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Abstract

Background

Late gadolinium enhancement (LGE) imaging is validated for diagnosis and quantification of myocardial infarction (MI). Despite good contrast between scar and normal myocardium, contrast between blood pool and myocardial scar can be limited. Dark blood LGE sequences attempt to overcome this issue.

Purpose

To evaluate T1 rho prepared (T1ρ) dark blood sequence and compare to blood nulled PSIR (BN) and standard myocardium nulled PSIR (MN) for detection and quantification of scar.

Study type

Prospective

Population

30 patients with prior MI

Field Strength/Sequence

Patients underwent identical 1.5T MRI protocols. Following routine LGE imaging a slice with scar, remote myocardium and blood pool was selected. PSIR LGE was repeated with inversion time set to null myocardium (MN), to null blood pool (BN) and T1ρ FIDDLE in random order.

Assessment:

3 observers. Qualitative assessment of confidence scores in scar detection and degree of transmurality. Quantitative assessment of myocardial scar mass (grams), and contrast-to-noise ratio (CNR) measurements between scar, blood pool and myocardium.

Statistical Tests:

Repeated measures ANOVA with Bonferroni correction, coefficient of variation, Cohen κ statistic.

Results:

$\text{CNR}_{\text{scar-blood}}$ was significantly increased for both BN(27.1±10.4) and T1ρ(30.2±15.1) compared to MN(15.3±8.4 P<0.001 for both sequences). There was no significant difference in $\text{CNR}_{\text{scar-myo}}$ between BN(55.9±17.3) and MN(51.1±17.8 P=0.512); both had significantly higher $\text{CNR}_{\text{scar-myo}}$ compared to the T1ρ(42.6±16.9 P=0.007 and P=0.014 respectively). No significant difference in scar size between LGE methods: MN(2.28±1.58g) BN(2.16±1.57g) and T1ρ(2.29±2.5g). Confidence scores were significantly higher for BN(3.87±0.346) compared to MN(3.1±0.76 P <0.001) and T1ρ(3.20±0.71 P<0.001).

Data Conclusion:

PSIR with TI set for blood nulling and the T1ρ LGE sequence demonstrated significantly higher scar to blood CNR compared to routine MN. PSIR with TI set for blood nulling demonstrated significantly higher reader confidence scores compared to routine MN and T1ρ LGE, suggesting routine adoption of BN PSIR approach might be appropriate for LGE imaging.

Key Words:

Late Gadolinium enhancement, myocardial infarction, ischaemic heart disease, bright blood, dark blood

Abbreviations:

BN	blood nulled PSIR LGE

CNR	Contrast to Noise ratio
EDV	End diastolic volume
EF	ejection fraction
ESV	end systolic volume
FIDDLE	Flow-Independent Dark-blood DeLayed Enhancement
LGE	late gadolinium enhancement
MACE	major adverse cardiovascular events
MI	myocardial infarction
MN	myocardium nulled PSIR LGE
MOLLI	modified Look-Locker inversion-recovery
MRI	magnetic resonance imaging
PSIR	Phase sensitive inversion recovery
RF	radiofrequency
ROI	Regions of interest
SL	spin locking
SSFP	steady state free precession
STEMI	ST segment myocardial infarction
SV	stroke volume
$T1\rho$	T1rho

Introduction

Late gadolinium enhancement imaging (LGE) is both diagnostic for myocardial infarction as well as prognostic in patients with ischaemic heart disease (1–3). The presence of late enhancement has been shown to confer increased risk of major adverse cardiovascular events (MACE) and cardiovascular mortality above and beyond clinical and angiographic findings (1, 4). Furthermore, the transmural extent of myocardial infarction (MI) demarcated on LGE imaging accurately identifies the likelihood of myocardial functional recovery following revascularisation (2, 5). Clinical progress has resulted in a reduction in the number of fatal ST-segment elevation myocardial infarctions (STEMI), however this has led to increased numbers of patients living with ischaemic scar. Thus accurate methods of scar quantitation/transmurality assessment are required to guide revascularisation decisions and for prognostication (6).

LGE imaging is typically performed 10-20 minutes following administration of a gadolinium-based contrast agent, by a two-dimensional (2D) inversion recovery (IR) spoiled gradient echo sequence (7). Conventionally this is preceded by a Look-Locker sequence enabling the MR operator to set an appropriate inversion time (TI) to null normal myocardium, and thus give high contrast between ‘bright’ scarred myocardium (where gadolinium contrast agent is retained), and the darker healthy myocardium. Phase sensitive inversion recovery (PSIR) sequences have been developed to overcome the need to precisely choose the correct TI to null the normal myocardium (8). A large proportion of infarctions are sub-endocardial because ischaemia causes a wavefront-phenomena of necrosis that affects the sub-endocardial fibres of the myocardium first (9). Despite good contrast between scar and normal myocardium, contrast between blood pool and myocardial scar can be limited leading to uncertainty for the reporting clinician as to the precise location of the scar-blood pool interface, which then can impact on the assessment of the transmural extent of the scar.

Several dark blood sequences have been described that attempt to overcome the issue of poor contrast between contrast enhanced blood pool and sub-endocardial infarction by addition of extra magnetization pulses (10–17). FIDDLE (Flow-Independent Dark-blood DeLayed Enhancement) incorporates an additional magnetisation preparation prior to the inversion pulse in a PSIR LGE sequence (16, 17). Numerous radiofrequency (RF) preparation types may be employed, such as T1rho ($T1\rho$), T2 preparation, additional inversion pulses etc. $T1\rho$ is the decay rate of magnetisation during application of a RF field applied parallel to the net magnetisation of spins, in the rotating frame. More complex composite RF preparations for $T1\rho$ weighting can be used to compensate for variations in the B1 field, and B0 inhomogeneity. The preparation pulse incorporates a spin locking time (SL) during which $T1\rho$ decay occurs (18). Then standard LGE imaging follows. The magnetisation preparation effects a different starting value for the magnetisation of tissues before LGE imaging. Then when LGE image acquisition immediately follows, adjusted contrast remains between these tissues. In each case, the intention is that blood pool remains the most incompletely recovered longitudinal magnetization compared to the other tissues of interest, thus yielding the lowest signal – dark blood – in the PSIR LGE image. A PSIR reconstruction reduces sensitivity to inversion time precision and removes the risk of tissues with different T1 relaxation times appearing isointense. Recently a method using a standard PSIR sequence with the inversion time set to null the blood pool rather than the myocardium was described in a group of 9 patients (19). This method, albeit in a small number of patients, led to improved scar to blood Contrast to Noise ratio (CNR) and improved reader confidence (19).

The aim of this study was to prospectively evaluate a novel $T1\rho$ FIDDLE dark blood sequence and compare this to the recently described blood nulled PSIR (BN) and the standard ‘clinical’ myocardium nulled PSIR (MN) technique for the detection and quantification of scar in the setting of ischaemic heart disease.

Methods

Study population

Patients with prior myocardial infarction were recruited between April 2017 and June 2017. Myocardial infarction was confirmed by cardiac biomarkers, electrocardiography and coronary angiography (20). Inclusion criteria were age ≥18 years, no contra-indication to contrast-enhanced cardiac MRI, glomerular filtration rate ≥60mL/min/1.73m^2. Patients with atrial fibrillation, non-MR compatible implants, renal failure or claustrophobia were excluded. The study was performed in accordance with the Declaration of Helsinki, approved by the National Research Ethics Service, with all patients providing informed written consent.

Cardiac MRI data acquisition

Cardiac MRI was performed on a 1.5 Tesla Philips Ingenia system (Philips Healthcare, Best, The Netherlands) equipped with a 28 channel digital receiver coil and patient-adaptive RF shimming. Image acquisition included survey images, assessment of myocardial function using standard SSFP cine imaging (spatial resolution 1.09x1.09x8mm^3, 30 cardiac phases TR/TE 3.0/1.48ms, flip angle 40º, field of view 360-360mm, SENSE acceleration) and 2D LGE imaging. For LGE imaging, an intravenous bolus of 0.15mmol/kg gadobutrol (Gadovist®, Bayer Inc.) was administered. At 10 minutes post-contrast, the optimal inversion time to null the myocardium was determined by a Look-Locker sequence. A routine 2D breathhold phase sensitive inversion recovery sequence with 12 slices covering the full LV (thickness 10mm, no gap, repetition time 6.1 ms/echo time 3.0 ms, flip angle 25º) was then performed using a spoiled

GRE readout and the 12 slices were acquired in separate breath-holds. A single short axis slice that included scar, remote healthy myocardium and blood pool was then selected, and a repeat Look-Locker sequence was performed for this slice to re-confirm appropriate inversion times for tissues of interest. The selected short axis slice was then re-acquired using the PSIR LGE sequence with the inversion time set to null myocardium (MN), the inversion time set to null the blood pool (BN) and a T1ρ FIDDLE sequence. A dedicated noise scan (identical pulse sequence without excitation pulses) was performed after each slice acquisition, in order to enable accurate measurement of the signal-noise level (19). The T1ρ-prepared and the two standard PSIR sequences were all performed in random order to avoid systematic bias caused by differences in contrast washout.

Imaging parameters were as follows:

2D breath-hold phase sensitive inversion recovery sequences with 12 slices covering the full LV, thickness 10mm, no gap, repetition time 6.1ms, echo time 3.0ms, flip angle 25^{o}, field of view 300x300mm, matrix 127/256, acquired in-plane resolution 1.59x2.20mm^2 reconstructed to 0.91x0.91mm^2, effective SENSE factor 2.2. The turbo factor was 20 (7 shots) with an acquisition duration of 123.3ms. The receiver bandwidth was 250.2 Hz/px. The same sequence was used for both the single slices of the MN and the BN with the TI set to null myocardium and blood pool respectively.

For the T1ρ FIDDLE sequence, the T1ρ preparation employed a ΔB0 and B1 insensitive spin lock (21) consisting of 90_x,SL_y,180_y,SL_{-y},90_{-x} pulses as seen in Figure 1, with the two spin lock (SL) pulses using a locking frequency of 500Hz. The spin lock time was 40ms. The SL pulses with opposed phase compensate for B1 variation, and the central 180 pulse compensates for B0 inhomogeneity. Following the T1ρ preparation routine the standard PSIR sequence is performed. ~~A modified Look-Locker inversion-recovery (MOLLI) T1-mapping scan (5s(3s)3s scheme) was performed to determine T1 values of the viable myocardium, LV blood, and scar tissue.~~

Cardiac MRI data analysis

Cardiac MRI data were analysed quantitatively using commercially available software (CVI42, Circle Cardiovascular Imaging Inc. Calgary, Canada). MR data analysis of the three types of LGE images was performed blinded in random order by a cardiologist (Observer 1 with 3 years cardiac MRI experience). For all patients, quantitative analysis was performed again 4 weeks later to assess intra-observer variability and to assess inter-observer variability for all patients by a second (Observer 2 with 3 years cardiac MRI experience) and third cardiologist (Observer 3 with 3 years cardiac MRI experience). For volumetric analysis, endocardial borders were traced on the LV cine stack at end-diastole and end-systole to calculate end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV) and ejection fraction (EF). Contours were traced to exclude papillary muscles and trabeculations.

Image analysis

Qualitative LGE assessment

Maximum scar transmurality was visually assessed using a 5 point scale (0=no LGE, 1=1-25%, 2=26-50%, 3=51-75%, 4=76-100%). Confidence in scar detection and degree of transmurality was assessed using a 4 point scale (1=non-diagnostic, 2=low, 3=moderate, 4=high confidence).

Quantitative LGE assessment

Quantitative assessment of the myocardial scar burden was performed using the semi-automated full-width half-maximum method (threshold of 50% of the maximum intensity within the scar) which has been proposed as the most reproducible method (22, 23). On the 2D BN, MN and T1ρ LGE short-axis images endocardial and epicardial contours were manually outlined (excluding trabeculations and papillary muscles); manual delineation of two separate user-defined regions of interest (ROIs) were then made on the LGE short axis slice where infarcted myocardium was present. One ROI was drawn in remote myocardium (where no scar was present); a second ROI was drawn within hyperenhanced myocardium where infarcted myocardium was present. Scar tissue mass (grams) was then calculated on the BN, MN and T1ρ LGE LV short axis slice based on these ROIs.

CNR measurement

ROIs were drawn on each single slice MN, BN, and T1ρ LGE images in areas of hyper-enhancement, a remote area of normal myocardium, and in the blood pool. ROIs contained at least 30 pixels, aside from the areas of hyper-enhancement where size of the ROI was governed by the size of the scar. A further ROI covering the entire LV myocardium was drawn on the corresponding noise image, the standard deviation of this measurement was then used to calculate CNR measurements. CNR was calculated as the ratio of the difference in mean signal intensity between ROIs on the LGE images to the standard deviation of signal intensity in the whole LV ROI from the separate noise image. CNR was calculated for difference between scar and blood pool ($CNR_{scar\text{-}blood}$), scar and myocardium ($CNR_{scar\text{-}myo}$) and between blood and remote myocardium ($CNR_{blood\text{-}myo}$).

Statistical analysis

Continuous variables are expressed as means ± SD. Categorical variables are expressed as N (%) or proportions. Normality of data was tested using a Shapiro-Wilk test. Repeated measures ANOVA with post hoc Bonferroni correction was used to compare means of the three groups. P<0.05 was considered statistically significant. Coefficient of variation was used to assess interobserver and intraobserver variability for scar size. Cohen κ statistic was used for interobserver and intraobserver agreement for transmurality assessment and the image confidence score. Statistical analysis was performed using IBM SPSS® Statistics 22.0 (IBM Corp., Armonk, NY).

Results

Study population

A total of 30 patients (26/30 male, mean age 63.8±10.7 years; mean BMI 26.3±3.6kg/m^2; mean LV ejection fraction 47±11%; LVEDV 167±53ml; LVEDVi 87±25ml/m^2; LVSV 75±17ml/m^2; LVESV 92±48ml) were prospectively examined.

MR imaging

Imaging using routine PSIR, blood nulled PSIR and T1ρ were successfully completed in all patients with no imaging failures. There was no significant difference in time of image acquisition between the three pulse sequences (MN 17:58±0.53minutes, BN 18.07±0.47minutes, T1ρ 18.11 ±0.46minutes P=1 between all.)

Qualitative image analysis

Transmurality assessment

The transmural extent was deemed significantly larger in the BN (66 ± 34%) and T1ρ (66 ± 36%) compared to MN 48 ± 37%, (P<0.001 compared to both BN and T1ρ). Interobserver agreement for transmurality assessment was excellent for all methods (observer 1:2 κ = 0.81 (MN), 0.95 (BN), 0.85 (T1ρ) observer1:3 κ=0.846 (MN), 0.901 (BN), 0.900 (T1ρ)). Intraobserver agreement for transmurality assessment was also good or excellent for all methods (κ = 0.70 (MN), 0.85 (BN), T1ρ 0.85 (T1ρ)).

Confidence scores for assessment of transmurality

No images were deemed non-diagnostic. Confidence scores were significantly higher for BN (3.87 ± 0.346) compared to MN (3.10 ± 0.76 P <0.001) and T1ρ (3.20 ± 0.71 P<0.001), there was no difference in confidence scores for T1ρ compared to MN (P=0.977). Interobserver agreement was excellent for the three methods (observer 1:2 κ=0.843 (MN), 0.865 (BN), 0.870 (T1ρ) observer1:3 κ=0.839 (MN), 0.896 (BN), 0.746 (T1ρ)). Intraobserver agreement was also excellent for all three methods (κ = 0.948 (MN), 0.839 (BN), 0.865 (T1ρ)). In one patient both BN and T1ρ identified sub-endocardial scar that was mistaken for outflow tract by both readers on the MN LGE image (figure 2; further representative images are seen in figures 3 and 4).

Quantitative image analysis

Scar size

There was no significant difference in scar size between the three LGE methods: MN (2.28 ± 1.58g) BN (2.16 ± 1.57g) and T1ρ (2.29 ± 2.5g) (MN:BN P=0.066, BN:T1ρ P=0.385, MN: T1ρ P=1). Interobserver coefficient of variation was good for all three methods (Observer 1:2 MN 9.32%, BN 7.63%, T1ρ 9.40% Observer 1:3 MN 8.86%, BN 7.09%, T1ρ 9.45%)

Intraobserver coefficient of variation for scar size was also good for all three methods (MN 7.36%, BN 7.39%, T1ρ 9.18%).

CNR analysis

The $CNR_{scar\text{-}blood}$ was significantly increased for both the BN (27.1 ± 10.4) and the T1ρ (30.2 ± 15.1) compared to the MN (15.3 ± 8.4 P<0.001 for both sequences) (Figure 4). There was no significant difference in $CNR_{scar\text{-}myo}$ between BN (55.9 ± 17.3) and MN (51.1 ± 17.8 P=0.512); these both had significantly higher $CNR_{scar\text{-}myo}$ compared to the T1ρ (42.6 ± 16.9 P=0.007 and P=0.014 respectively). The $CNR_{blood\text{-}myo}$ was significantly higher for MN compared to BN (28.0 ± 12 P<0.001); $CNR_{blood\text{-}myo}$ was also significantly higher for both MN and BN compared to T1ρ (13.6 ± 7.2 P<0.001 for both sequences).

Discussion

The main findings of this study are: i) both PSIR with TI set for blood nulling and the T1ρ LGE sequence demonstrated significantly higher scar to blood CNR compared to routine MN; ii) PSIR with TI set for blood nulling demonstrated significantly higher reader confidence scores compared to both routine MN and the novel T1ρ LGE sequence iii.) quantitative LGE scar size measurement showed no statistical difference between the three LGE methods.

Current conventional LGE imaging using IR and PSIR spoiled gradient echo sequences give high resolution images that are firmly established as the reference standard for viability imaging by cardiac MRI. Accurate determination of transmurality is vital to guide revascularisation; currently however a significant limitation is that of the limited contrast between hyperenhanced scar and residual contrast in the LV blood pool. Several previous studies have used a variety of different preparation pulses, including T2 preparation, double and triple inversion recovery, or T1ρ with spin locking to produce dark or black blood LGE images (10–16). Most recently focus has been concentrated on using a T2 preparation pulse to null the blood pool; Basha et al noted a significantly increased signal ratio between scar to blood using a T2 preparation pulse sequence versus a standard inversion recovery LGE sequence (24). Furthermore, recently a non-breath held motion corrected method using an inversion recovery T2 preparation combined with SSFP imaging demonstrated an increase in CNR of 13% for scar to blood compared to standard IR LGE sequence (15). This sequence has subsequently been assessed in 172 patients and identified significantly more LGE compared to standard LGE imaging (25). Most of these sequences currently remain research investigations and are vendor/platform specific and are yet to see mainstream clinical adoption. The recent study by Holtackers et al demonstrated an increased scar to blood contrast when nulling blood in a standard PSIR pulse sequence, without the need for additional preparation pulses (19).

Both the T1ρ and blood nulling PSIR LGE images in our study significantly increased the CNR between scar and blood pool compared to routine myocardium nulling PSIR images. Notably this only led to an increased reader confidence in the BN, but not however for the T1ρ sequence despite this increased CNR. The lower confidence scores for the T1ρ compared to the BN are likely representative of the lower $CNR_{blood-myo}$ for the T1ρ compared to the BN leading to difficulty in ascertaining the true anatomy of the left ventricle (distinction between remote myocardium and blood pool); this finding suggests that high $CNR_{scar-blood}$ is not the only facet necessary for high reader confidence. The anatomy of the ventricle can potentially be derived from the previously acquired SSFP images and transposed onto the T1ρ images in order to clarify scar location; this however would add time to reader interpretation. The BN images retain the excellent image quality that characterise routine 2D MN PSIR images, whilst increasing the confidence of the reader for the identification of scar border. Quantitatively derived scar size was not significantly different between the three LGE methods despite the two dark blood methods objectively identifying greater transmural extent of scar to the two readers. Other LGE studies have demonstrated an increase in scar size using dark blood sequences, however these have been by visual assessment only or using less conventional methods of LGE quantitation (19, 25). There is no histological correlation for these findings, this corroborates those seen previously where histological correlation was performed (17).

This study compared PSIR with blood nulling and myocardium nulling to a dark blood sequence using additional preparation pulses. A primary benefit of the BN method is that the acquisition used in pulse sequence is already established in routine clinical use and requires no additional magnetisation pulses to perform. Importantly, this makes it simple for standard clinical adoption as it requires very little radiographer/clinician training to employ. This is in contrast to the recently described T2 sequence that led to a comparative doubling of acquisition time for a stack of 9 short axis slices (typically 12 short axis slices are acquired suggesting this length of time would increase further) (15). As cardiac MRI becomes ever more established in clinical guidelines efficient workflow in cardiac MRI departments is vital especially given that viability assessment is currently the third highest indication for cardiac MRI assessment in Europe (26).

In this study, we only used single slices and did not cover the entire ventricle with the three different acquisitions. This approach however minimised the time elapsed between acquisition of the different sequences and consequent reduced the observed change in CNR to be due to the washout kinetics of the gadolinium contrast agent. There was no true histological reference standard to compare the actual presence or size of scar detected by the three sequences, consequently small areas of apparent enhancement seen with a single pulse sequence could be artifactual. A further limitation is that there were only small numbers of patients.

In conclusion, both BN images and T1ρ increase CNR for scar to blood compared to MN images with the TI set to null the myocardium. Routine adoption of the blood nulled PSIR would seem appropriate as reader confidence is heightened compared to MN images and T1ρ sequences; as this LGE sequence is already in clinical use it requires little training to enable widespread clinical implementation.

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Figure Legends

Figure 1. shows the T1 rho preparation for the FIDDLE (T1ρ) pulse sequence

Figure 2. A, B, C (Patient 1) shows a small sub-endocardial anterior infarct imaged with each of the pulse sequences. A is T1ρ, B is MN and C is BN. B shows limited contrast between the blood pool and scar and it could be mistaken for outflow tract, whereas in C the scar is clearly apparent. A demonstrates increased contrast between scar and blood pool but limited contrast between myocardium and blood pool.

Figure 3. A, B, C (Patient 2) shows an acute inferior infarction with RV involvement and microvascular obstruction (MVO). B is MN compared to A, and C (T1ρ and BN respectively) it is difficult to discern the extent of the RV infarction. D, E and F (Patient 3) show an acute lateral infarction with extensive MVO imaged with T1ρ, MN and BN respectively. It is difficult to discern the papillary muscle MVO except in the T1ρ (D).

Figure 4. shows 2 patients with chronic infarction imaged with each of the pulse sequences: A and D are T1ρ, B, E is MN and C, F BN.

Fig 5. shows CNR for the respective sequences. Downward lines of the asterisked (*) bars demarcate significant difference between the CNRs of the respective pulse sequences.