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TECHNICAL NOTE

Optimal Protocol for Contrast-enhanced Free-running 5D Whole-heart Coronary MR Angiography at 3T

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Free-running 5D whole-heart coronary MR angiography (MRA) is gaining in popularity because it reduces scanning complexity by removing the need for specific slice orientations, respiratory gating, or cardiac triggering. At 3T, a gradient echo (GRE) sequence is preferred in combination with contrast injection. However, neither the injection scheme of the gadolinium (Gd) contrast medium, the choice of the RF excitation angle, nor the dedicated image reconstruction parameters have been established for 3T GRE free-running 5D whole-heart coronary MRA. In this study, a Gd injection scheme, RF excitation angles of lipid-insensitive binominal off-resonance RF excitation (LIBRE) pulse for valid fat suppression and continuous data acquisition, and compressed-sensing reconstruction regularization parameters were optimized for contrast-enhanced free-running 5D whole-heart coronary MRA using a GRE sequence at 3T. Using this optimized protocol, contrast-enhanced free-running 5D whole-heart coronary MRA using a GRE sequence is feasible with good image quality at 3T.

Keywords: *contrast medium, coronary Magnetic Resonance angiography, fat suppression, free-running framework, gradient echo*

Introduction

Whole-heart coronary cardiovascular MR (CMR) is traditionally performed by triggering the acquisition to a resting phase of the cardiac cycle during free-breathing. Respiratory motion management is obtained either with end-expiratory navigator-gating on the right hemidiaphragm or through self-navigation deriving the respiratory displacement from within the acquired data or using a low-resolution image navigator (iNAV) technique.[1–3] However, these methods suffer from a certain level of inherent operator dependence, time inefficiency, and complicated workflow. Recently, whole-heart 3D radial data acquisitions that are free-breathing and non-electrocardiogram (ECG)-triggered (i.e., free-running) are gaining in popularity because they reduce scanning complexity by removing the need for specific slice orientations, respiratory gating, cardiac triggering, and, in some cases even ECG lead placement.[4–6] This approach aimed at resolving the different cardiac and respiratory motion states with a method called extra-dimensional golden-angle radial sparse parallel (XD-GRASP) MRI during the reconstruction routine.[7] This novel approach based on compressed sensing (CS) for the reconstruction of highly under-sampled multidimensional datasets allows for the reconstruction of 5D (x-y-z-cardiac-respiratory) coronary MR angiography (MRA).[5,6,8]

At 1.5T, free-running 5D whole-heart coronary MRA can be performed using balanced steady-state free precession (bSSFP) interrupted by fat saturation, uninterrupted using water-selective lipid-insensitive binominal off-resonance RF excitation (LIBRE).[6,8,9] For visualization of the coronary arteries with a free-running bSSFP sequence, a time-efficient non-interrupted fat suppression technique that incorporates homogenous fat suppression allowing for sufficient blood-muscle contrast is needed. LIBRE is a recently-developed water-excitation pulse that provides broadband fat suppression. It consists of two non-selective

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off-resonant rectangular RF sub-pulses that can be as short as 1.0 ms.[9,10] LIBRE has been shown to provide effective fat suppression insensitive to main field (B0) and RF field (B1) inhomogeneities.[9]

In contrast, at 3T, spoiled gradient-recalled echo (GRE) sequences are preferred to bSSFP for free-running 5D whole-heart coronary MRA because they are less sensitive to the increased off-resonance effects caused by increased magnetic field inhomogeneities, and they have lower specific adsorption rate (SAR).[4] Generally, GRE sequences provide poor blood-tissue contrast, when no gadolinium (Gd) contrast medium is administered. Further, free-running 5D whole-heart coronary MRA cannot use the T2 preparation pulse and fat suppression pulse since the continuous data acquisition is required. Therefore, to obtain sufficient blood muscle contrast, administration of T1-shortening Gd contrast medium is essential for 3T GRE free-running 5D whole-heart coronary MRA in combination with a non-interrupted time-efficient fat suppression technique such as LIBRE.[9,10] Thus, it is mandatory to optimize the RF excitation angle depending on the T1 value and the TR to obtain the maximal signal intensity and contrast of the target tissues for GRE imaging. However, the injection scheme of Gd contrast medium and the optimal RF excitation angle for LIBRE has not been established for 3T GRE free-running 5D whole-heart coronary MRA. Moreover, regularization parameters for CS reconstruction of the contrast-enhanced 3T GRE free-running 5D whole-heart coronary MRA could profit from a targeted optimization.

Consequently, the purpose of this study was to bridge these gaps by 1) optimizing the acquisition protocol for 3T GRE free-running 5D whole-heart coronary MRA, including the injection scheme of Gd contrast medium as well as the RF excitation angle for LIBRE, and 2) optimizing the regularization parameters for CS image reconstruction and, finally, to show the feasibility of the optimized images to visualize coronary arteries.

Materials and Methods

MR scanner and sequences

The study was approved by our Institutional Review Board (reference number H2020-056). All participants gave written, informed consent prior to participation in this study. All MR image acquisitions were performed on a 3T clinical MR scanner (MAGNETOM Vida; Siemens Healthcare, Erlangen, Germany) with an 18-channel body coil array and 72-channel spine coil array

The free-running framework for 5D whole-heart MRA incorporated a prototype non-interrupted fully self-gated 3D golden-angle radial spoiled GRE sequence. The acquisition used a non-slice selective LIBRE RF excitation pulse with sub-pulse duration of 0.7 ms and RF frequency offset of 980 Hz.[9] This sequence continuously acquired data over more than 500 consecutive cardiac cycles, while the acquisition was segmented into multiple interleaves using a spiral phyllotaxis trajectory. Each interleaf was rotated by the golden angle and was preceded by a readout oriented along the superior-inferior (SI) direction for cardiac and respiratory self-gating.[5] The following sequence parameters were used: TR/TE = 3.93/2.19 ms, receiver bandwidth = 868 Hz/px, FOV = 220 × 220 × 220 mm^3, readout matrix = 192, isotropic spatial resolution = 1.15 × 1.15 × 1.15 mm^3, number of segments = 22, for a total of 126478 radial lines and a constant total scan time of 8 min 17s.

For the optimization of the Gd injection scheme and subsequent phantom study, T1 mapping was performed using a modified look locker inversion recovery (MOLLI) sequence with a sampling scheme of 4(1)3(1)2 and in-line motion correction (flip angle = 35°, parallel imaging with acceleration factor = 2, TR/TE = 2.54/1.06 ms, and single-shot image acquisition duration 154 ms). FOV, matrix size, and slice thickness were adapted (FOV = 360 × 293 mm/280 × 228 mm, matrix size = 256 × 169/256 × 169, acquisition pixel size = 2.12 × 1.41 mm^2/1.65 × 1.09 mm^2, reconstruction pixel size = 1.41 × 1.41 mm^2/1.09 × 1.09 mm^2, and slice thickness = 8 mm/5 mm, for patient and phantom scans, respectively).

Gd injection scheme

The slow infusion scheme of Gd contrast medium for GRE free-running 5D whole-heart MRA was devised using the MR Safe intravenous infusion pump (MRidium 3860 +; IRadimed, FL, USA). The equipment setup and injection scheme are illustrated in Fig. 1. After setting up the equipment, slow infusion was initiated by the intravenous infusion pump with the injection rate of the total amount of gadobutrol (mL) divided by 8 (min) and continued until the end of the scan.

To evaluate the time course of contrast enhancement during Gd slow infusion and if the left ventricular (LV) ejection fraction (EF) impacts on the contrast enhancement, in two patients with normal and reduced LV EF who were referred to CMR for the clinical indication, T1 mapping at a mid-ventricular short-axis slice was repeated every 1 min after the start of gadobutrol slow infusion until 16 min using MOLLI during a waiting time for late gadolinium enhancement (LGE) imaging.

RF excitation angle for free-running 5D whole-heart coronary MRA at 3T

To optimize the RF excitation angle of the LIBRE pulses in the contrast-enhanced GRE free-running 5D whole-heart MRA at 3T, numerical simulations and phantom experiments were performed.

Numerical simulations

Numerical simulation was performed in Microsoft Excel (version 2019; Microsoft, Redmond, WA, USA) to predict

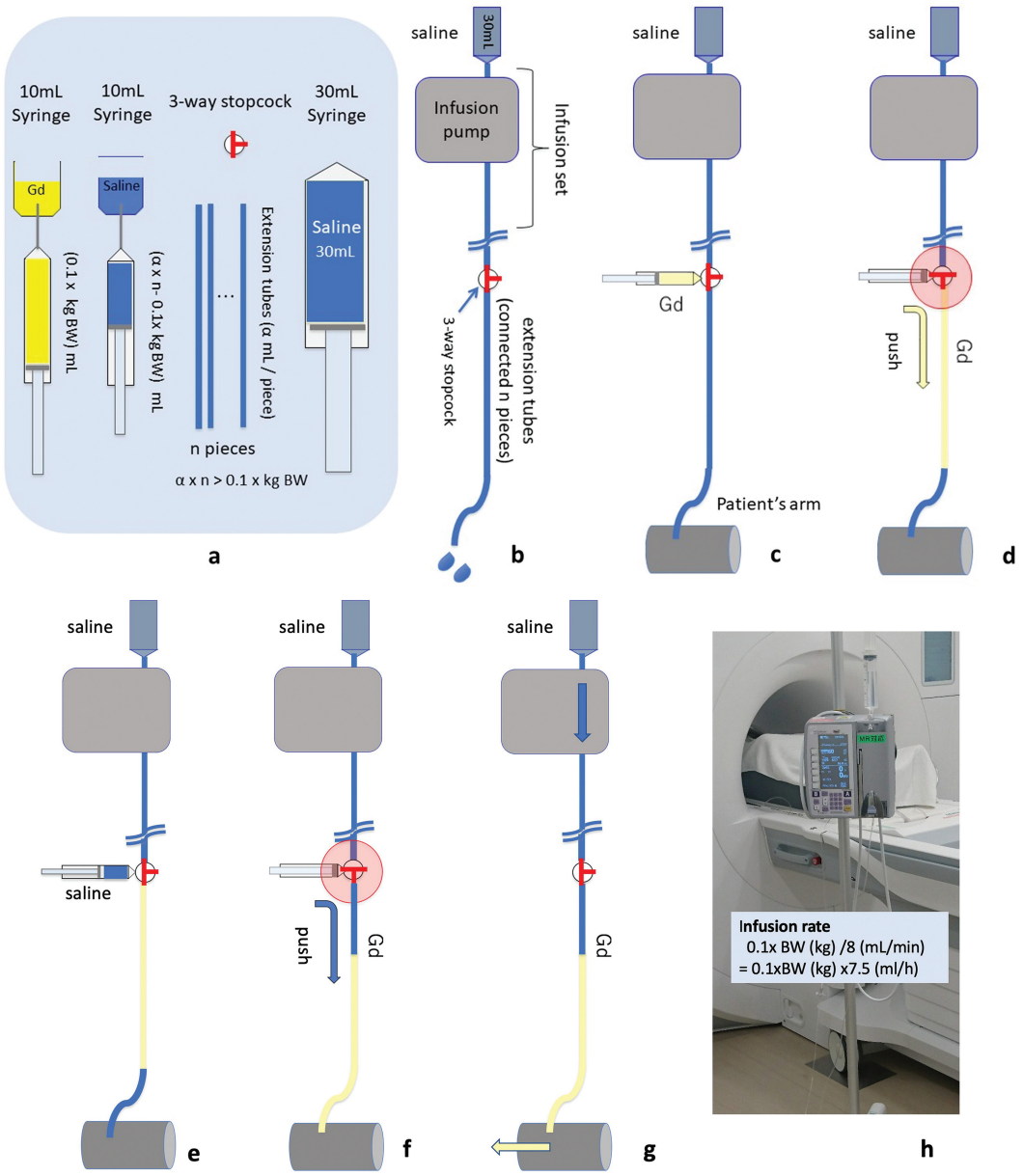

Fig. 1 The slow injection scheme for injectors is illustrated. Prepare MR Safe intravenous infusion pump, infusion set, 3 syringes, a 3-way stopcock, extension tubes (α mL/piece), gadobutrol, and saline. The number of extension tubes (n) are determined so that (α × n) (mL) > the total volume of gadobutrol (mL). (0.1 × kg body weight) (mL) of gadobutrol and (α × n- 0.1 × kg body weight) (mL) of saline is prepared in separate syringes (**a**). The system is filled with saline and set in the infusion pump (**b**). The system is connected to the venous cannula in the patient arm (**c**). The undiluted gadobutrol is loaded into the extension tube (**d**). Saline is added through the stopcock so that the tip of the Gd contrast medium reaches to the venous cannula (**e** and **f**). Slow infusion is initiated with the injection rate of the total amount of gadobutrol (mL) divided by 8 (min) and continued until the end of the scan (**g** and **h**). Gd, gadolinium.

the magnetization behavior on blood and myocardium (blood, T1 = 250 ms; myocardium, T1 = 400 ms and 600 ms) during the equilibrium phase of contrast enhancement after slow injection of gadobutrol based on the Bloch equation at a TR of 3.93 ms by gradually changing the RF excitation angle from 0° to 35°. Briefly, transverse magnetization of non-interrupted GRE was estimated using the following equations:

$$M_{z\,0} = 1$$

$$M_{z\,n} = M_{z\,0} + (M_{z\,n-1} \cdot \cos\alpha - M_{z\,0})\, e^{\frac{-TR}{T1}}$$

$$M_{xy\,n} = M_{z\,n} \cdot \sin\alpha$$

where M_z and M_{xy} are the longitudinal and the transverse magnetizations, respectively.

First, M_{xy} was computed as a function of the number RF excitation pulses with angle α. Then, at the number of pulses when M_{xy} reached a steady state, M_{xy} was computed as a function of RF excitation angle for a T1 of 250 ms, 400 ms, and 600 ms. This simulation informs the range of optimal RF excitation angles for the subsequent phantom experiments.

Phantom experiments

A gelatine-based hydrogel phantom was prepared by diluting gadobutrol (Gadovist; Bayer Yakuhin, Osaka, Japan) with aqueous solution of gelatin in order to mimic the T1 relaxation properties of blood and myocardium during the equilibrium phase of contrast enhancement after slow injection of gadobutrol. In addition, baby oil (Johnson & Johnson, Tokyo, Japan) mimicking epicardial fat was used. A phantom was made of five small plastic containers (4 × 5 × 2 cm each) of simulated T1 values for contrast-enhanced blood (~250 ms) and myocardium (~400 ms and ~600 ms), fat (baby oil, 200–300 ms), and non-contrast myocardium (~1200 ms). For the subsequent MR imaging, those were placed into water in a large container (22 × 25 × 6 cm).

The phantom was scanned using a MOLLI sequence and the free-running 5D whole-heart MRA framework with an electronically programmed heart rate of 60 bpm. Data collection by the free-running 5D whole-heart MRA framework incorporating LIBRE pulses was repeated for on-resonance RF excitation angles of 3°, 5°, 10°, 12°, 15°, 20°, 25°, and 30°. In the phantom experiments, images were reconstructed directly at the scanner based on 3D gridding and then used for the analyses.

Contrast-enhanced GRE free-running 5D whole-heart coronary MRA at 3T

***In vivo* study**

Contrast-enhanced free-running whole-heart data were collected in 12 consecutive patients who were clinically referred to CMR for screening of coronary artery disease (age: 70.3 ± 8.5y; 8 male) using the free-running 5D whole-heart MRA framework with a LIBRE on-resonance RF excitation angle of 15°, which was optimized by the preceding phantom experiments. Isosorbide dinitrate (5 mg) was administered sublingually to the patients before the injection of the Gd contrast medium. The whole-heart free-running data acquisition was started 6 min after the start of the slow infusion of gadobutrol (0.1 mmol/kg) and lasted for 8 min 17s using the slow infusion scheme devised in this study. The whole-body average SAR was recorded as the % of the SAR limit in the "first level" mode (4W/kg, as defined in the international standard IEC 60601-2-33).[11]

To compare the image quality and demonstrate the feasibility of the 3T contrast-enhanced GRE free-running 5D whole-heart coronary MRA in the patients using the optimized protocol, non-contrast whole-heart free-running MRA data were acquired in 4 healthy volunteers (age: 40.3 ± 8.1y; 4 male) with the same free-running 5D whole-heart MRA framework as used in the patients scan. Sublingual isosorbide dinitrate was not used in the volunteers.

Image reconstruction

Reconstruction was performed offline in MATLAB R2015b (The MathWorks, Natick, MA, USA) on a LINUX workstation with two six-core CPUs (Intel Xeon E5; Intel, Santa Clara, CA, USA), 512 GB of RAM, and an NVIDIA Tesla K40 GPU (Nvidia, Santa Clara, CA, USA). Physiological motion signal extraction was performed as previously described.[5] Principal component analysis was subsequently performed on these SI projections to extract respiratory and cardiac signals. These signals were then used to sort the readouts into non-overlapping cardiac bins with a temporal width of 50 ms, and into four non-overlapping respiratory bins containing equal numbers of readouts.[5]

The binned k-space data were then reconstructed into motion-resolved images using CS by solving the optimization equation (Table 1) with the Alternating Direction Method of Multipliers (ADMM) algorithm (iterations = 10).

Optimization of regularization parameters

Optimization of the regularization parameters for λr, λt, and λs was conducted using the data obtained in a single representative patient as performed in the previous studies.[4,6,12] As a first step, to optimize the respiratory regularization parameter λr, the other two regularization parameters λt and λs were set to fixed values of 0.001 and 0, respectively, and images were reconstructed by testing 4 different λr values (i.e., 0.001, 0.005, 0.01, and 0.1). For the second step, 8 different λt values (i.e., 0.001, 0.0025, 0.005, 0.0075, 0.01, 0.0125, 0.025, and 0.1) were tested in combination with the λr values selected in the first step. In the final step, 4 different values of λs (i.e., 0, 0.0005, 0.001, and 0.0025) were compared in combination with the λr and λt values previously selected (see Data analysis). All datasets were reconstructed using the optimized regularization parameters. The time for the reconstruction was recorded.

Data analysis

T1 mapping was analyzed using CMR analysis software (cvi42; Circle Cardiovascular Imaging, Calgary, Canada). All other measurements were performed on a picture archiving and communication system (PACS) workstation (EV Insight; PSP, Tokyo, Japan). In the two patients who underwent repeated T1 mapping during gadobutrol slow infusion, the relation between T1 in the LV blood pool and the time after the start of slow infusion was ascertained. In the numerical simulations and the phantom experiments, the relation

Table 1 The optimization equation.

Equation		$\hat{x} = \underset{x}{\operatorname{argmin}} \ \frac{1}{2} \parallel Ax - b \parallel_2^2 + \lambda_s \parallel \nabla_s x \parallel_1 + \lambda_t \parallel \nabla_t x \parallel_1 + \lambda_r \parallel \nabla_r x \parallel_1$
Variable	A	Encoding matrix including the non-uniform Fourier transformation and coil sensitivity
	$\hat{x}$	Reconstructed 5D image
	b	Acquired undersampled k-space data
	∇_s	Finite difference operator along the x, y, and z spatial dimensions
	∇_t	Finite difference operator along the temporal dimension (4th dimension)
	∇_r	Finite difference operator along the respiratory dimension (5th dimension)
	$\lambda_s, \lambda_t, \lambda_r$	Regularization weights
	$\parallel \cdot \parallel_1$	L1-norm
	$\parallel \cdot \parallel_2$	L2-norm

between M_{xy} signal intensity and RF excitation angle was generated in conjunction with T1 values.

In the phantom experiments, ROIs were drawn on each phantom in the 3D gridded image and T1 map to obtain signal intensity and T1 values, respectively.

For the optimization of the regularization parameters, five independent observers (MT, ST, YI, YK, and MI) qualitatively evaluated the image quality in terms of temporal fidelity of the respiratory motion in the first step, and apparent SNR, sharpness, and artifacts in the second and final steps. At each step, each observer scored each reconstructed image based on its quality, with a higher score indicating better image quality. The number of points to be attributed for a given optimization step depended on the number of images to be scored for that step (i.e., number of points = 10 × number of images to be scored) and could be freely distributed among all images to be scored. For example, for the first optimization step, 4 different λr values (i.e., 0.001, 0.005, 0.01, and 0.1) were compared, meaning that each observer had 40 points to freely assign among the four reconstructed images. Note that the observers could assign all points to one image if it was significantly better than the others or 10 points to all images if the quality was equivalent. The qualitative scores were then averaged across all observers. The λ value yielding the highest score was then selected for the next optimization step. Note that several λr values could be selected if their scores were not significantly different. As for the first step, one optimal λr values was selected. As for second step, one or more could be selected if their scores were not significantly different. In the final step, the single best regularization values were selected. All image datasets were displayed simultaneously on the PACS workstation in each optimization step. All information relevant to the reconstruction, including the regularization parameters, was blinded to the observers. Inter observer agreement was evaluated by intraclass correlation coefficient (ICC).

For the analysis of whole-heart coronary MRA images, two experienced radiologists (MT and MI) visually selected the cardiac phases separately for the left coronary artery and the right coronary artery (RCA) from the end-expiratory bin by consensus. In whole-heart coronary MRA, a contrast ratio (CR) analysis was performed for blood-myocardium ($CR_{blood\text{-}myo}$) and blood-epicardial fat ($CR_{blood\text{-}fat}$).[8] Coronary vessel sharpness and vessel length were quantified in RCA, the left main coronary trunk (LMT) + the left descending artery (LAD) and the left circumflex artery (LCx) for all acquired whole-heart volumes using SoapBubble tool.[13] Vessel sharpness was computed for the same length for all methods (proximal 4 cm).[8,10] In addition, the image quality of whole-heart coronary MRA was visually evaluated by the consensus of the same two experienced radiologists using the following scale: 0, coronary vessel absent or not visible; 1, poor (coronary vessel visible but diagnostic confidence low); 2, moderate (coronary artery adequately visualized and diagnostic quality image); and 3, good (coronary artery clearly depicted).

Statistics

Statistical analyses were performed using MedCalc (version 13.0.4.0; MedCalc Software, Ostend, Belgium). A paired or unpaired Student's *t*-test was performed as appropriate and $P < 0.05$ was considered statistically significant. All data are represented as average ± one standard deviation. The differences in the rated points among regularization parameters in

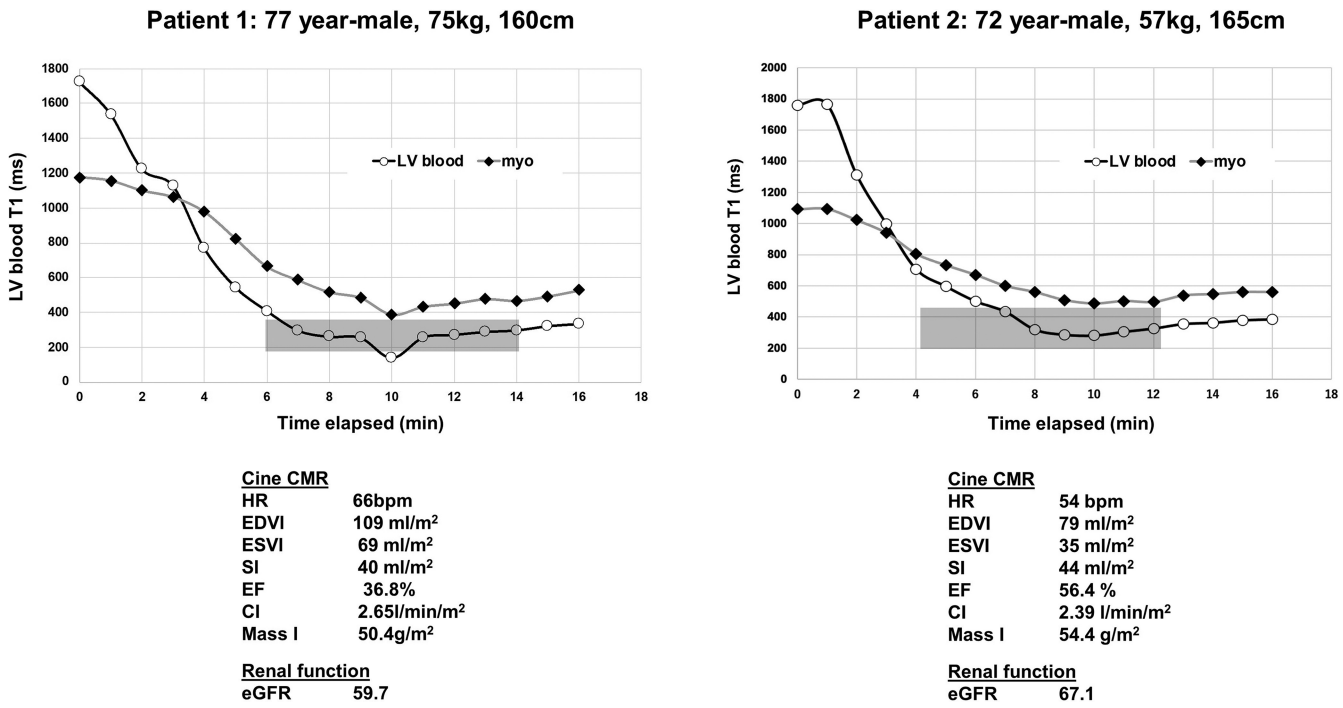

Fig. 2 T1 values in the LV blood pool and myocardium as a function of the time elapsed after the start of Gd slow infusion in two patients. In both patients, T1 values in LV blood and myocardium were stable around 250 ms and 400–600 ms, respectively, from 6 to 14 min. LV volume and function determined by cine CMR were summarized in the bottom. CMR, cardiovascular MR; Gd, gadolinium; LV, left ventricular.

each optimization step were tested using the Friedman test with multiple comparison. The regularization parameters having the rated points which did not differ significantly compared to the highest points were retained as candidates for the optimum regularization parameters in the first and second steps. In the final step, the combination of regularization parameters with the highest points was selected as the optimal parameters.

Results

Gd injection scheme

The relation between T1 in the LV blood pool and myocardium and the time after the start of gadobutrol slow infusion in the two patients is demonstrated in Fig. 2. Briefly, one patient had an LV EF of 36.8%, the other 56.4%. In both patients, T1 values in LV blood and myocardium were stable around 250 ms and 400–600 ms, respectively, 6 min to at least 14 min after the start of gadobutrol slow infusion both with normal and reduced LVEF allowing for the 8-min acquisition window for the free-running 5D whole-heart MRA framework.

RF excitation angle for free-running 5D whole-heart coronary MRA at 3T

Numerical simulations demonstrated that M_{xy} reached the steady state after at least 68 RF pulses (Fig. 3a–3c). The relation between M_{xy} and RF excitation angle for T1 of 250 ms (blood), 400 ms and 650 ms (myocardium) at the steady state demonstrated that by using an RF excitation angle of 10° the transverse magnetization is highest for blood (T1 = 50 ms) and that the CR between blood and myocardium increases together with the RF excitation angle (Fig. 3d–3e).

In phantom experiments, T1 values of 195 ms, 242 ms, 360 ms, 564 ms, and 1110 ms were measured, which mimicked fat, contrast-enhanced blood and myocardium, and non-contrast myocardium (Fig. 4a–4c). In the reconstructed images acquired by using free-running 5D whole-heart MRA framework, the signal intensity for the blood (T1 = 250 ms) was highest at an RF excitation angle of 10°–15°. The CR between blood and myocardium increased concomitantly with the RF excitation angle (Fig. 4d and 4e). To maximize the CR between blood and myocardium while maintaining the maximal blood signal intensity, an RF excitation angle of 15° was considered optimal for contrast-enhanced GRE free-running 5D whole-heart coronary MRA at 3T.

In vivo *contrast-enhanced GRE free-running 5D whole-heart coronary MRA at 3T*

Acquisition of the contrast-enhanced free-running 5D whole-heart MRA was successfully completed in 12 consecutive patients without any complications with a

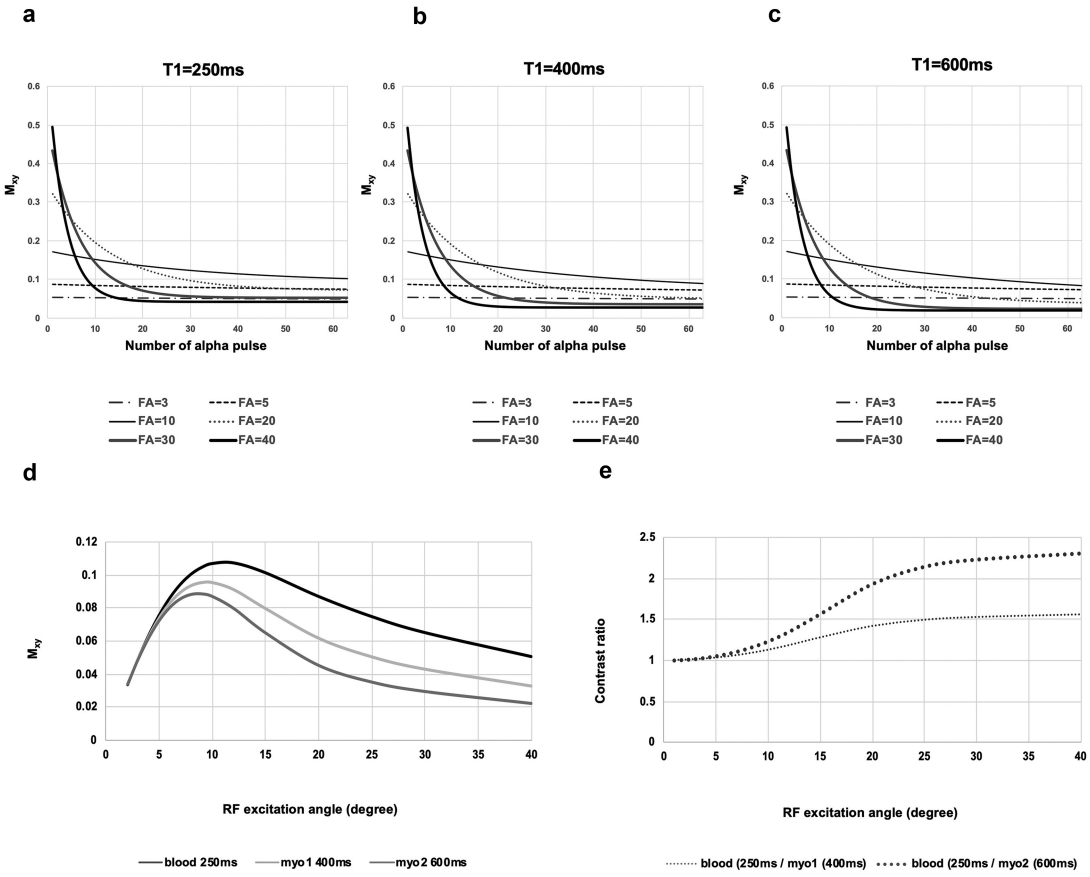

Fig. 3 Numerical simulation of the M_{xy} as function of the number of alpha pulses (**a**–**c**), and M_{xy} (**d**) and signal ratio (**e**) as function of RF excitation angle at the steady state. $M_{xy,}$ transverse magnetization.

constant scan time of 8 min 17s. The whole-body average SAR was 13.2 ± 1.9%. Patient height, weight, and body mass index (BMI) were 161.7 ± 8.4 cm, 57.5 ± 10.1 kg, and 22.2 ± 4.2, respectively.

Free-running data acquired in the single representative patient were used to optimize the regularization parameters. In the first optimization step, only λr of 0.001 was selected among the 3 different λr values of 0.001, 0.005, and 0.01 since the other two values yielded significantly lower ratings (Figs. 5a and 6). In the second step, 3 different λt (0.005, 0.0075, and 0.01) were selected for the final optimization step (Figs. 5b and 7). In the final step, from the combination of the 3 different λt (i.e., 0.005, 0.0075, and 0.01) and the 4 different λs (i.e., 0, 0.0005, 0.001, 0.0025) at a fixed λr values of 0.001, λt = 0.0075, and λs = 0.001 were selected (Figs. 5c and 8). Consequently, the final optimized regularization weights were λr = 0.001, λt = 0.0075, and λs = 0.001. ICC for the rating was 0.835, 0.742, and 0.633 for steps 1, 2, and 3, respectively.

All free-running 5D whole-heart MRA data were successfully reconstructed using the optimized regularization parameters (λr = 0.001, λt = 0.0075, λs = 0.001) with a reconstruction time of 13.5 ± 1.1h. The left and right coronary systems could be visualized clearly in all patients (Fig. 9). $CR_{blood\text{-}myo}$ and $CR_{blood\text{-}fat}$ were 1.5 ± 0.3 and 2.7 ± 1.3, respectively. The vessel sharpness of the RCA, LMT + LAD, and LCx was 49.6 ± 8.9%, 42.1 ± 9.1%, and 36.3 ± 6.8%, respectively. The measured vessel length of the RCA, LMT + LAD, and LCx was 11.3 ± 2.6 mm, 11.2 ± 4.4 mm, and 4.5 ± 1.7 mm, respectively. Table 2 summarizes image quality scores in each coronary artery segment of whole-heart coronary MRA in the patients and volunteers.

Discussion

In this study, we have optimized the injection scheme of Gd contrast medium and RF excitation angle for LIBRE pulses for contrast-enhanced GRE free-running 5D whole-heart coronary MRA at 3T, and demonstrated its feasibility in a patient population. The combination of the Gd slow infusion scheme devised in this study and the RF excitation angle of 15° determined in phantom experiments enables contrast-enhanced 3T GRE free-running 5D whole-heart coronary MRA during 8 min scanning time with a good image quality. The CR between blood and myocardium was 1.5 ± 0.3 in this study, which was in accordance with what is expected from the phantom experiments (1.3–2.5 at 15°), and was

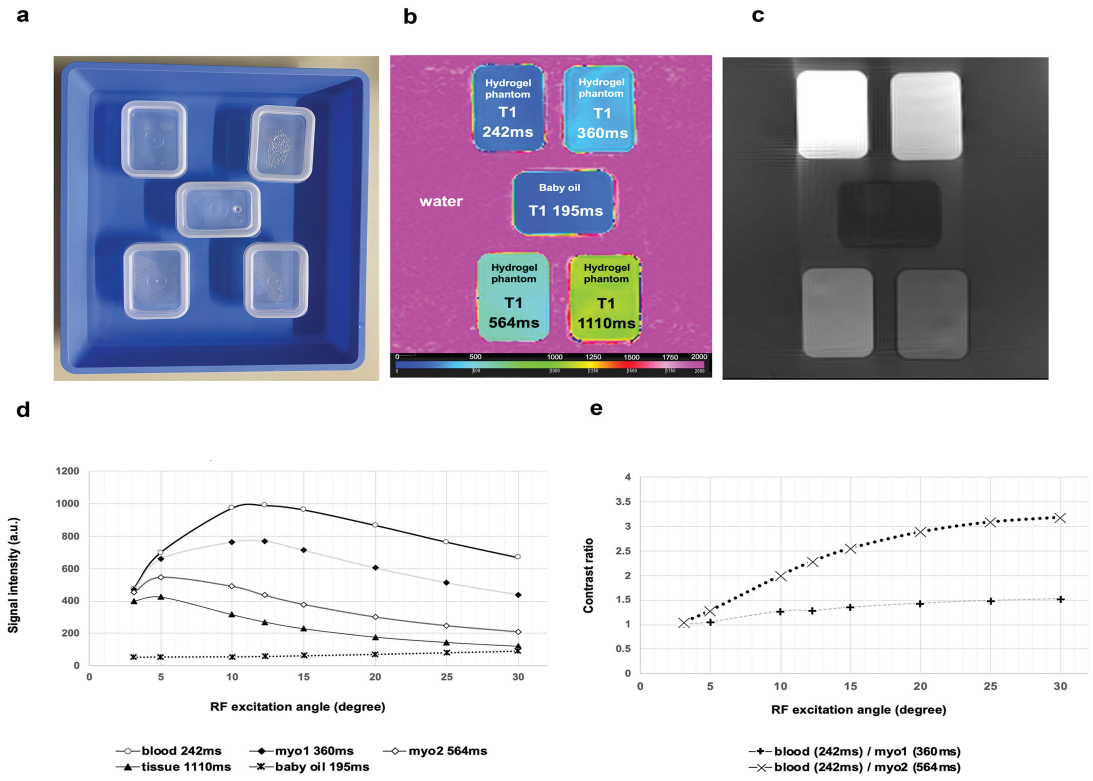

Fig. 4 Five phantoms were created (**a**). The T1 value was 195 ms, 242 ms, 360 ms, 564 ms, and 1110 ms (**b**). Reconstructed image of the phantoms scanned by free-running 5D whole-heart MRA framework with RF excitation angle of 15° demonstrates clearly a suppression of the fat compartment with increasing signal intensities with lower T1 value compartments (**c**). Signal intensity for fat, contrast-enhanced blood and myocardium, and non-contrast myocardium (**d**) and contrast ratio between blood and myocardium (**e**) as function of RF excitation angle. MRA, MR angiography.

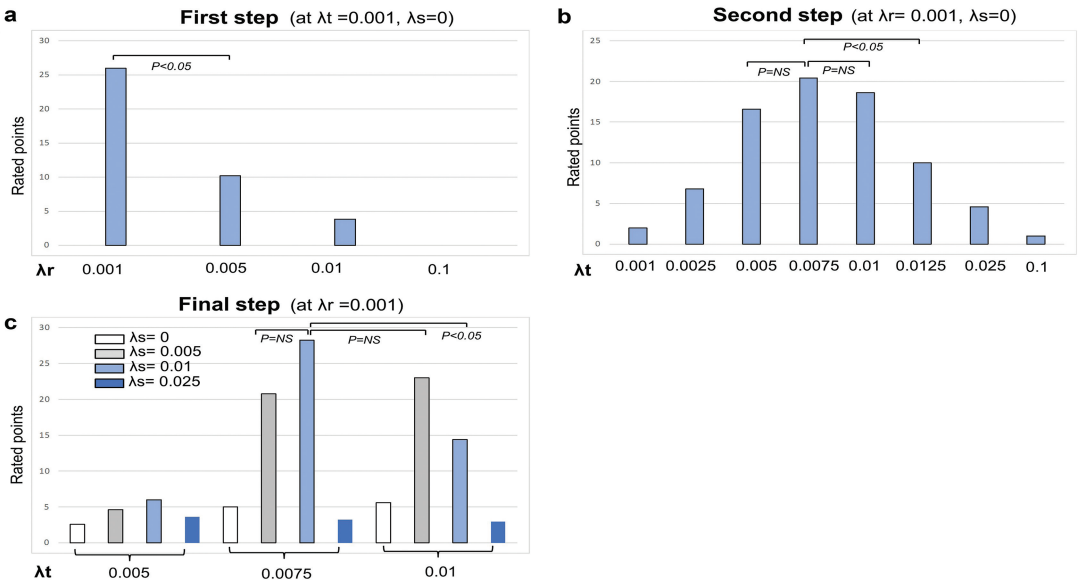

Fig. 5 Rated points for the first (**a**), second (**b**), and final (**c**) optimization steps are summarized. In the first step, $\lambda r = 0.001$ resulted in the highest points and was significantly larger than all other λr values and was selected as the optimal parameter. In the second step, $\lambda t = 0.0075$ had highest points; however, it was not significantly higher than $\lambda r = 0.005$ and $\lambda r = 0.01$. So, those were retained as potential candidates for the final optimization step. In the final step, the combination of $\lambda r = 0.001$, $\lambda t = 0.0075$, and $\lambda s = 0.001$ yielded the highest score and was selected as the optimal set of parameters.

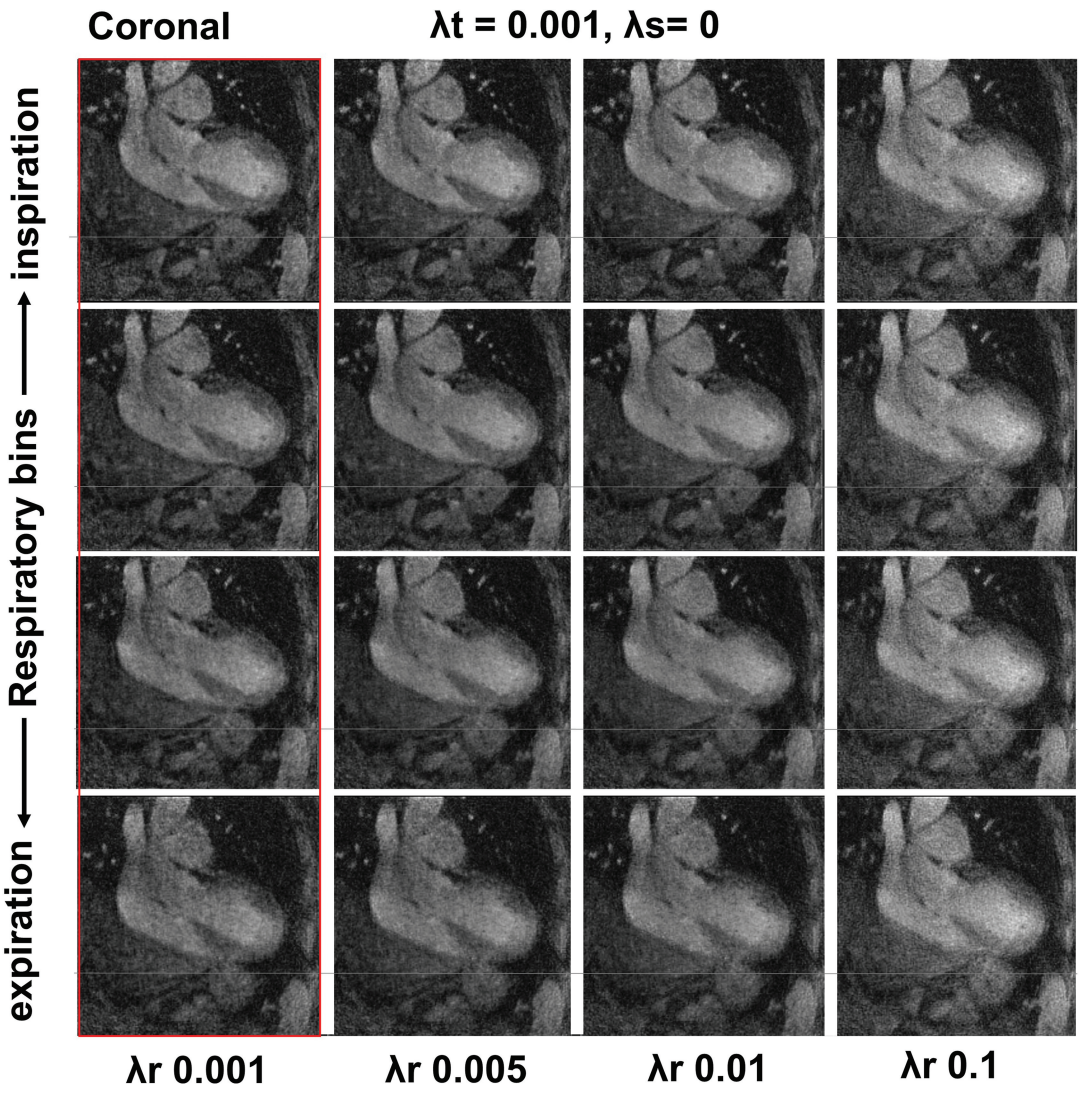

Fig. 6 First step. Four λr values (i.e., 0.001, 0.005, 0.01, and 0.1) were tested for temporal fidelity along the respiratory motion at fixed values of $\lambda t = 0.001$ and $\lambda s = 0$. Temporal fidelity was the best for $\lambda t = 0.001$ and selected among 3 different λr values. Coronal cine images of 4 respiratory bins at proximal LAD were shown. Gray lines were drawn in the lower quadrant of each panel as a reference. All images are displayed by the same window setting. Red outline represents the image with optimum λr. LAD, left descending artery.

comparable to that for the non-contrast 1.5T bSSFP free-running 5D whole-heart coronary MRA using LIBRE pulses (1.7 ± 0.5).[8] Vessel sharpness for RCA ($50 \pm 9\%$) and LAD ($42 \pm 9\%$) in this study was approaching that for the non-contrast 1.5T bSSFP free-running 5D whole-heart coronary MRA using LIBRE pulses (RCA, $55 \pm 11\%$; LAD, $49 \pm 13\%$)[8] and was higher compared with non-contrast self-navigated whole-heart coronary MRA with T2prep and LIBRE at 3T (RCA, $37 \pm 9\%$; LAD, $34 \pm 7\%$).[10] Furthermore, SAR in our scan protocol was $13.2 \pm 1.9\%$ of the SAR limit in the "first level" mode, documenting its safety in terms of RF heating. Regularization parameters for CS reconstruction were also optimized in our study according to the prior studies with CS MRI.[4,6,12,14] The regularization parameters are suitable for contrast-enhanced free-running 5D whole-heart coronary MRA GRE protocol with LIBRE pulse using slow infusion contrast enhancement scheme at 3T.

The 5D free-running whole-heart coronary MRA framework combines a continuous 3D golden-angle radial sampling with a self-gating signal extraction and a CS reconstruction technique. The collected data can be reordered rather freely and the temporal position within the cardiac cycle, the width of the reconstruction window, and even the respiratory level for which the data should be displayed, can be chosen flexibly after the scan.[5] Therefore, a significant change in image contrast during the data acquisition may influence the image quality in separated cardiac and respiratory dimensions. In this regard, a slow infusion of Gd contrast medium is required for keeping the contrast

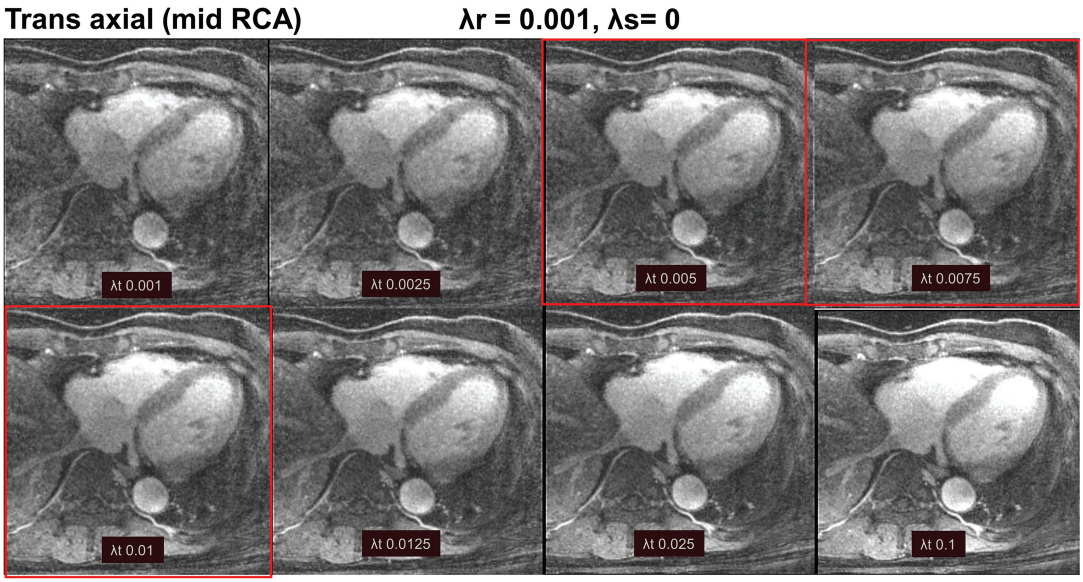

Fig. 7 Second step. Eight λt values (i.e., 0.001, 0.0025, 0.005, 0.0075, 0.01, 0.0125, 0.025, and 0.1) were tested for image quality at λr = 0.001 and λs = 0. Three λt (0.005, 0.0075, and 0.01) remained for the final step. Trans axial images at mid RCA are demonstrated. All images are displayed by the same window setting. Red outline represents the images with candidates for optimal λt. RCA, right coronary artery.

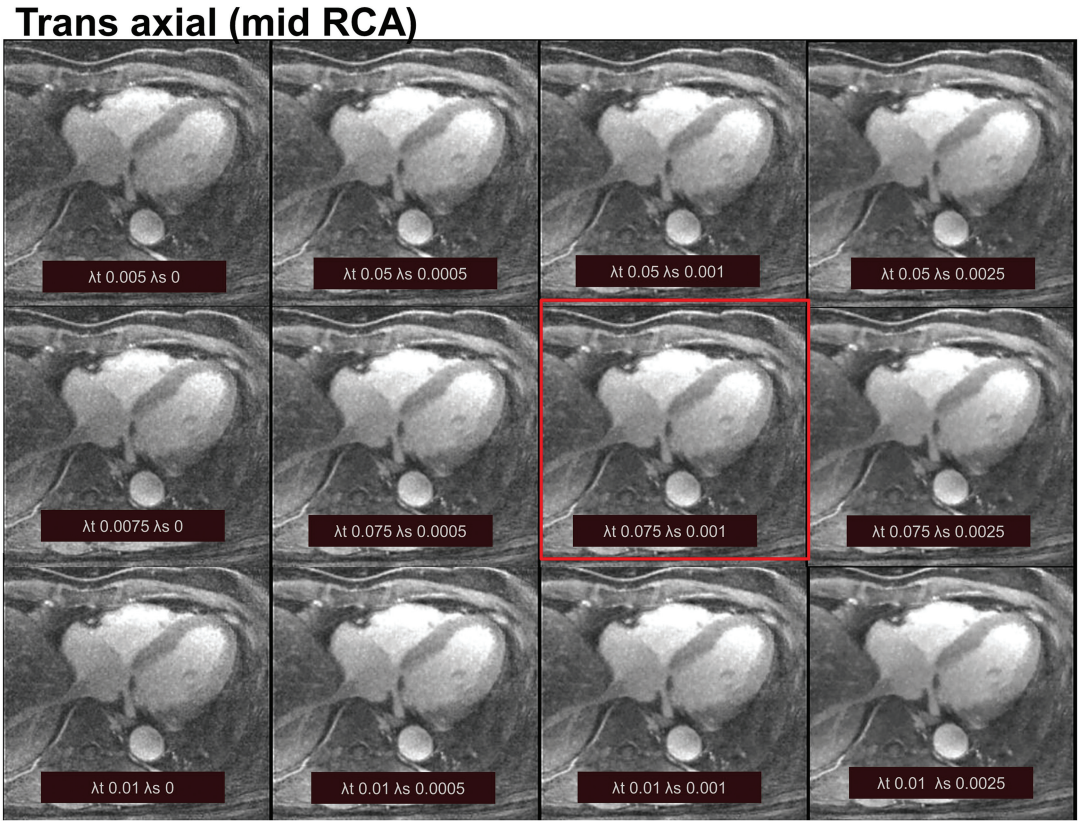

Fig. 8 Final step. Four λs values (0, 0.0005, 0.001, and 0.0025) were tested for image quality in combination with 3 λr values (0.005, 0.0075, and 0.01) at λr = 0.001. Finally, λr = 0.001, λt = 0.0075, and λs = 0.001 were selected as optimized regularization weights. Trans axial images at mid RCA are demonstrated. All images are displayed by the same window setting. Red outline represents the image with the optimum regularization parameters. RCA, right coronary artery.

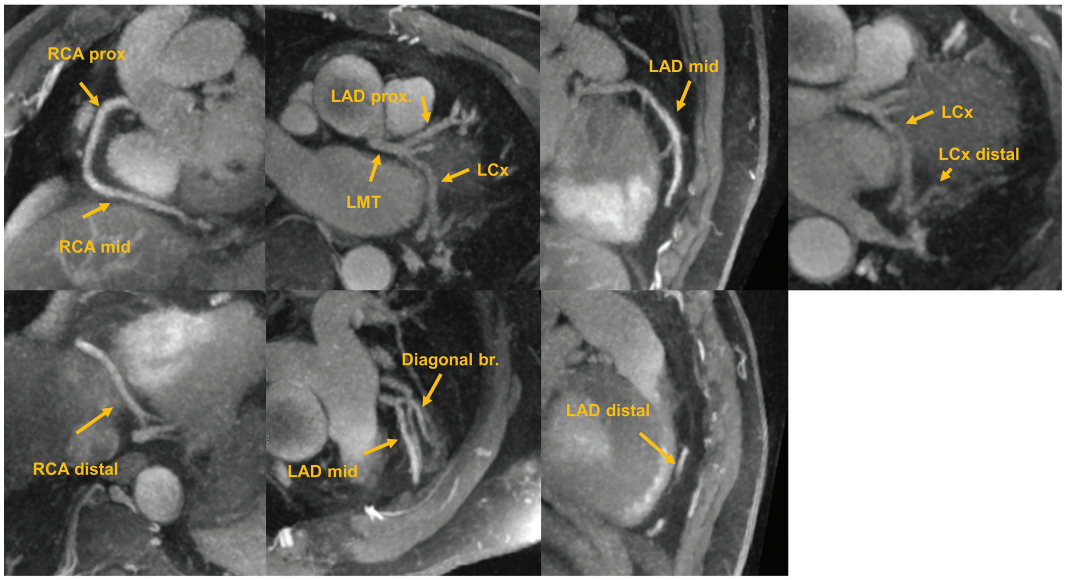

Fig. 9 Representative images of contrast-enhanced free-running GRE 5D whole-heart coronary MRA at 3T in a 65-yr-old patient with multiple coronary risk factors. The left and right coronary artery system including the LMT, RCA, LAD, and left circumflex artery was clearly depicted. GRE, gradient-recalled echo; LAD, left descending artery; LMT, left main trunk; MRA, MR angiography; RCA, right coronary artery.

Table 2 Subjective visual image quality scores of free-running slow-infusion contrast-enhanced GRE 5D whole-heart coronary MRA at 3T in patients and non-contrast images in volunteers.

Artery	Patients (n = 12)	Volunteers (n = 4)	*P* value
RCA			
1	3.0 ± 0.0	1.3 ± 0.5	0.0004
2	3.0 ± 0.0	0.75 ± 1.0	0.0004
3	2.8 ± 0.9	0.5 ± 1.0	0.0026
4	1.9 ± 1.2	0.0 ± 0.0	0.013
LMT			
5	3.0 ± 0.0	1.0 ± 0.0	0.0004
LAD			
6	2.9 ± 0.3	1.0 ± 0.0	0.0008
7	2.7 ± 0.8	0.8 ± 1.0	0.005
8	2.4 ± 0.8	0.0 ± 0.0	0.0027
9	1.7 ± 1.0	0.0 ± 0.0	0.0067
LCx			
11	2.8 ± 0.4	0.5 ± 0.6	0.0013
12	1.4 ± 1.3	0.0 ± 0.0	0.042
13	2.0 ± 1.2	0.0 ± 0.0	0.0124

The number in the first column indicates the number of coronary segments in the AHA 15 segment model. Visual image quality scores: 0, coronary vessel absent or not visible; 1, poor (coronary vessel visible but diagnostic confidence low); 2, moderate (coronary artery adequately visualized and diagnostic quality image); and 3, good (coronary artery clearly depicted). GRE, gradient-recalled echo; LCx, left circumflex artery; LAD, left descending artery; LMT, left main trunk; MRA, MR angiography; RCA, right coronary artery.

enhancement at a stable level in both the blood and myocardium during the MR data acquisition. The setup of our Gd injection scheme allows for a slow infusion of Gd contrast medium using a commonly available infusion pump with some extra extension tubes. The setup was inspired by previous studies.[15] An MR-safe infusion pump can be substituted by a normal infusion pump if it is located outside the MRI scanner room and if the extension tubes can be arranged through the hole of the Faraday cage. The concept of Gd slow infusion has been previously described by Bi et al.[16] Those previous methods depend on the dedicated power injector which requires setup for the specialized injection speed. Therefore, we developed a more universal approach using commonly available material. In this study, a single dose (0.01 mmol/kg) of gadobutrol was employed because administration of double dose Gd contrast medium is not allowed in the country where the study was conducted. However, higher doses may be advantageous for the greater enhancement of blood. The setup of the slow injection scheme can be readily adapted according to the dose and/or concentration of Gd contrast medium by modifying the number of extension tubes and/or infusion rate. For our slow infusion scheme, volume reduction without dose level changes is particularly beneficial to simplify the set-up and reduce the number of extension tubes. Based on the high concentration and high T1 relaxivity, gadobutrol had an advantage in indication for contrast-enhanced free-running 5D whole-heart coronary MRA at 3T.[17]

Bastiaansen et al. recently demonstrated that LIBRE allows for effective fat suppression insensitive to main field (B0) and RF field (B1) inhomogeneities both at 1.5T and 3T.[8–10] They have confirmed the robustness of LIBRE for suppressing the fat signal for a total pulse duration as short as 1.0 ms at 3T.[10] In our study, LIBRE pulses with a total pulse duration of 1.4 ms were incorporated for the first time into a contrast-enhanced free-running GRE whole-heart coronary MRA framework at 3T, showing the effective fat suppression both on *in vivo* and in *in vitro* images. In the previous study investigating free-running 5D coronary MRA with bSSPF at 1.5T, a longer total LIBRE pulse duration of 2.6 ms was employed with a total scan time of 11 min 33s (TR = 5.48 ms).[8] However, in our contrast-enhanced GRE approach using a slow infusion scheme, shorter total scan time is beneficial in order to complete the scan during the equilibrium phase of blood and myocardial contrast enhancement. Therefore, the short pulse duration of 1.4 ms was used, enabling the total scan duration of 8 min 17s. This is substantially shorter than the previously used LIBRE pulses in cardiac applications (e.g., in case of total pulse duration of 2.6 ms with otherwise the same scan parameters, total scan time is calculated as 9 min 59s). Substantially long reconstruction time is required for the current reconstruction scheme (13.5 ± 1.1h). However, coronary MRA is basically non-emergency scan. If a single patient is scanned in the afternoon, the reconstruction and reporting is completed in the early morning of the next day. In this scenario, even such long reconstruction time is considered to be acceptable for clinical use. However, if 2 or more patients are scanned, it will be difficult to provide the reporting on the regular basis in the routine clinical practice. The shorter reconstruction technique is desired.

We would like to acknowledge the main limitation of this study. Inevitably, the use of a manual contrast injection into the extension tubes necessitates the presence of a physician within the MR scanner room at the time of injection. However, the presence of a physician is reassuring for the patient particularly during the scan.

Conclusion

Gd injection scheme, RF excitation angles, and CS reconstruction regularization parameters were optimized for a contrast-enhanced free-running 5D whole-heart coronary MRA GRE protocol at 3T. Using the optimized protocol, whole-heart coronary MRA at 3T is feasible with a good image quality during 8 min of scanning time.

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Conflicts of Interest

Yoshito Ichiba, RT and Yoshiaki Komori, MSc are employees of Siemens Healthcare K.K., Tokyo, Japan. Mathias Stuber receives non-monetary research support from Siemens. Davide Piccini is an employee of Siemens Healthcare AG, Lausanne, Switzerland. The other authors have no conflicts of interest to declare. No relevant conflicts of interest related to the article are disclosed.

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