Quantitative myocardial perfusion can be achieved without contrast agents using flow-sensitive alternating inversion recovery (FAIR) arterial spin labeling. However, FAIR has an intrinsically low sensitivity, which may be improved by mitigating the effects of physiological noise or by increasing the area of artifact-free myocardium. The aim of this study was to investigate if systolic FAIR may increase the amount of analyzable myocardium compared with diastolic FAIR and its effect on physiological noise. Furthermore, we compare parallel imaging acceleration with a factor of 2 with compressed sensing acceleration with a factor of 3 for systolic FAIR. Twelve healthy subjects were scanned during rest on a 3 T scanner using diastolic FAIR with parallel imaging factor 2 (FAIR-PI2D), systolic FAIR with the same acceleration (FAIR-PI2S) and systolic FAIR with compressed sensing factor 3 (FAIR-CS3S). The number of analyzable pixels in the myocardium, temporal signal-to-noise ratio (TSNR) and mean myocardial blood flow (MBF) were calculated for all methods. The number of analyzable pixels using FAIR-CS3S (663 ± 55) and FAIR-PI2S (671 ± 58) was significantly higher than for FAIR-PI2D (507 ± 82; \( P = .001 \) for both), while there was no significant difference between FAIR-PI2S and FAIR-CS3S. The mean TSNR of the midventricular slice for FAIR-PI2D was 11.4 ± 3.9, similar to that of FAIR-CS3S, which was 11.0 ± 3.3, both considerably higher than for FAIR-PI2D, which was 8.4 ± 3.1 (\( P < .05 \) for both). Mean MBF was similar for all three methods. The use of compressed sensing accelerated systolic FAIR benefits from an increased number of analyzable myocardial pixels compared with diastolic FAIR without suffering from a TSNR penalty, unlike systolic FAIR with parallel imaging acceleration.

**KEYWORDS**
acquisition, cardiovascular MR, compressed sensing, myocardial perfusion, perfusion and permeability, perfusion spin labeling

**Abbreviations used:** ANOVA, analysis of variance; ASL, arterial spin labeling; bSSFP, balanced steady-state free precession; CS, compressed sensing; FAIR, flow-sensitive alternating inversion recovery; FOV, field of view; MBF, myocardial blood flow; PI, parallel imaging; ROI, region of interest; SD, standard deviation; SENSE, sensitivity encoding; TSNR, temporal signal-to-noise ratio.

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1 | INTRODUCTION

Arterial spin labeling (ASL) allows quantification of myocardial perfusion without the use of potentially toxic gadolinium-based contrast agents, which are commonly used for first-pass perfusion CMR. Exploiting intrinsic contrast mechanism enables repeated testing and perfusion evaluation in patients where contrast agents are contraindicated. Myocardial ASL involves "labeling" upstream arterial blood using radiofrequency pulses in the ascending aorta and proximal coronary arteries. Introducing a time delay between the labeling pulses and the image acquisition allows the labeled blood to reach the myocardium in the field of view (FOV), which yields a modulation in measured signal relative to the amount of blood received in the tissue. A second image can be acquired without labeling, which allows quantification of the tissue perfusion through subtraction of the two images, accounting for the $T_1$ recovery during the delay period, and estimating the baseline $M_0$ magnetization (typically by the acquisition of a third image without magnetization preparation).

An implementation of myocardial ASL, flow-sensitive alternating inversion recovery (FAIR), involves the acquisition of two sets of magnetization-prepared images: one "control" image preceded by a slice-selective inversion pulse overlapping the FOV and one "tagged" image with a nonselective inversion pulse. An additional $M_0$ image is also acquired to enable perfusion quantification. The image acquisition is limited to the middiastolic rest period to minimize cardiac motion. Furthermore, to achieve high perfusion sensitivity, a delay time of the order of 1 to 2 seconds is required. Although this may introduce cardiac motion-related artifacts due to the difference in cardiac phase between the slice-selective inversion pulse and the following image acquisition, this can be minimized by performing the inversion pulse in the same cardiac phase but in the preceding cardiac cycle relative to the image acquisition.

A technical challenge of myocardial ASL is the intrinsically low sensitivity of the method due to the small percentage of tissue within each myocardial voxel that is subject to perfusion. As a result, previous implementations of FAIR have employed strategies to improve the signal-to-noise ratio (SNR) of the measurements, including the use of 3 T scanners with balanced steady-state free precession readout, multiple averages, image acceleration using parallel imaging (PI) to mitigate against noise from cardiac motion, and respiratory motion correction. Alternative ASL techniques have also been proposed to increase the sensitivity to myocardial perfusion.

In recent years, compressed sensing (CS) has emerged as a technique for image acceleration. CS exploits the ability to compress the signal provided that it is sparse in some transformable domain, such as the wavelet domain, thus enabling data acquisition with high undersampling factors. In a previous study, PI acceleration was demonstrated to improve FAIR precision without affecting accuracy by shortening the data readout during the middiastolic rest period. Although the middiastolic rest period is typically longer than the end-systolic rest period during resting conditions, systolic image acquisition would capture the myocardium at maximum thickness and thus may increase the number of analyzable pixels in the myocardium. Furthermore, systolic data acquisition would be preferable during stress perfusion when the diastolic quiescent duration shortens considerably. The aim of this study was to investigate if systolic FAIR may increase the amount of analyzable myocardium compared with diastolic FAIR and its effect on physiological noise. Furthermore, we compare PI acceleration with a factor of 2 with CS acceleration with a factor of 3 for systolic FAIR. The study was performed in 12 healthy subjects at rest.

2 | METHODS

2.1 | Cardiac FAIR pulse sequence and postprocessing

A previously published cardiac FAIR pulse sequence was implemented on a 3 T clinical scanner where six control, six tagged and one $M_0$ image were used to reconstruct a single perfusion map. The image acquisition consisted of a balanced steady-state free precession (bSSFP) readout. Furthermore, images were acquired in diastole and systole using PI with an acceleration factor of 2 (FAIR-PI2D and FAIR-PI2S) and in systole using CS with an acceleration factor or 3 (FAIR-CS3S). PI was performed with sensitivity encoding (SENSE), while the CS algorithm was a vendor-provided, wavelet-based algorithm with inline reconstruction. The imaging parameters for the different imaging strategies are shown in Table 1. A 30 mm slice thickness was used for the inversion pulse of the control images while the tagged images were acquired with a nonselective inversion pulse. All images were acquired during breath-holding where one pair of tagged and control images were acquired in a breath-hold and spaced ~8 seconds apart. The order of tagged and control images alternated for each breath-hold to minimize potential bias due to incomplete $M_0$ recovery. The FAIR pulse sequence was double-gated, where both inversion pulses and image acquisitions were triggered to the cardiac rest period in adjacent cardiac cycles. Similar to previously published studies using double-gating, the center of k-space for the image acquisition and the inversion pulses had the same trigger delay. The $M_0$ image was acquired in a separate scan without any contrast preparation to estimate the baseline magnetization.

To account for any differences in positions between breath-holds and different image types, rigid body (translation and rotation) image registration was performed first for the control and tagged images separately, followed by rigid body correction between the image types. The image registration was implemented using the MATLAB (MathWorks, Natick, MA, USA) function imregister. First, a region of interest (ROI) for motion tracking was selected around the left ventricle in the $M_0$ image and propagated to all tagged and control images. Then all cropped tagged and
Control images were registered to the first image in their respective time series using a mean squares similarity metric. To allow for correction of differences in inversion times during the scans, the actual inversion times were stored for all images. The data were corrected using the formula:

\[ I_{\text{ITIcorr}} = M_0 + (I - M_0) e^{\Delta T_1} \]

where \( I \) is the signal intensity in the target or control images, \( \Delta T_1 \) is the difference between actual and nominal (average for all six images) inversion time and \( T_1 \) is the longitudinal relaxation time of blood of \(~1700\, \text{ms} \). Measured signal intensities for the six tagged and control images before and after inversion time correction are shown in Figure 1. Following the inversion time correction, a single tagged and control image were obtained by averaging across the series. The resulting images were then registered to the \( M_0 \) image using a mutual information rigid body registration to account for any respiratory motion between images. Finally, myocardial blood flow (MBF) was calculated using the formula for double-gated myocardial ASL:

\[ \text{MBF} = \frac{1}{2M_0} \left( \frac{C}{T_{1C}\cdot e^{-\frac{T}{T_{1C}}}} - \frac{T}{T_{1T}\cdot e^{-\frac{T}{T_{1T}}}} \right) \]

where \( C \) and \( T \) are the control and tagged images, respectively. Note that separate inversion times were used for the tagged and control images, based on the mean inversion time from the \( T_1 \) correction using Equation 1. The FAIR postprocessing pipeline is illustrated in Figure 2.

**TABLE 1** Imaging parameters

| Parameter                  | FAIR-PI2D | FAIR-PI2S | FAIR-CS3S |
|----------------------------|-----------|-----------|-----------|
| Cardiac phase              | Diastole  | Systole   | Systole   |
| Acceleration method        | SENSE     | SENSE     | Compressed sensing |
| Acceleration factor        | 2         | 2         | 3         |
| Flip angle (°)             | 50        | 50        | 50        |
| Ramp-up pulses             | 20        | 20        | 25        |
| FOV (mm)                   | 300 x 300 | 300 x 300 | 300 x 300 |
| Pixel bandwidth (Hz)       | 1890      | 1890      | 1890      |
| \( \Delta x \) (mm²)       | 2 x 2 x 10 | 2 x 2 x 10 | 2 x 2 x 10 |
| Acquisition matrix         | 150 x 150 | 150 x 150 | 150 x 150 |
| TR (ms)                    | 2.2       | 2.2       | 2.2       |
| TE (ms)                    | 1.1       | 1.1       | 1.1       |
| T_{acq} (ms)               | 165       | 165       | 110       |
2.2 MRI experiments

This study was approved by the regional ethics committee. Twelve healthy subjects (age: 29.4 ± 3.9 years; eight males and four females) were recruited and provided written informed consent. All 12 subjects had no history of prior or current cardiovascular disease or medication. All experiments were performed on a 3 T clinical scanner (Achieva, Philips Healthcare, Best, the Netherlands) with a 24-channel torso coil. To compare the three myocardial FAIR pulse sequences, a midventricular slice was acquired during rest in short-axis with FAIR-PI2D, FAIR-PI2S and FAIR-CS3S in a randomized order. Assuming a heart rate of 60 bpm, a set of FAIR (tagged and control) images were acquired in 12 seconds, including an 8-second rest period to allow for M2 recovery. The FAIR scan was repeated six times for each method to generate the same amount of signal averages. For each repetition, the order of control and tagged images was alternated to eliminate bias. No dietary restrictions (eg, caffeine) were stipulated for the volunteers prior to participation. All scans were ECG-triggered and the systolic and diastolic rest periods were visually determined from a four-chamber cine image with a temporal resolution of 15 ms.

2.3 Image analysis and statistics

The reconstructed images were transferred to an offline workstation for postprocessing using MATLAB, as outlined in Figure 2. The myocardium of the left ventricle was manually segmented, and perfusion was calculated as the mean MBF (in milliliters per grams per minute) in the segmented ROI. The number of pixels included in the segmented myocardium was recorded for all MBF maps. To estimate the effects of cardiac motion, physiological noise was estimated by calculating MBF maps for each control-tagged image pair and dividing the mean MBF with the standard deviation (SD) across the six maps. This metric was first described by Poncelet et al and is typically referred to as temporal SNR (TSNR),4 The TSNR and mean MBF were calculated for FAIR-PI2D, FAIR-PI2S and FAIR-CS3S. Differences were compared using a one-way analysis of variance (ANOVA). A threshold of P less than .05 was used to reject the null hypothesis that the methods yield the same TSNR or mean MBF. If the null hypothesis was rejected, posthoc t-tests were performed to determine which groups were statistically different with a significance threshold of P less than .05.

3 RESULTS

The mean heart rate ± SD for the 12 healthy volunteers during rest was 64 ± 10 bpm. The average number of pixels ± SD in the segmented myocardium for FAIR-PI2D was 507 ± 82, significantly less than for FAIR-PI2S, which was 671 ± 58 (P = .001). Similarly, the number of segmented...
pixels using FAIR-CS3S (663 ± 55) was significantly higher than for FAIR-PI2D (P = .001), while there was no significant difference between FAIR-PI2S and FAIR-CS3S. Representative segmentations of the left ventricular myocardium, fused onto the raw control images, are shown in Figure 3, which also shows the MBF histograms from the segmentation for all three techniques. Representative perfusion maps from three healthy volunteers are shown in Figure 4, demonstrating comparable perfusion values and similar image quality using systolic and diastolic FAIR with PI2 and CS3 acceleration.

The mean MBF and TSNR for the three techniques in the midventricular short-axis slice for all 12 healthy subjects are summarized in Figure 5. The group-wise mean ± SD of the mean MBF (in ml/g/min) for the entire midventricular slice for FAIR-PI2D, FAIR-PI2S and FAIR-CS3S was 1.5 ± 0.5, 1.4 ± 0.4 and 1.4 ± 0.6, respectively. Similar mean MBF were measured for all three techniques for both regional measurements and for the entire slice. The ANOVA test showed that there were no statistically significant differences in mean MBF between any groups. The mean TSNR of the midventricular slice for FAIR-PI2D, FAIR-PI2S and FAIR-CS3S was 11.4 ± 3.9, 8.4 ± 3.1 and 11.0 ± 3.3, respectively. The mean TSNR difference between FAIR-PI2D and FAIR-PI2S was statistically different (P < .05), as was the difference between FAIR-CS3S and FAIR-PI2S (P < .05). However, the regional TSNR measurements did not yield any statistically significant differences between FAIR-PI2D, FAIR-CS3S and FAIR-PI2D.

4 | DISCUSSION

In this work we have investigated the merits of systolic image acquisition to increase the amount of analyzable myocardium of FAIR ASL. Furthermore, we have compared conventional PI acceleration with a factor of 2 with CS with a factor of 3 for systolic FAIR. We found that systolic imaging appears to be advantageous for myocardial FAIR due to the increased myocardial thickness during this cardiac phase, which yields fewer
partial volume effects compared with conventional diastolic imaging. This leads to a higher number of pixels in the analyzable myocardium. Furthermore, the use of CS appears to reduce the amount of physiological noise in the MBF maps, as measured using TSNR, to a similar level as the diastolic MBF maps acquired with PI. The amount of physiological noise of the estimated perfusion is one of the main limitations of noncontrast myocardial perfusion techniques, and the advantages provided by systolic imaging using CS may improve the sensitivity of myocardial FAIR to detect perfusion defects in patients.

The merits of systolic imaging have also been noted in a similar quantitative cardiac application, namely, myocardial T1 mapping. Similar to myocardial FAIR, T1 mapping is based on single-shot acquisitions whose duration may extend beyond the quiescent period of the systolic rest period. Notwithstanding this limitation, systolic imaging appears to be advantageous for these applications. As noted in previous work on T1 mapping, systolic imaging benefits from robustness to high heart rates and tachyarrhythmia. The end-systolic rest period is relatively invariant to changes in heart rate while the middiastolic rest period is strongly correlated with the heart rate. When the cardiac cycle is short, due to stress or arrhythmia, the diastolic quiescent period may become shorter than the systolic rest period or almost disappear entirely. Therefore, systolic imaging may be particularly beneficial to enable robust, high-quality myocardial FAIR acquisition during stress testing or in the event of sustained arrhythmia.

As noted in previous studies, accelerating the image acquisition reduces the detrimental effects of physiological noise due to cardiac motion. Using PI the acquisition time was 165 ms per image, which is typically much longer than the systolic quiescent period. We found a significant reduction in TSNR for FAIR-PI2S compared with FAIR-PI2D, which indicates an increased amount of cardiac motion in the systolic acquisition. However, by accelerating the systolic data acquisition to 110 ms using CS, the TSNR was increased to a comparable level with the diastolic maps, which suggests that the systolic cardiac motion had been effectively minimized. A recent study comparing diastolic and systolic cardiac FAIR using PI acceleration found a similar reduction in TSNR using systolic compared with diastolic FAIR, while the global MBF was lower than with diastolic acquisition. In the current study, we did not find any mean differences in global MBF between systole and diastole. Differences in acquisition

**FIGURE 4** Perfusion maps obtained in three healthy volunteers (HV1, HV3 and HV6) using diastolic FAIR with parallel imaging factor 2 (FAIR-PI2D) and systolic FAIR with parallel imaging factor 2 (FAIR-PI2S) and compressed sensing factor 3 (FAIR-CS3S).
strategies may explain these discrepancies: a shorter acquisition window (165 ms for PI2) and ECG triggering were used in the current study while Javed et al used an acquisition window of 192 ms and fingertip plethysmograph triggering. The reduction in acquisition time in our study is largely due to an ~30% shorter repetition time of 2.2 ms compared with 3.1 ms in Javed et al. This is a significant advantage as it enables more efficient data acquisition, translating into a shorter acquisition window and/or higher spatial resolution. However, further reducing the acquisition time will be important for systolic FAIR due to the higher likelihood of cardiac motion. To this end, advanced image acceleration techniques such as CS hold great promise to reduce the physiological noise for systolic perfusion images where the acquisition time may approach the duration of the systolic rest period of ~80-100 ms. In the current study, we used a vendor-provided wavelet-based CS technique. Alternative CS techniques using total variation, low-rank schemes, adaptive sparsity transform generation or new deep learning techniques may allow acceleration with higher factors to further reduce the physiological noise. However, it should be noted that CS intrinsically removes some noise during the iterative thresholding procedure. Although it is beyond the scope of this study to investigate how different CS parameters influence the MBF noise profile, it is important to recognize that this reconstruction approach may disguise subtle local perfusion changes. However, in this study we observed slight changes between different regions of the myocardium, consistent with previous studies where higher MBF was found in the septum. This variation was found for both CS and conventional PI suggesting that comparable changes caused by perfusion defects may be detectable using CS.

The midventricular group mean MBF values obtained with the implemented cardiac FAIR method of ~1.5 ml/g/min are comparable, but at the higher end, relative to previous studies using the same technique, which range from 1.0 to 1.5 ml/g/min. Notable differences compared with previous implementations of cardiac FAIR are a shorter repetition time (2.2 ms here compared with ~3.2-4 ms in previous studies), the absence of fat suppression prepulse and potentially different postprocessing pipelines. In the current study, we performed inversion time correction on the six sets of control and tagged images prior to averaging, motion correction and MBF calculation. Alternatively, MBF may be calculated for each set of images (one MBF map for each breath-hold) and then averaged. This would avoid the need for inversion time correction as the recorded inversion times for all images would be directly applied to Equation 2. However, the drawback with this approach is that motion correction is required between the tagged and control images six separate times and is more likely to introduce registration errors due to the substantial difference in contrast between the noisy images. By contrast, with the proposed approach, the six different images with roughly the same

![Figure 5](image-url)
contrast are registered to each other with minimal error then averaged to yield higher quality tagged and control images prior to the single mutual information registration. Further work is required to optimize the MBF postprocessing and improve respiratory motion correction. A free-breathing cardiac FAIR would be desirable, which would facilitate patient studies but increase the necessity for robust and accurate motion correction.12,13

We found similar mean MBF values for systolic and diastolic FAIR. This contrasts with findings from coronary flow measurements where peak blood flow typically occurs during diastole when the myocardium relaxes, increasing the pressure gradient between the aortic root and coronary arteries.33 Based on the observation that coronary flow is higher in diastole than systole, a similar increase in myocardial perfusion could be expected during the diastolic phase. Studies using quantitative contrast-enhanced myocardial perfusion techniques have found similar MBF during rest while higher MBF were found for diastolic acquisitions during stress.34,35 However, it should be noted that ASL techniques such as myocardial FAIR rely on perfusion-sensitizing inversion pulse in the same cardiac phase but preceding cardiac cycle as the image acquisition. Therefore, the measured MBF using myocardial FAIR reflects the integration of perfusion across the entire cardiac cycle, and the systolic and diastolic MBF should in theory be the same, even during stress. Further studies during stress conditions are required to verify this claim.

In conclusion, systolic imaging allows cardiac FAIR acquisitions with larger analyzable myocardium compared with diastolic imaging. Furthermore, the use of CS-accelerated systolic FAIR does not suffer from a TSNR penalty, unlike systolic FAIR with PI acceleration. Systolic imaging is particularly useful during stress testing as it is more stable in timing, both in terms of trigger delay and rest period duration, while the diastolic rest period may become significantly shortened.

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ORCID
Markus Henningsson https://orcid.org/0000-0001-6142-3005

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