

Motion-corrected free-breathing late gadolinium enhancement combined with a gadolinium contrast agent with a high relaxation rate: an optimized cardiovascular magnetic resonance examination protocol

Cui Yan^{1,#}, Junjiao Hu^{1,#}, Yanyu Li¹,
Xingzhi Xie¹, Zhimin Zou¹, Qiyu Deng¹,
Xiaoyue Zhou², Xiaoming Bi³, Mu Zeng¹  and
Jun Liu¹ 

Abstract

Objective: This prospective study investigated the feasibility of an optimized cardiovascular magnetic resonance (CMR) examination protocol using the motion-corrected (MOCO), balanced steady-state free precession (bSSFP), phase-sensitive inversion recovery (PSIR) sequence combined with a gadolinium contrast agent with a high relaxation rate in patients who cannot hold their breath.

Methods: Fifty-one patients with heart disease underwent CMR examinations twice and these were performed with different late gadolinium enhancement (LGE) imaging sequences (fast low-angle shot [FLASH] sequence vs. MOCO sequence) and different gadolinium contrast agents (gadopentetate dimeglumine vs. gadobenate dimeglumine) with a 48-hour interval. LGE image quality, total time spent in the whole study, and time taken to perform LGE imaging were compared for the two CMR examinations.

¹Department of Radiology, Second Xiangya Hospital of Central South University, Changsha, China

²MR Collaboration, Siemens Healthineers Ltd., Shanghai, China

³MR Research and Development, Siemens Medical Solutions, USA Inc., Los Angeles, CA, USA

[#]Cui Yan and Junjiao Hu contributed equally to this work.

Corresponding author:

Mu Zeng, Department of Radiology, Second Xiangya Hospital of Central South University, 139 Renmin Road Central, Furong District, Changsha, Hunan, 410000, China.

Email: zengmu@csu.edu.cn



Results: LGE images with the MOCO bSSFP PSIR sequence showed significantly higher image quality compared with those with the segmented FLASH PSIR sequence. There was a significant difference between the total scan time for the two examinations and different LGE sequences.

Conclusions: The MOCO bSSFP PSIR sequence effectively improves the quality of LGE images. Changing the CMR scanning protocol by combining the MOCO bSSFP PSIR sequence with a gadolinium contrast agent with a high relaxation rate effectively shortens the scan time.

Clinical trial registration number: ChiCTR-ROC-17013978.

Keywords

Motion-corrected, balanced steady-state free precession, phase-sensitive inversion recovery (MOCO bSSFP PSIR) sequence, contrast agent, cardiovascular magnetic resonance protocol, late gadolinium enhancement, heart disease, gadobenate dimeglumine

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Background

Cardiovascular magnetic resonance (CMR) plays an indispensable role in diagnosing cardiac diseases, where late gadolinium enhancement (LGE) imaging mainly detects fibrosis and infarctions in the myocardium.¹ Usually segmented fast low-angle shot (FLASH) acquisition with phase-sensitive inversion recovery (PSIR) reconstruction is used for LGE imaging at 3 Tesla (T). A delay of 10 to 15 minutes after contrast media injection is used for optimal LGE images, but this prolongs the CMR examination time in clinical practice.

The conventional segmented FLASH PSIR sequence requires patients to hold their breath several times during the exam to eliminate respiratory motion-induced artifacts.² However, for patients who have difficulty in holding their breath owing to heart failure, among other reasons, significant image artifacts are expected that could affect the clinical diagnosis.^{3,4} A motion-corrected (MOCO) balanced steady-state free precession (bSSFP) PSIR sequence could solve this problem.⁵ Such a sequence uses single-shot imaging to eliminate the

need for breath-holding. Because the MOCO bSSFP PSIR sequence does not require breath-holding, the need for giving the breath hold command before data acquisition and additional time for the patient to recover after each breath hold is eliminated. This in turn reduces the time taken in LGE imaging and the total scan time, and improves clinical throughput and the patient's comfort.⁶

In the standard CMR workflow, conventional gadolinium contrast agents (e.g., gadopentetate dimeglumine [Gd-DPTA]) require a delay of 10 to 15 minutes after injection of contrast media. Therefore, another gadolinium contrast agent with shorter delay time is required. Pintaske et al.⁷ showed that the relaxation rate of gadobenate dimeglumine (Gd-BOPTA) was much higher than that of Gd-DPTA. A higher relaxation rate means a shorter delay time for optimal LGE images. Several studies have shown that high-relaxation Gd-BOPTA enables LGE imaging with a reduced dose of contrast media, and a shortened delay time between injection and imaging without compromising clinical diagnosis.^{8–11}

This study aimed to develop an optimized CMR examination workflow with a shorter scan time based on the MOCO bSSFP PSIR sequence and Gd-BOPTA (high relaxation rate) in patients experiencing difficulties with breath holding. The main study goals were as follows: 1) to determine whether the MOCO bSSFP PSIR sequence can reduce motion artifacts and, 2) to examine the feasibility of using the MOCO bSSFP PSIR sequence combined with a contrast agent with a high relaxation rate and an optimized CMR workflow for improving examination efficiency.

Methods

This prospective study was carried out in accordance with the Drug Clinical Trial Management Regulations and approved by the ethics committee of The Second Xiangya Hospital of Central South University in Changsha, Hunan Province in September, 2017. Informed consent was obtained from each patient. Our clinical trial registration number is ChiCTR-ROC-17013978.

Patient population

This study included patients who were unable to maintain breath holding according to respiratory rate monitoring and were diagnosed with various types of heart disease. The exclusion criteria included renal failure and general contraindications for CMR.

Image acquisition

All patients underwent two CMR examinations with a 48-hour interval between them. A 3 T clinical scanner (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany) was used for imaging. During the first examination, patients underwent morphological scans, such as T1- and

T2-weighted imaging. Subsequently, cine images were acquired using segmented bSSFP acquisition before administration of the contrast agent. A total of 0.2 mmol/kg bodyweight of Gd-DPTA (Magnevist, Bayer-Schering Pharma AG, Berlin, Germany) was then intravenously injected for rest perfusion images, followed by LGE imaging 10 minutes after contrast administration. Contrast agent was injected at a rate of 3 mL/s, followed by a 20-mL saline flush using the same injection rate. The prospectively electrocardiographic-gated segmented FLASH PSIR sequence was used for LGE images with breath holding.

During the second examination, cardiac cine imaging was performed after intravenous injection of 0.1 mmol/kg body weight of Gd-BOPTA (MultiHance; Bracco Imaging SpA, Milan, Italy). LGE images were acquired immediately afterward,¹² at which point the time from the contrast media injection was approximately 7 minutes. The injection rate of the contrast agent was the same as that for the first examination. The MOCO bSSFP PSIR sequence was applied in combination with prospective electrocardiographic gating for LGE imaging with the patient under free breathing. For the MOCO bSSFP PSIR sequence, eight repetitions were acquired and correction of motion was performed using a non-rigid registration algorithm.⁵ A subpixel registration was applied in the algorithm to minimize the mean square intensity difference between the two nearby images acquired among the eight repetitions. A reference frame was selected that was similar to most other frames with regard to the root mean square difference.¹³ Each independent registration step consisted of an optimization procedure that minimized a similarity measure of the two images to find the best transformation that maps a given frame into the reference frame.¹⁴ Finally, the LGE image was

created by the average of the eight repetitions with correction of motion. The inversion time was set to 300 ms for the LGE sequence. If the inversion time did not appear appropriate, a T1 scout sequence was performed to determine the appropriate inversion time. Imaging parameters of the two sequences are shown in Table 1 and scan protocols for the two examinations are shown in Figure 1.

Cardiac cine imaging and LGE imaging in the two examinations were obtained in the two-chamber plane, four-chamber plane, and a stack of 8 to 10 slices of short-axis planes. Three slices were acquired in the two-chamber and four-chamber planes.

Image analysis

LGE images were evaluated by two radiologists with 5 years of experience in cardiovascular imaging. All analyses were performed using a Siemens Syngo.via workstation (Siemens Healthcare, Erlangen, Germany).

Evaluation

LGE image quality was visually assessed by two radiologists. They evaluated the LGE

images at the same time without any knowledge of the experiment. On the basis of the degree of artifacts and the capacity of LGE images to distinguish normal myocardium, LGE areas, and the left ventricular cavity, image quality was scored from 1 to 4 from worst to best as follows: 4=excellent, sharp image without artifacts; 3=good, mild artifacts, but the image is still diagnostic; 2=fair, moderate artifacts that mildly affect diagnostic quality; and 1=poor, severe artifacts, and a non-diagnostic image.

The starting and ending times for the whole CMR workflow and the LGE imaging were recorded. The total time spent on the whole CMR examination and time taken to perform LGE imaging were calculated for both examinations.

Statistical analysis

All data analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). First, the Shapiro–Wilk test was used to confirm whether the data set conformed to a normal distribution. Data that conformed to a normal distribution are shown as mean \pm standard deviation. Data that did not

Table 1. Imaging parameters of the segmented FLASH PSIR and single-shot MOCO bSSFP PSIR sequences.

Parameters	Segmented FLASH PSIR	MOCO bSSFP PSIR
Repetition time (ms)	5.90	4.20
Echo time (ms)	1.15	1.12
Inversion time (ms) ^a	300	300
Flip angle (degrees)	20	40
FOV (mm)	400–420	400–420
Imaging matrix	256×152	256×152
Slice thickness (mm)	8	8
Bandwidth (Hz/pixel)	781	1085
Motion correction	No	Yes
Segments	54	–
Average	1	8

^aDefault sequence.

FLASH, fast low-angle shot; PSIR, phase-sensitive inversion recovery; MOCO bSSFP, motion-corrected balanced steady-state free precession FOV, field of view.

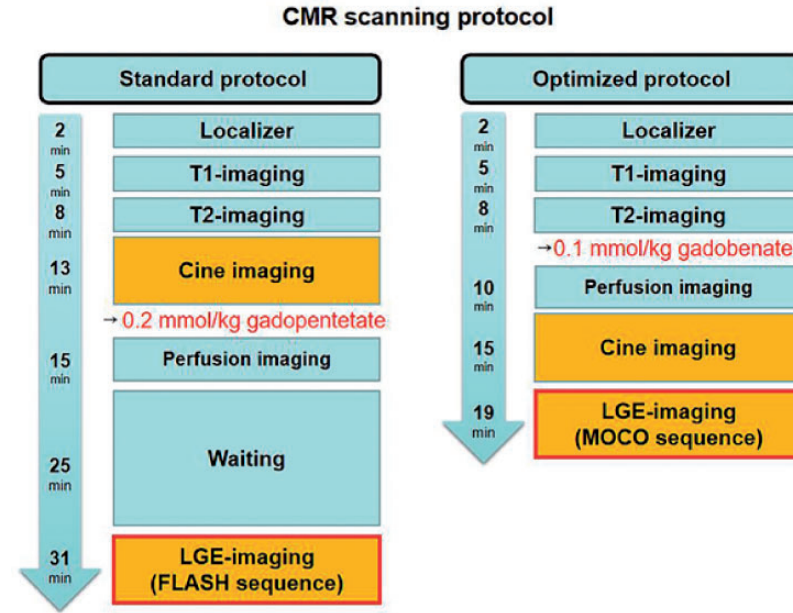


Figure 1. Illustration showing standard (left) and optimized (right) cardiovascular magnetic resonance (CMR) protocols. The optimized CMR protocol effectively shortened the CMR scan duration time where cine imaging was performed after injection of 0.1 mmol/kg gadobenate dimeglumine. Late gadolinium enhancement (LGE) imaging was performed using the motion-corrected balanced steady-state free precession (MOCO bSSFP) phase sensitivity inversion recovery (PSIR) sequence 7 minutes after drug injection. This was compared with the standard CMR protocol where cine imaging was performed before injection of 0.2 mmol/kg gadopentetate dimeglumine and LGE imaging was performed using the segmented fast low-angle shot (FLASH) PSIR sequence.

conform to a normal distribution are shown by the median and interquartile range. Normally distributed data were analyzed using the paired-sample t-test. Non-normally distributed data were analyzed using the Wilcoxon signed-rank test. Weighted Kappa statistics were used to evaluate inter-reader agreement for the image quality score (IQS). A higher kappa value indicated a higher inter-reader agreement. $P < 0.05$ was considered to be statistically significant.

Results

Fifty-one patients, including 34 men and 17 women with a mean age of 52.55 ± 14.85 years (range: 11–77 years), were included.

All patients completed both imaging sessions and there were 33 patients among them with LGE areas in the LGE images. No allergic reaction to contrast agent was observed throughout the study. The patients' clinical disease information is shown in Figure 2.

A normality test indicated that the whole scan time for each CMR examination conformed to a normal distribution. Data for the time taken to perform LGE imaging and IQS were not normally distributed.

Table 2 shows some features of the optimized CMR protocol (MOCO bSSFP PSIR) compared with the standard CMR protocol. LGE images that were obtained with the segmented FLASH PSIR sequence had artifacts of different degrees that

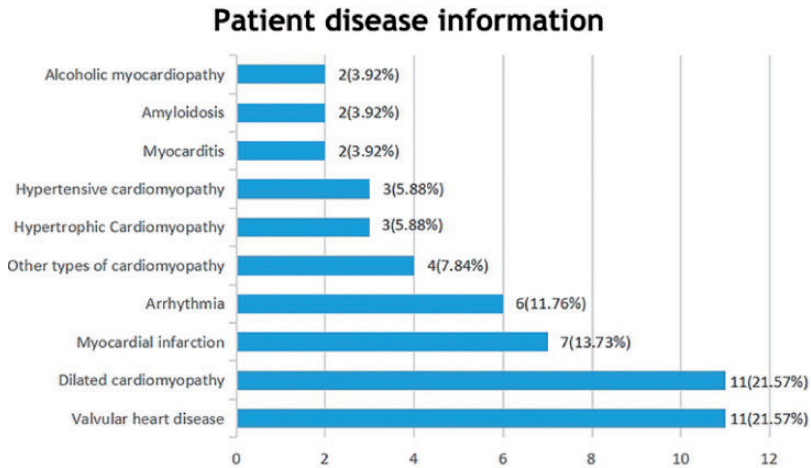


Figure 2. Classification of the patients' clinical disease. The horizontal bar indicates the number of patients with certain heart disease and the percentage in parentheses is the proportion of patients with this type of disease within the cohort of 51 patients. Among all patients, the numbers of patients with dilated heart disease and valvular heart disease were the highest ($n = 11$ each), which accounted for 21.57% of the total.

Table 2. Comparison of features obtained by the standard and optimized CMR protocols.

	Standard protocol	Optimized protocol	P value
IQS	2 (3, 2)	4 (4, 3)	<0.001
Total time (minutes)	29.05 ± 3.10	19.45 ± 2.80	<0.001
Time of LGE imaging (minutes)	5.92 (0.93)	3.67 (0.95)	<0.001

Data are shown as mean ± standard deviation or median (interquartile range).

IQS, image quality score; LGE, late gadolinium enhancement.

affected diagnostics, while the MOCO bSSFP PSIR sequences yielded little to no artifacts. The IQS of the MOCO bSSFP PSIR sequence was significantly higher than that in the FLASH PSIR sequence ($P < 0.001$).

Figure 3 shows representative images acquired with these two sequences. Additionally, the number of patients in each IQS score segment of the two sequences was counted. The IQS with the segmented FLASH PSIR sequence was mostly 2 points (26 patients) and one patient obtained an IQS of 1 point. The IQS of the MOCO bSSFP PSIR sequence was 4 points in 38 patients and 3 points for all

remaining patients. The image quality with the MOCO bSSFP PSIR sequence was significantly better than that with the segmented FLASH PSIR sequence ($P < 0.001$, Figure 4). Inter-reader agreement for the IQS was good for the segmented FLASH PSIR sequence (weighted $k = 0.80$; 95% confidence interval: 0.65–0.93) and the MOCO bSSFP PSIR sequence (weighted $k = 0.75$; 95% confidence interval: 0.53–0.94).

The scan time required for both examinations, as well as time spent on each LGE protocol, are shown in Table 2. The second MOCO bSSFP PSIR sequence took significantly less total time than the first FLASH

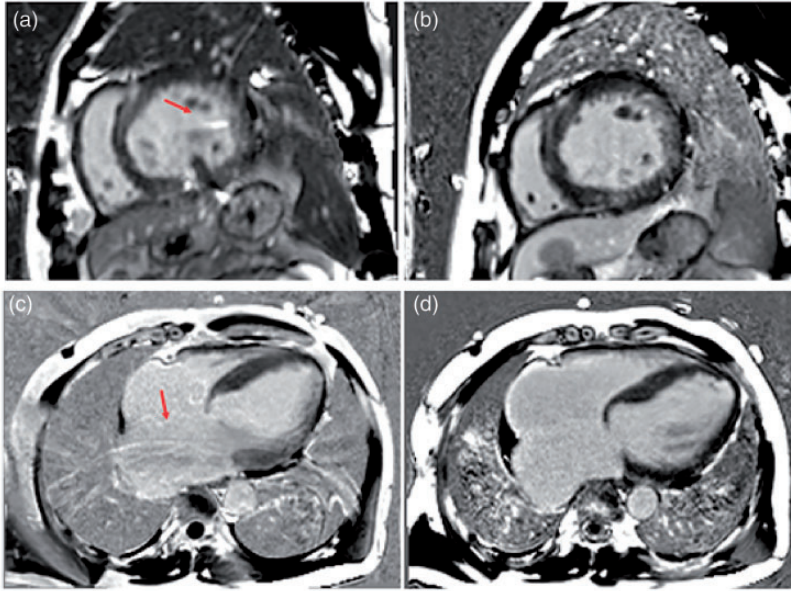


Figure 3. Representative late gadolinium enhancement (LGE) images acquired with segmented fast low-angle shot (FLASH) phase-sensitive inversion recovery (PSIR) and single-shot motion-corrected balanced steady-state free precession (MOCO bSSFP) PSIR sequences in two patients. The upper row shows two short-axis images (a, b) of a 41-year-old patient with valvular heart disease and the lower row shows two four-chamber images (c, d) of a 55-year-old patient with valvular heart disease. LGE images in the left column (a, c) were obtained using the segmented FLASH PSIR sequence, while LGE images in the right column (b, d) were obtained using the MOCO bSSFP PSIR sequence. Note that visible artifacts (red arrows) in the segmented FLASH PSIR LGE images are absent in the MOCO bSSFP PSIR LGE images.

PSIR sequence (difference = 9.60 ± 2.51 minutes, $P < 0.001$). The MOCO bSSFP PSIR sequence LGE scanning time was significantly shorter than that of the segmented FLASH PSIR sequence, with a difference of nearly 2 minutes ($P < 0.001$).

Discussion

LGE is widely used in CMR examinations and it is important for clinical diagnosis of heart disease. The conventional segmented FLASH PSIR sequence is a commonly used sequence for assessing myocardial fibrosis and infarctions, but its quality is affected by patients' capacity to hold their breath. Therefore, there is an urgent requirement for alternative solutions for assessing these conditions, particularly for patients who

have difficulty in holding their breath. The MOCO bSSFP PSIR sequence could solve this issue.⁵ This sequence eliminates the requirement for breath-holding and removes ghosting artifacts observed in the conventional segmented acquisition method resulting from suboptimal breath-hold or heart rate variation during data acquisition. Averaging of motion-corrected images further improves signal-to-noise ratio and quality of resulting images.

In the current study, a single-shot MOCO bSSFP PSIR sequence resulted in improved image quality compared with the conventional segmented FLASH PSIR sequence. The combination of a contrast media with a high relaxation rate and an improved scanning protocol and the MOCO bSSFP PSIR sequence reduced the

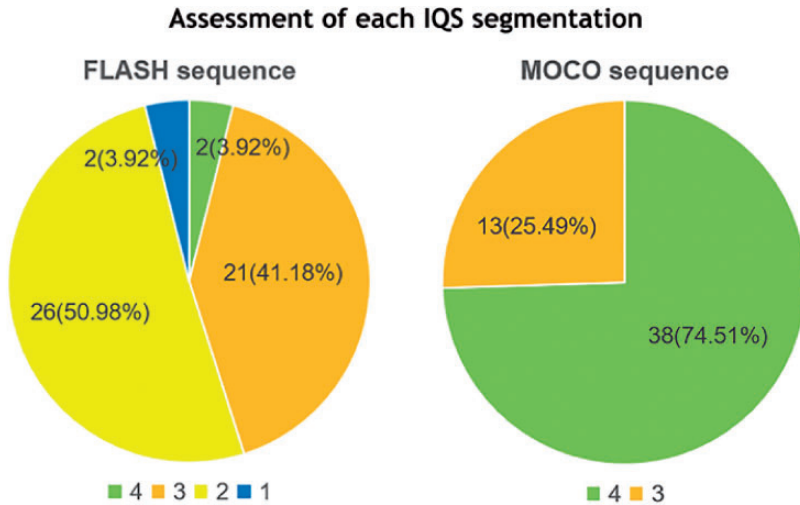


Figure 4. Image quality scores (IQSs) of images were acquired using the segmented fast low-angle shot (FLASH) phase-sensitive inversion recovery (PSIR) (left image) and motion-corrected balanced steady-state free precession (MOCO bSSFP) PSIR (right image) sequences. An IQS with the segmented FLASH PSIR sequence was dominant with 2 points (26 patients). IQSs of the MOCO bSSFP PSIR sequence were mostly 4 points (38 patients) and no patients obtained an IQS of 1 or 2. The color green represents 4 points, orange represents 3 points; bright yellow represents 2 points, and blue represents 1 point.

total exam time. Furthermore, the need for breath holding during LGE imaging was eliminated using a free-breathing MOCO bSSFP PSIR sequence.

These results show that the MOCO bSSFP PSIR sequence has several advantages over the segmented FLASH PSIR sequence as follows. First, single-shot acquisition in the MOCO bSSFP PSIR sequence enables free-breathing imaging. In contrast, the segmented FLASH PSIR sequence acquires one image in multiple heart beats with segmented acquisition and good breath holding is required to achieve high image quality. The capability of acquiring LGE images under free breathing also enables the possibility of scanning patients who otherwise could not be scanned. An example of this situation is pediatric patients who are not able to cooperate with breath hold commands or patients who suffer from cardiac arrhythmia.¹⁵ Second, LGE images that are acquired using the MOCO bSSFP PSIR

sequence show effectively reduced respiratory motion artifacts and improved image quality compared with those acquired with the conventional segmented FLASH PSIR sequence. The bSSFP readout in the MOCO bSSFP PSIR sequence leads to a higher signal-to-noise ratio than that from FLASH readout, and non-rigid registration and averaging of multiple images in the MOCO bSSFP PSIR sequence further enhances the resulting image signal-to-noise ratio. Third, the segmented FLASH PSIR sequence requires 6 minutes for scanning all slices, while the MOCO bSSFP PSIR sequence only requires approximately 4 minutes. This is consistent with the results of a study by Captur et al.⁶ who showed that the MOCO bSSFP PSIR sequence required 6 minutes, while the scanning time of the segmented FLASH PSIR sequence was 9 minutes. This particular result is different from the current study, where the scanning time of the MOCO bSSFP PSIR sequence was much shorter

than that for the segmented FLASH PSIR sequence. The reasons for this difference between studies may be due to the differences in the type of magnetic resonance machine used, the number of slices scanned, and the scanning parameters.

Several studies have compared other techniques with the conventional method in patients with insufficient breath hold capability, but they showed inferior image quality as follows. Sievers et al.¹⁶ evaluated an ultrafast free-breathing LGE technique that used single-shot acquisition without correction of motion. These authors found that although this technique could detect myocardial infarction during free breathing with high accuracy, sensitivity was mildly reduced and the signal-to-noise ratio was higher compared with the conventional segmented LGE method. In our study, the MOCO bSSFP PSIR sequence not only obtained better image quality than the conventional segmented sequence, but also detected LGE, as well as the conventional segmented sequence.

In addition to altering the sequence for LGE imaging, we also adjusted the order of CMR protocols to further shorten the scan time of the CMR examination. The scanning order of cine imaging was changed to be after rest myocardial perfusion imaging with intravenous administration of a gadolinium contrast agent. Therefore, this protocol was able to take full advantage of the waiting time between drug injection and LGE imaging, which shortened the whole CMR scan time and improved efficiency of the examination. D'Angelo et al.¹² found an excellent correlation between pre- and post-contrast cine imaging. This previous finding supports the change of order for acquiring cine images in our study. This change eliminates the time required for cine imaging before contrast administration, while fully using the waiting time between perfusion imaging and viability imaging.

To satisfy the time requirement of obtaining the best LGE images with the MOCO bSSFP PSIR method, another gadolinium contrast agent with a high relaxation time and a shorter delay time was used (Gd-BOPTA), which further reduced the overall scanning time of the CMR examination. Using this contrast agent, the dose was reduced to 0.1 mmol/kg body weight for LGE imaging. Cheong et al.⁹ showed that the best image quality was achieved with a delay of 5 minutes between injection and LGE imaging using 0.1 mmol/kg of Gd-BOPTA. In the current study, the time delay between contrast administration and LGE imaging was dictated by the total time required for perfusion imaging and cine imaging. Therefore, LGE imaging was performed 7 minutes after the contrast agent injection. With development of technology, the time taken in cine imaging may be reduced from 6 to 7 minutes to 1 to 3 minutes. Tomoyuki et al.^{17,18} compared compressed sensing real-time cine CMR in single-breath hold or free breathing with the standard cine CMR. They found that the compressed sensing cine CMR shortened the scan time to approximately 24 s for eight short-axis images and provided slightly lower quality, but acceptable images. This finding suggests that the scan time for cine imaging will be shortened to 1 to 3 s per slice in the near future. Although our study did not focus on cine imaging, contrast agents with a high relaxation rate to match a shorter scan time for cine imaging are absolutely necessary. Bauner et al.¹⁹ and Balci et al.²⁰ found that using 0.1 mmol/kg of Gd-BOPTA achieved equal or better LGE image quality compared with using 0.2 mmol/kg of Gd-DTPA. The current study achieved similar results, while using Gd-BOPTA significantly shortened the entire CMR scan time and required only half the dose of conventional contrast agents. Zou et al.²¹ suggested that reducing the dose of gadolinium contrast agent to

0.1 mmol/kg may eliminate many risk factors and reduce the risk of renal systemic fibrosis. Therefore, using 0.1 mmol/kg of Gd-BOPTA in the optimized CMR protocol not only achieves high-quality images and shortens the overall CMR scan time, but also reduces the risk of renal-derived system fibrosis while reducing the cost.

Our study suggests that a single-shot MOCO bSSFP PSIR sequences effectively reduces motion artifacts caused by respiratory motion and improves the quality of LGE images. This finding is of great clinical significance for patients who cannot hold their breath during a CMR examination. At the same time, when combining this protocol with a single dose of a contrast agent with a high relaxation rate (Gd-BOPTA), the time requirement of obtaining the best LGE images with the MOCO bSSFP PSIR method is satisfied. This type of improved CMR examination protocol further shortens the whole scan time. Such a reduced scan time in combination with the possibility of LGE imaging under free breathing alleviates the burden on patients. This has the potential for CMR to be more broadly adopted clinically.

This study has the following limitations. First, a sample size calculation was not performed and the experimental sample size was relatively small in this study. Therefore, the limited number of samples may have affected the statistical significance of our results. Additionally, the study was performed at a single imaging center on a single imaging system. Therefore, whether this optimized CMR protocol will be equally effective at other clinics that are different from our setting remains to be determined. Further study will require expanding the type of magnetic resonance imaging magnets, the number of imaging centers, and the sample size. Second, this study did not collect LGE images at multiple time points because limitations of scanning time. LGE images were obtained only after injection of

0.2 mmol/kg of Gd-DTPA for 10 minutes instead. For 0.1 mmol/kg of Gd-BOPTA, a delayed image was present for only 7 minutes. Therefore, the delay time in this study may not have been best for the two drugs, and ultimately might have affected the experimental results to some extent. Third, to reduce the whole CMR scan time and satisfy the time requirement of obtaining the best LGE images with the MOCO bSSFP PSIR method, there are three variables in the two CMR protocols as follows: LGE sequence, gadolinium contrast agent, and the order of cine imaging. Instead of changing these variables step by step, the experiment changes them all at once. Whether the improved image quality was due to different LGE sequence or a better contrast agent remains unknown. This adds some uncertainty to the results. Finally, we did not compare cardiac function derived from two different cine image sets, although we did not anticipate any difference.

Conclusion

Using a single-shot MOCO bSSFP PSIR sequence can effectively reduce respiratory motion artifacts and improve the quality of LGE images, particularly for patients who have difficulty in holding their breath. An optimized CMR examination protocol in combination with a contrast agent with a high relaxation rate at a reduced dose can be used to further reduce the duration of CMR scans.

Author contributions

Jun Liu conceived the study. Mu Zeng contributed to the study design and drafted the manuscript. Cui Yan and Junjiao Hu performed analysis and drafted the manuscript. Yanyu Li performed data collection. Xingzhi Xie, Zhimin Zou, Qiyu Deng, Xiaoyue Zhou, and Xiaoming Bi performed data processing and statistical analysis. All authors revised the manuscript

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Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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ORCID iDs

Mu Zeng  <https://orcid.org/0000-0002-2904-8193>

Jun Liu  <https://orcid.org/0000-0002-0344-4745>

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