower computational expenses than magnitude-subtraction methods. The average offline reconstruction times were 58 seconds for KSPIC (4.2 seconds for the fast partial CS reconstruction), 53 seconds for KS/KSPC, 91 seconds for MS/MS-IC, and 108 seconds for CMS/CMS-IC (implemented in MATLAB [The MathWorks, Natick MA, 4-core CPU /3.6 GHz, 32 GB RAM]).

5 | DISCUSSION

In this study, a new reconstruction method based on k-space subtraction, KSPIC, is proposed for accelerated subtractive NCE-MRA. The KSPIC method applies the IC procedure in k-space based on a weighted subtraction of BB and DB k-space data, and uses a phase-correction procedure to restore negative polarity and remove background artifacts.

Phase correction is inspired by the phase-sensitive detection method used in inversion-recovery imaging.26-30 The MR images are generally displayed as magnitude images, which avoids the need for correcting phase shifts in MR data caused by gradient ramping, eddy currents, motion, and the phase delay of electronic circuits.40 However, negative magnetization in inversion-recovery imaging, such as at short T1s, are inverted to positive values by taking signal magnitude. The same phenomenon exists in subtractive NCE-MRA, in which some negative signals are produced by k-space subtraction.

When PF sampling is applied, the phase-correction procedure can be regarded as part of the homodyne reconstruction, but acquiring the low-resolution phase reference from the raw BB or DB data instead of the actual subtracted data. It has been reported in a previous study that for reconstruction methods based on k-space subtraction, the low-resolution reference obtained from DB data can provide better performance than that from subtracted data in PF reconstruction, but the reasons and quantitative comparisons were not fully evaluated.12 From the perspective of PF reconstruction, using raw data as the phase reference has the following advantages. First, the phase reference from raw data can remove background artifacts caused by reversed polarity and reduce phase errors caused by phase differences between the BB and DB data (section 2.4). Second, the phase reference acquired from subtracted data is corrupted by phase singularities when the subtraction equals zero, which can affect the PF reconstruction and lead to signal loss and distortions of arteries. Because of these advantages, phase correction is also suggested as an additional procedure for subtractive MRA techniques without PF sampling.

Using the phase reference from DB data shows better suppression of artifacts out of the subject (Figure 8A). This is because those artifacts with negative polarity are generated...
FIGURE 8  Evaluation of k-space central region for phase correction. A, Example MIPs (top row) and axial slices (bottom row) using the phase reference from bright-blood and dark-blood data, where the yellow arrowheads denote background artifacts that are more extensive on the left figure, and the yellow line denotes the location of axial slices. B, Quantitative evaluation of reconstruction with different lengths of phase-correction region (length : width = 2:1). C, Phase reference acquired from bright blood, dark blood, and subtracted data with different sizes of phase-correction region. Red arrowheads denote phase changes in arteries that can impair arterial signal in reconstruction. D, Central signal loss in arteries in the image using a large phase-correction region size (the yellow arrowheads on the right image)
from the DB data rather than BB data, and their phase can only be provided by the DB data. The size of the central k-space region also has an influence on the performance of phase correction. The phase map obtained from a small central region of k-space from raw data can provide the background phase reference, showing the slowly varying phase variation related to hardware considerations. In comparison, phase references from larger central regions contain detailed phase variation related to anatomical tissues, which impair the precise correction of background phases.

Applying the IC procedure can suppress the residual signal of background tissues. Intensity correction uses a robust regression method to calculate the regression coefficient of voxel intensities of background tissues on BB and DB images, and it performs a weighted subtraction using the regression coefficient as the weighting factor. However, the linear regression needs to be performed on reconstructed individual BB and DB images and is difficult for k-space subtraction-based methods. The fast convergence of the split Bregman algorithm enables a fast partial CS reconstruction, so that IC can be performed on the partially reconstructed images before the full reconstruction.

Compared with magnitude subtraction-based methods, k-space subtraction-based methods can take advantage of the sparsity of subtracted data and show reduced background signals. The KSPIC method further reduced background tissue contamination by using IC. The objective measurement and subjective scoring results both show that the background suppression of KSPIC is better than CMS-IC and MS-IC, even though IC is used in all of these methods.

Intensity correction can also potentially increase the data sparsity and improve CS and PI reconstruction. In this study, the improvement in sparsity is not obvious in cardiac-gated sparsity and improve CS and PI reconstruction. In this study, though IC is used in all of these methods.

delay alternating with nutation for tailored excitation flow-KSPIC in other subtractive NCE-MRA techniques, such as and DB data. Future work will evaluate the performance of 3D FSE because of the similar muscle signal intensity on BB and DB images. The KSPIC method further reduced background tissue contamination by using IC. The objective measurement and subjective scoring results both show that the background suppression of KSPIC is better than CMS-IC and MS-IC, even though IC is used in all of these methods.

Intensity correction can also potentially increase the data sparsity and improve CS and PI reconstruction. In this study, the improvement in sparsity is not obvious in cardiac-gated 3D FSE because of the similar muscle signal intensity on BB and DB data. Future work will evaluate the performance of KSPIC in other subtractive NCE-MRA techniques, such as delay alternating with nutation for tailored excitation flow-sensitive dephasing (DANTE-FSD), which has been investigated in our previous study and shown significantly higher background signal intensity on BB images than the DB images. Although cardiac-gated 3D FSE typically has a longer acquisition time because of the need for two acquisitions to perform a subtraction, this increased acquisition time might now be compensated for by the high acceleration factors offered by KSPIC. The averaged acquisition times were 3.2 (15×) or 2.3 (20×) minutes for data sets with the matrix size of 320 × 320 × 80, which is even shorter than some other nonsubtractive peripheral NCE-MRA approaches, such as velocity-selective magnetization-prepared MRA (5.3 minutes for acquisitions with a similar matrix size and 3-4 minutes for 8× CS-accelerated acquisitions with a smaller size).

The CE-MRA method also involves image subtraction between the images acquired before and after the contrast injection. Previous studies have reported that complex subtraction in k-space has better performance than magnitude subtraction in both CE-MRA with PI acceleration and dynamic CE-MRA without acceleration. The KSPIC method can potentially be applied to subtractive CE-MRA to further improve the reconstruction performance and allow greater AFs. Arterial spin labeling is another subtractive MRI technique used in both angiography and perfusion imaging, which can also be a potential implementation area of KSPIC.

Only femoral examinations in healthy volunteers were evaluated, which is a limitation of this study. Subtractive 3D FSE-based techniques have been demonstrated to have less stable and accurate performance in patients with arterial pathology in comparison with digital subtraction angiography, CE-MRA, and another NCE-MRA technique—quiescent interval slice selective. Future work in patients will assess acceleration based on KSPIC and evaluate whether it can improve the diagnostic performance and/or reduce examination times. The feasibility of KSPIC in other body areas will also be evaluated, such as calf, thorax, and abdomen.

6 | CONCLUSIONS

A new reconstruction method based on complex subtraction with intensity correction, KSPIC, was developed for highly accelerated femoral cardiac-gated 3D FSE. Compared with conventional MS, conventional KS and CMS reconstruction methods, KSPIC has the best reconstruction performance in the quantitative and qualitative measurements, permitting good image quality to be maintained up to higher AFs. In the prospective acceleration evaluation, KSPIC can accelerate the acquisition by factors of up to 20 (with average scan times of 2.3 minutes) without significant decreases of subjective quality scores in terms of vessel delineation, noise and artifacts, and background signal contamination. Further evaluation is needed to assess the diagnostic performance in patients with peripheral arterial disease.

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DATA AVAILABILITY STATEMENT

The KSPIC code and an example data set that supports the findings of this study are openly available in GitHub at https://github.com/hl476-cam/KSPIC.
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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the Supporting Information section.

**FIGURE S1** Quantitative evaluation results (A-C) and reconstruction time (D) of channel compression and channel combination with different virtual channel numbers. The data from 32 channels were compressed into fewer virtual channels before the image reconstruction, and the reconstructed individual channel images were combined using either adaptive combination (blue line) or root-sum-of-squares (red line). The evaluation was performed on three data sets retrospectively undersampled using an acceleration factor (AF) of 10×. The adaptive combination has much higher scores in all three measurements, especially when the virtual channel number is small.

**TABLE S1** Parameters used in retrospective and prospective acceleration studies

**TABLE S2** L1-iterative self-consistent PI reconstruction solved by split Bregman and projection over convex sets

**TABLE S3** Quantitative analysis results (mean ± SD) of k-space subtraction reconstruction (KS), magnitude subtraction reconstruction (MS), combined magnitude subtraction (CMS), and KS with phase correction. Note: Images were retrospectively accelerated by 4×, 12×, and 20× from 10 volunteer data sets.

**TABLE S4** Quantitative analysis results (mean ± SD) of MS with intensity correction (MS-IC), CMS with IC (CMS-IC), and KS with phase and IC (KSPI). Note: Images were retrospectively accelerated by 4×, 12×, and 20× from 10 volunteer data sets.

**TABLE S5** Signal ratio of background tissues to arteries. Note: Images were retrospectively accelerated by 4×, 12×, and 20× from 10 volunteer data sets.

**TABLE S6** Subjective scores (mean ± SD) of images prospectively accelerated by 10×, 15×, 20×, and 25× from 10 volunteer data sets

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