T(Rho) And Magnetization Transfer And INvErsion Recovery (TRAMINER)-Prepared Imaging: A Novel Contrast-Enhanced Flow-Independent Dark-Blood Technique for the Evaluation of Myocardial Late Gadolinium Enhancement in Patients With Myocardial Infarction

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Purpose: To evaluate a new dark-blood late gadolinium enhancement (LGE) technique called "T(Rho) And Magnetization transfer and INvErsion Recovery" (TRAMINER) for the ability to detect myocardial LGE versus standard "bright-blood" inversion recovery (SIR) imaging.

Materials and Methods: This Institutional Review Board (IRB)-approved, Health Insurance Portability and Accountability Act (HIPAA)-compliant prospective study included 40 patients (62 ± 14 years [mean $\pm$ standard deviation (SD)], 29 males) with suspected myocardial infarction (MI) referred for the assessment of myocardial viability. The patients underwent a 1.5T cardiac magnetic resonance imaging (MRI) including postcontrast SIR and TRAMINER acquisitions. Normalized images were evaluated by two readers. Subjective (3-point Likert scale) and objective image qualities were compared using Mann–Whitney *U*-test and paired *t*-test, respectively. Interobserver agreement, LGE detection rate, and level of certainty were compared using Cohen's kappa, Wilcoxon-test, and Mann–Whitney *U*-test, respectively. Results are reported as mean $\pm$ SD or mean [95% confidence interval].

Results: Overall, image quality was rated similar between TRAMINER and SIR; however, TRAMINER performed better on a visual assessment of the ability to differentiate LGE from blood (Likert scale: 3.0 [3.0–3.0] vs. 2.0 [1.7–2.2], $P < 0.0001$). TRAMINER provided significantly higher signal intensity range (69.8 ± 10.2 vs. 9.6 ± 7.6, $P < 0.0001$) and a 4-fold higher signal intensity ratio (4.2 ± 1.9 vs. 1.1 ± 0.1, $P < 0.0001$) between LGE and blood signals. TRAMINER detected more patients (19/40 vs. 17/40) and segments (91/649 vs. 79/649) with LGE with higher level of certainty (2.9 [2.8–3.0] vs. 2.7 [2.5–2.8], $P = 0.0185$). Interobserver agreement was good to excellent for LGE detection.

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Conclusion: TRAMINER provides better contrast between LGE and blood and consequently may have increased ability to discriminate thin subendocardial and papillary muscle enhancement from the blood signal, which can have an indistinct appearance using SIR.
Level of Evidence: 2

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The amount of ischemic myocardial late gadolinium enhancement (LGE) visualized by cardiovascular magnetic resonance imaging (MRI) has been shown to predict prognosis,[1–3] highlighting the importance of accurate detection and quantification of myocardial infarct (MI) through LGE. Standard inversion recovery (SIR) techniques currently available for MI detection are so-called "bright-blood" methods where the contrast-to-noise ratio between blood and the hyperenhanced, irreversibly damaged myocardial area is small. Their signal similarity often makes the discrimination of LGE from blood at the tissue–blood interface challenging and may lead to false-negative interpretations of LGE images in patients with subendocardial MI.[4]

While various solutions have been proposed to improve the distinction of LGE from the bordering blood pool,[4–9] most of these methods require the combination of different image sets, limiting accuracy due to discrepancies in image coregistration,[4,5] or require special preparation, eg, application of two separate inversion times (TI).[10] A dark blood acquisition technique with the ability to independently differentiate the blood and hyperenhanced myocardial signals without these disadvantages would thus be highly beneficial in patients with MI involving the subendocardium or papillary muscles. However, the standard dark-blood preparation[11] is suboptimal in the presence of contrast agent, since the readout would need to occur in early diastole to null blood. During this phase, cardiac motion, misregistration of readout and prepared slice, and insufficient blood exchange would result in nondiagnostic images. A recently introduced technique, the flow independent dark blood delayed enhancement (FIDDLE), has been shown to overcome most of the above-mentioned limitations, possess improved sensitivity and specificity towards the detection of MI compared to SIR, and has been validated with histology.[12] However, its magnetic preparation typically has very high energy requirements that may prevent its application on clinical MRI scanners without high-end radiofrequency (RF) power amplifiers.

Accordingly, we sought to evaluate a novel contrast-enhanced flow-independent dark-blood LGE technique called "T(Rho) And Magnetization Transfer and INvErsion Recovery" (TRAMINER), which uses a modified magnetic preparation with lower power and energy requirements compared to FIDDLE, but delivers similar image contrast. We evaluated this technique for the ability to detect myocardial LGE versus "bright-blood" SIR imaging.

Materials and Methods

Dark-Blood TRAMINER Pulse Sequence

Figure 1 shows the timing diagram of the novel TRAMINER pulse sequence. In heartbeat 1, it contains a preparation module, a single-shot balanced steady-state free-precession (bSSFP) readout of the magnetically prepared data, and a TI defined from the spatially nonselective inversion recovery (NSIR) pulse to reading out the contrast-relevant data portion. The second heartbeat of this electrocardiogram (ECG)-triggered sequence serves for magnetization recovery. Reference data for phase-sensitive IR (PSIR)[13] image reconstruction is acquired in the third heartbeat. Only the PSIR images are TRAMINER images and are clinically evaluated.

The components of the preparation module are a series of three adiabatic B1-insensitive rotation-4 (BIR-4) pulses (duration 16.4 msec, B1 7.27 μT, bandwidth 1 kHz, full-width at half-maximum found by pulse simulation) each with a net zero degree flip angle, alternating with 1.5 msec time delays, a trailing NSIR pulse (duration 10.2 msec, B1 2.33 μT, bandwidth 1 kHz), and a spoiler gradient (10 msec, 12 mT/m) at the end. The BIR-4 pulses simultaneously impose T_2-weighting due to the T_2(Rho) relaxation in the spin-lock regime[14] and magnetization transfer contrast,[15] both attenuating tissue magnetization while minimally affecting blood and effectively creating blood–tissue separation. Specifically, due to their net zero degree flip angle, the BIR-4 pulses create on-resonance magnetization transfer analogous to a sequence of tip down, time delay, and flip back pulse described by Schneider et al.[16]

After the NSIR pulse, T_1-recovery occurs in blood, noninfarcted, normal myocardium called remote myocardium, and MI according to their respective T_1. In the presence of a T_1-shortening contrast agent, blood recovers faster than remote myocardium but begins recovery from a more negative level of magnetization due to the prior blood–tissue separation, causing the recovery curves for blood and remote myocardium to intersect. The TI is set so that the contrast-relevant portion of the data is acquired before this intersection, where blood signal is slightly below the remote myocardium signal. MI magnetization is much higher at this point. In the PSIR reconstructed TRAMINER images, this ordering of the relaxation curves results in visualization of blood as black, MI as bright, and myocardium as dark gray, which is close to, but larger than, blood signal. All preparations are spatially nonselective so that they are independent of flow, unlike the standard dark blood preparation.[11]

Study Population

Our Institutional Review Board approved the protocol and written informed consent was obtained from each patient. The study was conducted in HIPAA compliance. From August 2014 to January 2016, 40 patients were enrolled at our institution. Patients aged 18–90 were included if they were referred for a clinically indicated MRI for viability assessment in known or suspected prior MI.

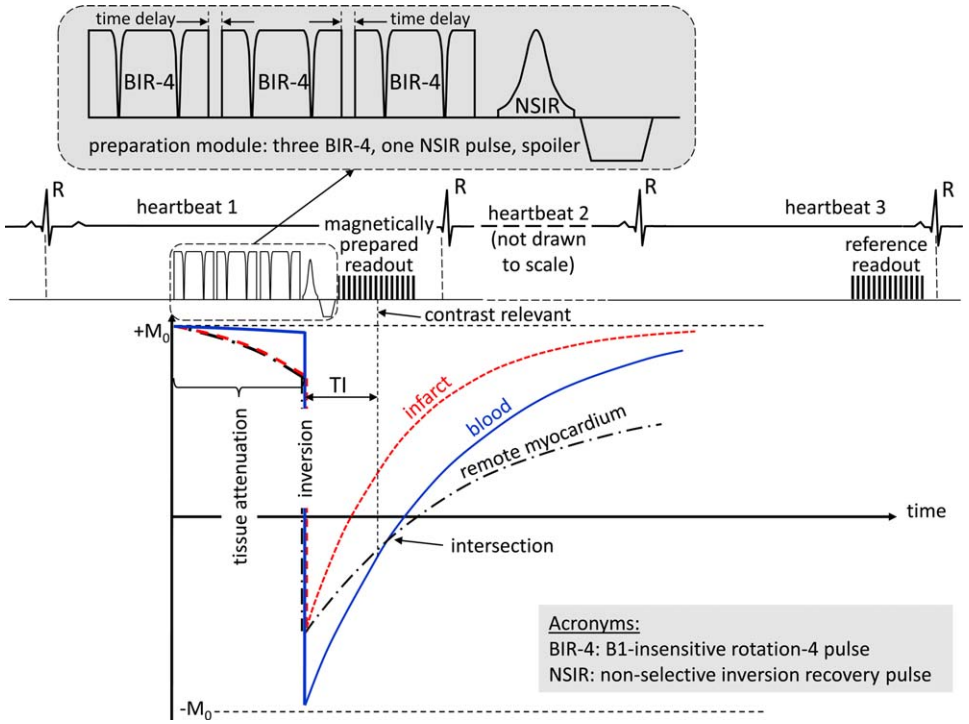

FIGURE 1: Timing diagram of the electrocardiogram (ECG) triggered single-shot TRAMINER pulse sequence with magnetic preparation module, balanced steady state free precession (bSSFP) readout of magnetically prepared data in heartbeat 1, and reference data in heartbeat 3 needed for phase-sensitive inversion recovery (PSIR). Heartbeat 2 is used for magnetization recovery. Detailed view of the preparation module: series of three adiabatic B1-insensitive rotation-4 (BIR-4) pulses with a net zero degree flip angle each, time delays, a nonselective IR (NSIR) pulse, and a trailing spoiler gradient. The zero-degree BIR-4 pulses simultaneously impose T_2-weighting due to T_2(Rho) relaxation in the spin-lock regime and magnetization transfer contrast, both separating blood and tissue magnetization. T_1-recovery starts at the NSIR pulse. Blood, infarcted, and remote myocardium recover according to their respective T_1, in the presence of a T_1-contrast agent. Recovery curves for blood and remote myocardium intersect. Inversion time (TI) is set to capture the signal before the intersection so that blood is visualized as black (lowest signal), myocardium as dark gray, and MI as bright (highest signal). All preparations are spatially nonselective and thus flow-independent.

Demographics and medical history were obtained from the patient's medical record. When available, ECG, troponin levels, and results from invasive catheter angiography (ICA) were used to confirm MI in discordant cases.

MR Protocol

Images were acquired using a 1.5T system (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany). Patients were scanned head-first in the supine position and signal reception was obtained using a 6-element body array and a multichannel spine phased-array RF coil. SIR and TRAMINER images were acquired in four-chamber and short-axis (basal, mid-ventricular, and apical) views 15 minutes after the administration of contrast agent (0.1 mmol/kg gadobenate-dimeglumine, MultiHance, Bracco, Princeton, NJ). The order of the two acquisitions was randomized. The time to collect all SIR and TRAMINER images was approximately 6 minutes.

BRIGHT BLOOD STANDARD IR (SIR) ACQUISITION. SIR images were acquired using an ECG-triggered single-shot bSSFP sequence with an IR pulse. To ensure best spatial registration between magnetically prepared and reference data, each slice was acquired during a breath-hold of three cardiac cycles. The following acquisition parameters were applied: field-of-view (FOV) 280 × 380 mm^2, slice thickness 8 mm, acquisition matrix 142 × 192, in-plane resolution 2.0 × 2.0 mm^2, echo/repetition time (TE/TR) 1.1/2.6 msec; readout bandwidth 965 Hz/pixel, and flip angle 50°. Generalized autocalibrating partially parallel acquisition (GRAPPA) with acceleration factor 2 and Cartesian readout were applied. The optimal TI was set to null the signal intensity (SI) of normal myocardium based on a Look–Locker TI-scout acquisition. TI was adjusted upward throughout the scans to maintain this image intensity despite washout of contrast agent.

DARK-BLOOD TRAMINER ACQUISITION. TRAMINER images were collected immediately before or after the SIR acquisition. All imaging parameters were matched with the SIR images except for TI. TI was determined empirically starting with 200 msec and decreasing until normal myocardium was only slightly brighter than blood in the PSIR image. Consistent with the SIR scans, TI was adjusted upward throughout the exam to maintain these gray levels.

Specific Absorption Rate Assessment

Our study strictly adhered to US Food and Drug Administration (FDA) guidelines for specific absorption rate (SAR, <4 W/kg averaged over the whole body for any 15-min period) and used appropriate RF power safety checks (SAR monitor) on the clinical scanner. Two measures for SAR were calculated. First, the time-averaged SAR of the TRAMINER preparation module was

calculated by numerical integration of the square of the pulse envelopes[17] and division by the module duration. SAR of the IR pulse was calculated in an identical manner. SAR of the TRAMINER preparation was expressed relative to the SAR of the IR pulse, which was defined as 100%. Second, the time-averaged SAR for the entire SIR and TRAMINER sequence including preparation modules, readout modules, time delays, and recovery heartbeats were calculated by the scanner's SAR monitor and reported in W/kg.

Image Analysis

All image analysis was performed by two independent observers (G.M. with 5 and A.V.S. with 8 years of experience in cardiovascular MR, respectively). The observers first evaluated the SIR image sets in random order. After a 14-day hiatus to minimize recall bias, the readers assessed the TRAMINER images in a random order. Image quality and LGE assessments were performed on a dedicated workstation (Siemens Leonardo).

SUBJECTIVE IMAGE QUALITY ASSESSMENT. Image quality was subjectively rated on a 3-point Likert scale (1, poor; 2, acceptable; 3, excellent). The degree of differentiation of MI from blood, MI from normal myocardium, and blood from normal myocardium was assessed for both techniques.

OBJECTIVE IMAGE QUALITY ASSESSMENT. Due to signal normalization done by PSIR, noise measurements are not reliable in TRAMINER images[13]; consequently, signal-to-noise and contrast-to-noise ratios were not calculated. Furthermore, SIR and TRAMINER images are scaled differently. Therefore, compartments depicted as dark in TRAMINER (blood and healthy myocardium) have SI that is different from dark compartments in SIR images (healthy myocardium). To quantitatively compare the signal difference between the techniques, the pixelwise SI in both TRAMINER and SIR images was linearly normalized into a 0–100 SI scale using the following equation:

$$SI_{v,new} = \frac{SI_{\max,new} - SI_{\min,new}}{SI_{max} - SI_{mim}} \times (SI_{v,orig} - SI_{min}) + SI_{min,new}$$

where $SI_{v,new}$ is the normalized SI value of any voxel, SI_{min} and SI_{max} are the lowest and highest SI in the image, $SI_{min,new}$ and $SI_{max,new}$ are the lower and upper ends of the new scale (0 and 100, respectively), and $SI_{v,orig}$ is the actual SI value of the same voxel.

Following normalization, SI was measured for normal myocardium, MI areas, and the blood pool using circular regions of interest (ROIs) in each. To quantify the SI difference available to differentiate among the tissue compartments, the dynamic SI range between MI-blood, MI-remote, and blood-remote were assessed. The SI ratio (R_{SI}) based on the normalized SI values were calculated between each tissue compartment and compared between the techniques.

LGE ASSESSMENT. Image sets were analyzed on a per-patient and per-segment basis using the American Heart Association 17-segment model.[18] The presence of myocardial LGE was evaluated using a binary score (0, negative; 1, positive for LGE) and the LGE detection rate was calculated for each technique. In addition, the level of certainty was rated on a per-patient and per-segment basis using a 3-point Likert scale (1, low; 2, intermediate; 3, high).[19] Cine image sets were available adjacent to the SIR images for comparison in case the edge between the MI and blood was not apparent.

Segmental MI transmurality was assessed by the two readers to compare if SIR and TRAMINER provide similar visual impressions of MI transmural extent using a 4-point scale (1, subendocardial LGE with $\leq$25% involvement; 2, 26–50% involvement; 3, 51–75% involvement; and 4, transmural LGE corresponding to greater than 75% involvement).[20] Transmurality scores were compared between the readers and also between the two techniques.

The MI percentage (%MI) of the left ventricular (LV) myocardium was assessed by assigning segmental transmurality scores to each segment, as previously described.[21,22] Microvascular obstruction, if present, was included in the selected MI area.

Statistical Analysis

Statistical analysis was performed using MedCalc, v13.3.1.0 (Ostend, Belgium). The distribution of the data was assessed with the Shapiro–Wilk test. Continuous variables were reported as mean $\pm$ standard deviation, scores as mean [95% confidence interval], and categorical variables were reported as absolute frequencies and proportions.

Differences in subjective image quality ratings were assessed by averaging the score provided by the two readers and then comparing SIR and TRAMINER by using the Mann–Whitney *U*-test. Agreement in subjective image quality ratings was assessed using intraclass correlation coefficients (ICCs) with the level of agreement as follows: poor, ICC $<$ 0.21; fair, ICC = 0.21–0.40; moderate, ICC = 0.41–0.60; good, ICC = 0.61–0.80; and excellent, ICC $>$ 0.80. ICC results were reported with 95% confidence interval (CI) in square brackets. Objective image quality measures were analyzed using a paired *t*-test.

Differences in LGE detection rate between TRAMINER and SIR acquisitions and between readers was assessed using Wilcoxon and Cohen's kappa statistics, respectively, with the level of agreement defined as follows: poor, $\kappa < 0.21$; fair, $\kappa = 0.21$-0.40; moderate, $\kappa = 0.41$-0.60; good, $\kappa = 0.61$-0.80; and excellent, $\kappa > 0.80$. Differences and interobserver agreement in the level of certainty were evaluated using the Mann–Whitney *U*-test and ICC, respectively. Differences in segmental transmurality scores were evaluated using the Mann–Whitney *U*-test, while the ICC test was used to assess interobserver agreement with the level of agreement as described above. Differences in MI percentage between TRAMINER and SIR techniques were analyzed with paired *t*-test. $P < 0.05$ was considered statistically significant.

Results

Patient Population

Baseline patient characteristics are shown in Table 1. A total of 40 patients and 680 myocardial segments were analyzed. Thirty-one (4.5%) segments were excluded from the analysis due to image artifacts or inadequate myocardial coverage. LGE patterns detected in this patient population were consistent with MI. Representative cases are shown in Fig. 2.

TABLE 1. Patient Population ($n = 40$)

Age (years)	62 ± 14
Gender (male)	29 (72.5%)
Race	
African American	20 (50.0%)
Caucasian	20 (50.0%)
Weight (kg)	83.3 ± 15.2
Height (cm)	169.3 ± 29.3
Body Mass Index (kg/m^2)	27.5 ± 3.9
Body Surface Area (m^2)	2.0 ± 0.2
Diabetes mellitus	12 (30.0%)
Hypertension	19 (47.5%)
Dyslipidemia	14 (35.0%)
Smoking	13 (32.5%)
Prior percutaneous coronary intervention	5 (12.5%)
Prior coronary artery bypass surgery	3 (7.5%)
Ejection fraction	51 ± 11.9 %

Data are displayed as mean ± standard deviation or frequency (%).

SAR Assessment

In all patients, imaging was performed within all SAR constraints. Two SAR measurements were obtained. First, the relative SAR accounting for the preparation modules only was 100% for the IR pulse of the SIR sequence, and 906.5% for the TRAMINER preparation. Second, the SAR for each entire sequence, including preparation modules, single-shot readouts, delay and recovery times, was calculated by the scanner as 0.589 W/kg (100%) for SIR and 0.740 W/kg (126%) for TRAMINER yielding 26% more SAR for the TRAMINER sequence.

Image Analysis

SUBJECTIVE IMAGE QUALITY ASSESSMENT. Subjective image quality ratings and corresponding interobserver agreement are summarized in Table 2. The ability to discriminate MI from blood was rated significantly higher using TRAMINER compared to the SIR approach. There were no significant differences in other subjective image quality parameters. Interobserver agreement in image quality ratings was good to excellent for both acquisition techniques.

OBJECTIVE IMAGE QUALITY ASSESSMENT. The TRAMINER technique provided significantly higher SI difference between blood and MI ($P < 0.0001$), indicating

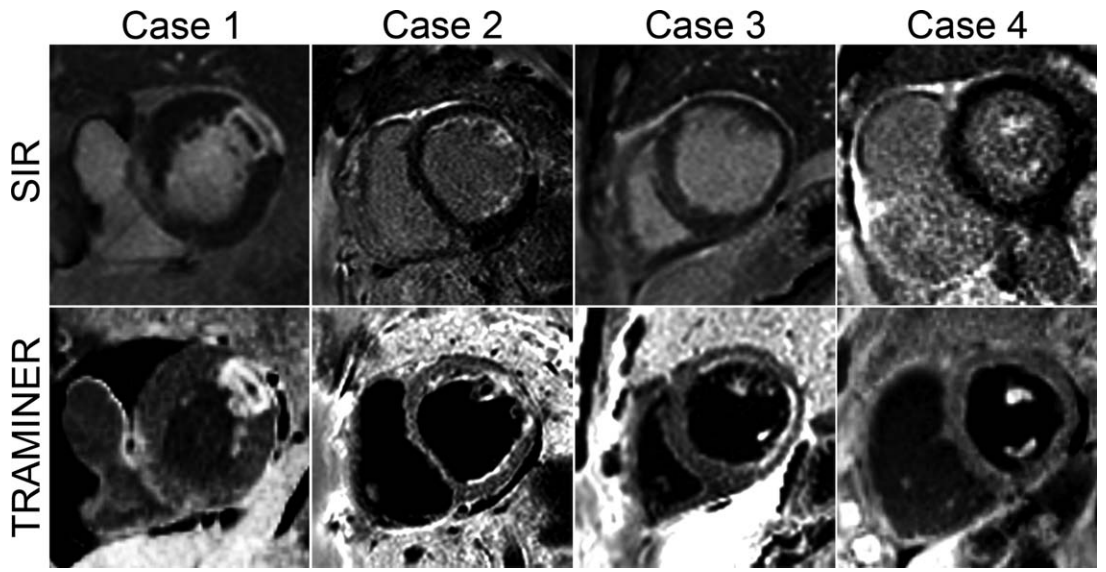

FIGURE 2: Representative SIR and TRAMINER images with transmural (Case 1) subendocardial (Cases 2 and 3) and papillary muscle (Case 4) LGE. Case 1: 68-year-old man with known left circumflex coronary artery occlusion and consequent basal anterolateral transmural MI with microvascular obstruction. LGE was visualized similarly by both techniques. Case 2: 35-year-old man with known severe systolic biventricular dysfunction with a left ventricular ejection fraction of 20%. SIR image indicates subendocardial LGE in the left anterior descending and left circumflex coronary artery territories confirmed by findings in the TRAMINER image. Case 3: 60-year-old man with subendocardial MIs in the diagonal and obtuse marginal coronary artery territories. The presence of myocardial LGE in SIR images is not convincing due to the overlap between the signal intensities in the blood and hyperenhanced myocardium. The TRAMINER image, however, clearly shows LGE in the anterior and inferolateral, inferior segments. In addition, papillary muscle involvement is also visualized. ICA confirmed >90% luminal stenosis in the corresponding coronary artery branches. Case 4: 78-year-old man with LGE affecting both LV papillary muscles. While LGE was visualized by the SIR technique, the TRAMINER approach provides better delineation of the papillary muscle MIs and consequently higher confidence.

TABLE 2. Subjective Image Quality Measures (Mean [95% Confidence Interval]) and Interobserver Agreement (ICC [95% Confidence Interval])

Category	SIR		TRAMINER		*P*-value[a]
	Rating	ICC	Rating	ICC	
Differentiation MI – blood	2.0 [1.7–2.2]	0.76 [0.74–0.78]	3.0 [3.0–3.0]	0.90 [0.88–0.91]	< 0.0001
Differentiation MI – remote	3.0 [3.0–3.0]	0.84 [0.82–0.86]	2.8 [2.6–3.0]	0.81 [0.79–0.83]	0.1503
Differentiation blood – remote	2.9 [2.8–3.0]	0.87 [0.85–0.88]	2.9 [2.8–3.0]	0.80 [0.77–0.82]	0.9815

SIR, standard inversion recovery; TRAMINER, T(Rho) And Magnetization Transfer and INvErsion Recovery; ICC, intraclass correlation coefficient; MI, myocardial infarct.
[a]For comparison between image quality ratings.

improved ability for discrimination. There was no difference in the magnitude of the signal range between remote myocardium and MI between the techniques ($P = 0.1934$), suggesting sufficient contrast for MI visualization (Table 3). TRAMINER provided about 4-fold higher R_{SI} between blood and MI compared to the SIR approach.

LGE ASSESSMENT. TRAMINER detected LGE in two more patients than SIR (Table 4). In these two patients, the presence of MI was confirmed by other clinical findings including ECG, troponin levels, and ICA. In the first patient, shown as Case 3 in Fig. 2, MI was confirmed by >90% luminal stenosis in the corresponding coronary artery branches at ICA. In the second patient, subendocardial LGE was detected in the basal inferolateral myocardium, which was consistent with 90% stenosis in the LCX found on ICA.

Both techniques showed excellent interobserver agreement. The level of certainty was significantly higher for TRAMINER compared to SIR (Table 4). Interobserver agreements in certainty ratings were excellent for both approaches.

On a per-segment basis (Table 4), 91 segments in 19 patients showed LGE with TRAMINER, of which 25 did not show LGE on SIR images. The level of certainty for LGE detection in the latter segments was rated significantly lower for SIR compared to TRAMINER (1.8 [1.1–2.4] and 3.0 [3.0–3.0], respectively, $P = 0.0031$). TRAMINER was negative for LGE in 11 of the 79 segments where SIR detected LGE, corresponding to six patients. However, the level of certainty was rated lower per patient for SIR compared to TRAMINER (2.7 [2.5–2.8] and 2.9 [2.8–3.0], respectively, $P = 0.0185$).

The distribution of the different transmurality grades among the 68 corresponding segments positive for LGE by both SIR and TRAMINER and mean transmurality grades are shown in Table 5. Interobserver agreement of visual transmurality assessment was excellent for both SIR and TRAMINER (ICC 0.86 [0.78–0.91] and 0.94 [0.91–0.96], respectively).

The mean %MI of the LV myocardium assessed by SIR and TRAMINER was $13.6 \pm 5.1\%$ and $15.7 \pm 5.8\%$, respectively, with no significant difference between the two methods ($P = 0.0691$).

TABLE 3. Objective Image Quality Parameters (Mean ± Standard Deviation) Based on Normalized SI Values

Category	SIR	TRAMINER	*P*-value
SI blood (au)	75.1 ± 10.8	22.5 ± 9.1	< 0.0001
SI remote (au)	38.9 ± 12.9	45.2 ± 17.0	0.0082
SI MI (au)	82.3 ± 10.4	93.5 ± 5.6	0.0030
SI range blood – MI	9.6 ± 7.6	69.8 ± 10.2	< 0.0001
SI range remote – MI	43.6 ± 11.2	48.2 ± 6.9	0.1934
SI range blood – remote	36.2 ± 11.3	22.6 ± 9.1	< 0.0001
R_{SI} blood – MI	1.1 ± 0.1	4.2 ± 1.9	< 0.0001
R_{SI} remote – MI	2.3 ± 1.2	2.1 ± 0.3	0.4323
R_{SI} blood – remote	2.1 ± 0.7	0.5 ± 0.2	< 0.0001

SIR, standard inversion recovery; TRAMINER, T(Rho) And Magnetization Transfer and INvErsion Recovery; SI, signal intensity; MI, myocardial infarct; au, arbitrary units; R_{SI}, signal intensity ratio.

TABLE 4. LGE Detection Rate and Its Interobserver Agreement (κ), as Well as Level of Certainty (Mean [95% Confidence Interval]) and Its Interobserver Agreement (ICC [95% Confidence Interval])

Category	SIR		TRAMINER		*P*-value[a]
	Detection rate	**κ**	**Detection rate**	**κ**	
Per patient	17/40	0.948	19/40	0.900	0.3750
Per segment	79/649	0.846	91/649	0.861	0.0726
	Certainty rating	**ICC**	**Certainty rating**	**ICC**	***P*-value[b]**
Per patient	2.7 [2.5–2.8]	0.81 [0.79–0.83]	2.9 [2.8–3.0]	0.86 [0.83–0.89]	0.0185
Per segment	2.8 [2.8–2.9]	0.77 [0.75–0.79]	2.9 [2.9–3.0]	0.82 [0.80–0.84]	< 0.0001

LGE, late gadolinium enhancement; SIR, standard inversion recovery; TRAMINER, T(Rho) And Magnetization Transfer and INvErsion Recovery; ICC, intraclass correlation coefficient.
[a]For comparison between detection rates.
[b]For comparison between image quality ratings.

Discussion

In this preliminary study, we evaluated the clinical feasibility of the dark-blood LGE prototype TRAMINER sequence for the assessment of myocardial viability in patients with MI. Using TRAMINER, the phase-sensitive image shows the blood SI as black, while the signal in the MI appears bright. The SI in the remote myocardium is dark gray in order to enhance the visualization of the cardiac anatomy. This distribution of gray-levels is achieved by setting the TI to acquire the contrast relevant data before the intersection of the remote myocardium and blood recovery curves. The higher contrast generated between blood and MI compartments may provide increased detectability of LGE, especially in cases with thin subendocardial and papillary muscle MIs, which can have an indistinct appearance with SIR.

While the SAR and power requirements of the TRAMINER preparation module alone may seem extreme, the SAR of the entire TRAMINER sequence is only moderately elevated compared to the SIR sequence. Assessing SAR of the entire sequence is more realistic than for a single preparation, since all sequence parts including preparation modules, readouts, time delays, and recovery heartbeats are always executed together. In this ECG-triggered single-shot sequence, many time delays and one recovery heartbeat, during which no RF pulses are applied, advantageously reduce the overall SAR of the sequence. Therefore, during clinical imaging the time-averaged SAR of the TRAMINER sequences was low enough to not require any SAR-based restrictions. Initial experiments at 3T did not encounter any SAR problems either. The main power requirement stems from the SSFP single-shot readout, which is identical for SIR and TRAMINER.

In this study, subjective and objective image quality assessment compared to SIR showed better blood/MI discrimination in TRAMINER images while maintaining the contrast between MI and remote myocardium. Overall interobserver agreement was good to excellent in all measures for both techniques, although TRAMINER provided higher confidence for LGE detection.

TRAMINER detected LGE in two more patients and more segments compared to SIR. In these two patients with acute MI, additional clinical results confirmed the presence of MI, supporting the TRAMINER-based findings. There were also multiple segments where LGE was seen with TRAMINER but not SIR; however, the presence of MI in these additional segments could not be confirmed due to the lack of a pathology reference standard for in vivo human validation. Previous animal studies using a dark-blood

TABLE 5. Transmurality Grading in Segments Positive for LGE by Both Techniques ($n = 68$)

Category	SIR	TRAMINER	*P*-value
Grade 1 (≤25%)	17 (25.0%)	13 (19.1%)	
Grade 2 (26-50%)	23 (33.8%)	29 (42.6%)	
Grade 3 (51-75%)	13 (19.1%)	9 (13.2%)	
Grade 4 (>75%)	15 (22.1%)	17 (25.0%)	
Average grade (mean [95% CI]	2.3 [2.1–2.6]	2.4 [2.1–2.7]	0.4742

SIR, standard inversion recovery; TRAMINER, T(Rho) And Magnetization transfer and INvErsion Recovery; CI, confidence interval.

sequence with a similar preparation pulse confirmed the high accuracy of the technique compared to triphenyltetrazolium chloride staining.[12,23] There were also segments in which the TRAMINER technique did not detect MI while SIR did. All of these segments involved the apex or the apical third where the evaluation of LGE is often confounded by partial volume averaging. The significance of these findings is also unclear, given the low level of certainty for the presence of LGE in these segments.

LGE was further evaluated by visual quantitative assessment. While %MI was slightly higher using TRAMINER given that LGE was detected in more segments than SIR, there was no statistical difference between the techniques indicating the quantitative potential of the TRAMINER approach.

Various solutions have been developed to improve the differentiation of myocardial LGE from blood in cases where the SI of these anatomical compartments is not visually distinct.[4–9] Earlier work by Kim et al suggested that LGE images be reviewed concurrently with cine acquisitions in order to accurately evaluate diastolic wall thickness.[24] To simplify this approach, an automated algorithm has been developed that propagates same-phase endocardial and epicardial contours registered in cine images to LGE images.[25] A multicontrast delayed-enhancement approach using a series of T_1- and T_2-weighted images has also been proposed to improve the identification of subendocardial MI.[4,5] T_2-preparation and IR have been combined into one sequence to either reduce the blood pool signal[8] or to null it.[6] While nulling delivers the best MI/blood contrast, it is tedious to perform clinically, as it requires low contrast agent concentration in the blood pool. Other groups have used stimulated echoes[7] or diffusion preparation[9] to reduce blood pool signal, but the images suffered from low signal-to-noise ratio. The first dark-blood LGE sequence provided two images with different contrast properties in a single acquisition by combining two different TIs to separately null the blood and the normal myocardium.[10] However, its clinical use was limited by its flow sensitivity and the need to null two T_1 species simultaneously.

The closely related FIDDLE technique has been proposed for the visualization of thin subendocardial and papillary muscle MIs by increasing the tissue contrast between blood and hyperenhanced myocardium due to its black-blood property.[12] Both FIDDLE and TRAMINER are similar in that they are flow-independent, require a PSIR reconstruction, and like SIR, require adjustment of a single timing parameter (TI). TRAMINER requires less energy than FIDDLE to achieve a given tissue attenuation but has the potential disadvantage that tissue attenuation is achieved by a mixed T_2 and magnetization-transfer contrast. These differences stem from FIDDLE's use of typically 15–20 off-resonance magnetization-transfer pulses that require more energy than the three to four TRAMINER preparations, but that yield a cleaner magnetization-transfer contrast. Consequentially, it is expected that TRAMINER may have advantages at 3T due to its efficient use of energy.

We acknowledge the following limitations. Our study is significantly limited by the relatively small number of patients with MI and the lack of a reliable reference standard. Although SIR is the in vivo reference standard for the detection of MI, it has its own limitations and was not used as a reference method in our study. Due to the in vivo nature of this patient study, histopathological techniques were not involved; however, future animal studies may be necessary for validation. As we included patients with acute and suspected chronic MI, the average age of the MI in our study population cannot be accurately determined. Additional studies are also necessary to test the TRAMINER technique in other cardiac pathologies. A further limitation of the study is that the parameters of the BIR-4 pulses were empirically optimized before patient scans to achieve desired tissue–blood separation, but were not systematically evaluated. In addition, the SI of right ventricular (RV) blood can be less dark than LV blood in TRAMINER images due to the T_2 component of the image contrast generation and the slight difference in T_2 between the LV and RV blood pool. In practice, the effect is only observed in patients with severely impaired pulmonary function. Furthermore, as SIR and TRAMINER images were acquired with a slight delay in between them, our results might be influenced by the change in the contrast environment during this time. Finally, despite the randomization of the reading order of the cases, and the preventive measures we implemented to reduce recall bias, the results may still reflect a better reader performance, as TRAMINER was read as the second technique.

In conclusion, TRAMINER provides increased contrast between myocardial LGE and blood and may thus have an increased ability to discriminate thin subendocardial enhancement from the blood signal, which may have an indistinct appearance using SIR.

Conflict of Interest

U.J.S. is a consultant for and/or receives research support from Bayer, Bracco, GE Healthcare, Guerbet, Medrad, and Siemens Healthcare. W.G.R. is an employee of Siemens. C.N.D.C. and A.V.S have received consulting fee from Guerbet. The other authors declare that they have no financial disclosures.

References

1. Kwon DH, Halley CM, Carrigan TP, et al. Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyperenhancement cardiac magnetic resonance study. JACC Cardiovasc Imaging 2009;2:34–44.
2. Kwong RY, Chan AK, Brown KA, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on

event-free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation 2006;113:2733–2743.

3. Roes SD, Kelle S, Kaandorp TA, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol 2007;100:930–936.
4. Kellman P, Chung YC, Simonetti OP, McVeigh ER, Arai AE. Multi-contrast delayed enhancement provides improved contrast between myocardial infarction and blood pool. J Magn Reson Imaging 2005;22: 605–613.
5. Bandettini WP, Kellman P, Mancini C, et al. MultiContrast Delayed Enhancement (MCODE) improves detection of subendocardial myocardial infarction by late gadolinium enhancement cardiovascular magnetic resonance: a clinical validation study. J Cardiovasc Magn Reson 2012;14:83.
6. Basha T, Roujol S, Kissinger KV, Goddu B, Manning WJ, Nezafat R. Black blood late gadolinium enhancement using combined T2 magnetization preparation and inversion recovery. J Cardiovasc Magn Reson 2015;17(Suppl 1):O14.
7. Ibrahim el SH, Weiss RG, Stuber M, et al. Stimulated-echo acquisition mode (STEAM) MRI for black-blood delayed hyperenhanced myocardial imaging. J Magn Reson Imaging 2008;27:229–238.
8. Liu CY, Wieben O, Brittain JH, Reeder SB. Improved delayed enhanced myocardial imaging with T2-Prep inversion recovery magnetization preparation. J Magn Reson Imaging 2008;28:1280–1286.
9. Salerno M, Epstein FH, Kramer CM. Diffusion-prepared dark blood delayed enhancement imaging for improved detection of subendocardial infarcts. J Cardiovasc Magn Reson 2009;11(Suppl 1):O10.
10. Farrelly C, Rehwald W, Salerno M, et al. Improved detection of subendocardial hyperenhancement in myocardial infarction using dark blood-pool delayed enhancement MRI. AJR Am J Roentgenol 2011; 196:339–348.
11. Edelman RR, Chien D, Kim D. Fast selective black blood MR imaging. Radiology 1991;181:655–660.
12. Kim HW, Rehwald WG, Wendell DC, et al. Black-blood contrast-enhanced MRI: validation of a novel technique for the diagnosis of myocardial infarction. In: Proc 23rd Annual Meeting ISMRM, Toronto; 2015. p 662.
13. Kellman P, Arai AE, McVeigh ER, Aletras AH. Phase-sensitive inversion recovery for detecting myocardial infarction using gadolinium-delayed hyperenhancement. Magn Reson Med 2002;47:372–383.
14. Taheri S, Sood R. Spin-lock MRI with amplitude- and phase-modulated adiabatic waveforms: an MR simulation study. Magn Reson Imaging 2006;24:51–59.
15. Moran PR, Hamilton CA. Near-resonance spin-lock contrast. Magn Reson Imaging 1995;13:837–846.
16. Schneider E, Prost RW, Glover GH. Pulsed magnetization transfer versus continuous wave irradiation for tissue contrast enhancement. J Magn Reson Imaging 1993;3:417–423.
17. Brown RW, Cheng Y-CN, Haacke EM, Thompson RM, Venkatesan R. Magnetic resonance imaging: physical principles and sequence design. Hoboken, NJ: Wiley-Blackwell; 2014.
18. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–542.
19. Tominaga J, Sakai F, Johkoh T, et al. Diagnostic certainty of idiopathic pulmonary fibrosis/usual interstitial pneumonia: The effect of the integrated clinico-radiological assessment. Eur J Radiol 2015;84: 2640–2645.
20. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized P. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson 2008;10:35.
21. Sievers B, Elliott MD, Hurwitz LM, et al. Rapid detection of myocardial infarction by subsecond, free-breathing delayed contrast-enhancement cardiovascular magnetic resonance. Circulation 2007; 115:236–244.
22. Kim HW, Farzaneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction: current and emerging applications. J Am Coll Cardiol 2009;55:1–16.
23. Wendell D, Jenista E, Rehwald WG, et al. Validation of a novel dark-blood delayed enhancement technique for the detection of papillary muscle scar. J Cardiovasc Magn Reson 2016;18(Suppl 1):Q6.
24. Kim RJ, Shah DJ, Judd RM. How we perform delayed enhancement imaging. J Cardiovasc Magn Reson 2003;5:505–514.
25. Tao Q, Piers SR, Lamb HJ, van der Geest RJ. Automated left ventricle segmentation in late gadolinium-enhanced MRI for objective myocardial scar assessment. J Magn Reson Imaging 2015;42:390–399.