

Fully-modelled blood-focused variable inversion times for 3D late gadolinium-enhanced imaging

Jack J. Allen^{a,b}, Jennifer Keegan^{a,b}, George Mathew^b, Miriam Conway^{a,b}, Sophie Jenkins^{a,b},
Dudley J. Pennell^{a,b}, Sonia Nilles-Vallespin^{a,b}, Peter Gatehouse^{a,b,*},
Sonya V. Babu-Narayan^{a,b,1}

^a National Heart and Lung Institute, Imperial College London, London, United Kingdom

^b Royal Brompton Hospital. Part of Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

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ABSTRACT

Purpose: Variable heart rate during single-cycle inversion-recovery Late Gadolinium-Enhanced (LGE) scanning degrades image quality, which can be mitigated using Variable Inversion Times (VTIs) in real-time response to R-R interval changes. We investigate *in vivo* and in simulations an extension of a single-cycle VTI method previously applied in 3D LGE imaging, that now fully models the longitudinal magnetisation (fmVTI).

Methods: The VTI and fmVTI methods were used to perform 3D LGE scans for 28 3D LGE patients, with qualitative image quality scores assigned for left atrial wall clarity and total ghosting. Accompanying simulations of numerical phantom images were assessed in terms of ghosting of normal myocardium, blood, and myocardial scar.

Results: The numerical simulations for fmVTI showed a significant decrease in blood ghosting (VTI: 410 ± 710 , fmVTI: 68 ± 40 , $p < 0.0005$) and scar ghosting (VTI: 830 ± 1300 , fmVTI: 510 ± 730 , $p < 0.02$). Despite this, there was no significant change in qualitative image quality scores, either for left atrial wall clarity (VTI: 2.0 ± 1.0 , fmVTI: 1.8 ± 1.0 , $p > 0.1$) or for total ghosting (VTI: 1.9 ± 1.0 , fmVTI: 2.0 ± 1.0 , $p > 0.7$).

Conclusions: Simulations indicated reduced ghosting with the fmVTI method, due to reduced Mz variability in the blood signal. However, other sources of phase-encode ghosting and blurring appeared to dominate and obscure this finding in the patient studies available.

1. Introduction

Atrial Fibrillation (AF) is the most prevalent form of cardiac rhythm disturbance and is linked with an increased risk of stroke and heart failure [1]. Late Gadolinium Enhancement (LGE) [2] is a clinically effective Cardiac Magnetic Resonance (CMR) tool for imaging myocardial scarring. In the setting of AF imaging, LGE can be used to map Left Atrial (LA) wall scarring before and after electrophysiology ablation therapy. Pre-ablation scans aid therapy candidate selection and procedure planning. Post-ablation imaging can assess the scar pattern delivered by the ablation procedure and help reveal reasons for AF recurrence [3].

LGE imaging uses an inversion-recovery pulse sequence to produce

image contrast between normal and damaged tissue, using an Inversion Time (TI) chosen to null signal from normal myocardium (*i.e.* TI_{null}). The TI is usually chosen by qualitatively assessing TI scout images acquired before the LGE scan [4,5], although it may be estimated retrospectively [6] or derived from a T_1 map [7].

In clinical practice, most LGE scans are 2D, acquired by breath-hold segmented imaging [2] or by selective averaging of motion-corrected single-shot images [8]. 2D LGE is used for Left Ventricle (LV) imaging but is unsuitable for LA wall imaging, since the LA wall is thin (approximately 2–4 mm) compared to the slice thickness of 2D LGE [9], which exacerbates the partial volume effect, obscuring LA wall fibrosis distribution. Therefore, LA wall LGE requires finer spatial resolution, particularly thinner slices, which can be provided by 3D phase-

Abbreviations: LGE, Late Gadolinium-Enhanced; VTI, Variable Inversion Time; fmVTI, fully-modelled Variable Inversion Time.

* Corresponding author at: Royal Brompton Hospital, Sydney Street, London SW3 6NP, United Kingdom.

E-mail address: p.gatehouse@rbht.nhs.uk (P. Gatehouse).

¹ Joint senior authors.

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encoding. Further, thin contiguous slices can be reformatted in any orientation from the acquired volume array of 3D voxels [4,10,11]. 3D LGE requires a longer scan time than 2D, in the region of 5–15 min depending on factors described later. This necessitates the use of respiratory gating, normally achieved using diaphragm navigators.

Cardiac gating is used with the aim of consistently acquiring LGE image data during the diastolic period of the cardiac cycle. Each data segment acquisition is triggered by the R-wave of the electrical cardiac signal, as detected by an electrocardiogram (ECG). The elapsed time between each R-wave trigger is known as the R-R interval. Data may be acquired during every cardiac cycle (i.e. single-cycle gating) or during alternate cycles. For single-cycle gating (discussed later), the R-R interval variation caused by AF leads to longitudinal magnetisation inconsistency among the cardiac cycles of a 3D LGE acquisition, translating to a variation in received signal amplitude across both phase-encoded directions. This leads to poor myocardial nulling, image ghosting along both phase-encode directions, and blurring of fine details such as atrial walls [12–14]. The AF-induced ghosting artefacts may originate from blood or myocardium and appear along any mixture of the two phase-encoding directions. Improved 3D LGE image quality in the presence of arrhythmia would reduce the frequency of non-diagnostic scans, aiding the assessment of native, surgical and ablation scar tissue in patients with AF and other arrhythmias. This would allow increased accuracy in patient stratification and personalised scar models for intervention guidance, facilitating increased efficiency and effectiveness in arrhythmia care.

As is conventional for 2D LGE, alternate-cycle gating reduces arrhythmia sensitivity compared to single-cycle, due to the increased time available for magnetisation recovery between data segments. Here, the data segment is defined as the diastolic time period in which multiple low flip angle excitations are applied to obtain a number of k-space lines for the 3D LGE raw data during each utilised cardiac cycle, as depicted in Fig. 1. For patients with a generally fast heart rate, third-cycle gating should be used instead of alternate-cycle. A further development originally in 2D LGE is the acquisition of proton density-weighted data in the alternate cycles, which supports Phase-Sensitive Inversion-Recovery (PSIR) LGE reconstruction [8] to restore the sign polarity of reconstructed pixels, making it less sensitive to the correct nulling of normal myocardium by the choice of T_{Inull} [15]. This is not possible with single-cycle 3D LGE because the proton density images required to support PSIR reconstruction cannot be obtained on unused alternate cycles.

A downside of alternate-cycle 3D LGE is that it extends the already lengthy 3D acquisition, risking patient bulk-motion during this time and increasing the impact of contrast agent washout during the 3D scan. The total 3D LGE scan duration can be reduced by several strategies such as coarser resolution and increased 3D slice (partition) thickness, but these all compromise the overall objective: imaging the thin LA wall. Parallel imaging also reduces scan duration, at the cost of SNR which is already somewhat challenged in the small voxels of a 3D LGE LA scan. Compressed sensing or deep learning methods may be used to accelerate data acquisition but are not yet practical for clinical settings [16–18] and involve their own limitations of reconstruction approximations and reduced fundamental SNR as fewer phase-encoded raw data echoes are sampled, even if this SNR loss is to some extent fitted over by advanced reconstruction techniques. Therefore, to achieve a clinically feasible sequence duration it may be considered desirable to investigate the use of single-cycle gating.

Single-cycle gating has been used to image the LA [3,19–21] and LV [5,22,23]. However, there is a need to investigate methods for single-cycle 3D LGE sequences with adaptations to reduce the magnetisation variability caused by arrhythmia. Some pulse sequence modifications have been proposed to mitigate magnetisation inconsistency among the cardiac cycles used to collect data for 3D LGE. For example, a saturation pulse may be used to saturate the longitudinal magnetisation (M_z) at some interval before each inversion pulse, either entirely [24] or

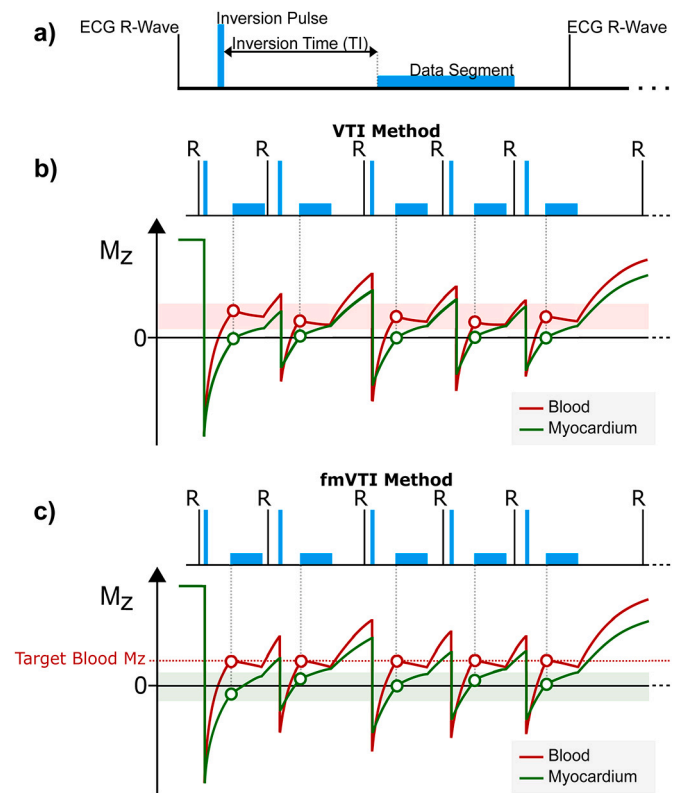


Fig. 1. (a) A simplified diagram for a cardiac-gated LGE pulse sequence, demonstrating the key components for describing the effects of the two variable TI algorithms mentioned in this work. Navigator pulses were used (as described in reference [29]) and also fat saturation pulses, but are not shown in the interest of simplicity. (b, c) Illustrations of the longitudinal magnetisation (M_z) evolution for the VTI (b) and fmVTI (c) methods, using an identical R-R interval pattern for b and c. Solid lines depict M_z , dotted lines display the TI (grey) for each interval (b, c) and the target blood M_z (red, c). Shaded regions highlight blood M_z variation (red) in b and myocardial M_z variation (green) in c. Note the effect of the data segments on the M_z recovery curves. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

partially [14]. The latter uses a dynamic saturation flip angle to impose a consistent non-zero myocardial M_z in each cardiac cycle. Alternatively, for single-cycle 3D LGE each TI may be calculated on a beat-by-beat basis to account for R-R interval changes and moderate M_z variation for a tissue with a specific target T_1 [12,25]. Unlike the work of Weingärtner *et al* [24] and Hu *et al* [14], this Variable TI (VTI) approach does not saturate M_z , making it a more efficient use of the available magnetisation. A steadily increasing inversion time [26] can mitigate the effects of diminishing contrast agent concentration during the 3D LGE scan but does not account for beat-to-beat R-wave interval variation. In comparison to a fixed TI, the 3D LGE VTI work [12] has been shown to improve image quality, increasing the blood signal-to-ghosting ratio and blood-myocardium contrast-to-ghosting ratio in patients with AF.

In this work, we demonstrated our extension of the VTI method [12] to a fully-modelled VTI (fmVTI) algorithm, modelling M_z for blood and remote myocardium during the entire 3D LGE scan and targeting a consistent (patient-specific) blood M_z across the TIs. While other targets might be considered, the aim of fmVTI in this work was to reduce blood ghosting whilst maintaining low remote myocardial signal. We built upon the *in vivo* patient scan improvement shown previously by the VTI method when compared with the standard fixed TI approach [12]. We performed an *in vivo* evaluation of the VTI and fmVTI algorithms in terms of image quality in 3D LGE patients. The original VTI work [12]

established the *in vivo* superiority of VTI with respect to the standard fixed TI approach. Therefore, it was not necessary for us to directly compare the VTI and fmVTI methods with the fixed TI method.

2. Theory

This section describes the theory underpinning the two variable TI algorithms used in this work: VTI and fmVTI. Fig. 1 illustrates the principles and aims of each algorithm. Fig. 1a shows a simplified diagram of a cardiac-gated LGE pulse sequence, including only the sequence components relevant to the M_z evolution diagrams in Fig. 1b and c. Note the definition of “data segment” in Fig. 1a: the acquisition of multiple raw data lines during the cardiac cycle.

2.1. Variable TI

The VTI algorithm for 3D LGE [12] calculates TI for each data segment of an inversion-recovery segmented spoiled gradient echo sequence, using the following equation [27]:

$$TI_n = T_1^{myo} \left(\ln 2 - \ln \left(1 + e^{\frac{TR_{n-1}}{T_1^{myo}}} \right) \right) \quad (1)$$

where n is the data segment index, T_1^{myo} is the estimated T_1 of normal myocardium and TR_{n-1} is the elapsed time between the two most recent ECG triggers (as defined by Keegan *et al* [12]). As in [12], T_1^{myo} is the longitudinal relaxation time for viable myocardial tissue in regions without visual evidence of scarring or fibrosis. To obtain T_1^{myo} , a conventional 2D breath-hold inversion recovery LGE reference scan is run. This sequence may need to be run multiple times, adjusting TI each time until normal myocardial tissue is satisfactorily nulled according to a qualitative visual assessment by the scanner operator. The TI to achieve this nulling is known as TI_{ref} in the previous VTI work [12] and this manuscript. The parameter T_1^{myo} is estimated as $TI_{ref}/0.693$, before being iteratively adjusted to account for the estimated repeat time of the reference scan used to find TI_{ref} . The repeat time used in this reference scan is detailed in the Methods section. For example, for fast heart rates the operator might set this repeat time to 3 or 4 times the estimated mean R-R interval. Further explanation is included in the Methods section. TI_n is the calculated TI to be applied for each 3D LGE sequence repeat (*i.e.* cardiac cycle) n . For the initial data segment (*i.e.* $n = 1$), TR_{n-1} is effectively infinite and Eq. (1) simplifies to:

$$TI_1 = T_1^{myo} \ln 2 \quad (2)$$

Fig. 1b illustrates the desired M_z evolution for VTI, showing the myocardial M_z close to zero at each TI (which is at the beginning of each centre-out data segment). Blood M_z variations for varying R-R intervals are evident, as expected because the blood T_1 is not considered in the VTI method's calculations.

2.2. Fully-modelled Variable TI (fmVTI)

The fmVTI algorithm extends the VTI method to include the effect of the spoiled gradient-echo data segment acquisition on the M_z recovery, which is ignored in the VTI method.

A further difference between fmVTI and VTI is that fmVTI adjusts TI to prioritise consistent blood M_z across the cardiac cycles while maintaining low remote myocardial M_z , aiming to null normal myocardium and minimise blood ghosting. If normal myocardium is successfully nulled, residual ghosting from the normal myocardium will be minimal. Fig. 1c illustrates the fmVTI M_z evolution for blood and for normal myocardium, showing that myocardial M_z variation occurs but is relatively close to zero. For the application of fmVTI, three patient-specific input parameters are required from the scan operator: 1) an estimation of the mean R-wave trigger interval, 2) the post-Gadolinium blood T_1 , 3) the post-Gadolinium T_1 of normal myocardium in the ventricular

septum, where post-Gadolinium means these are measured just before starting the fmVTI 3D LGE scan. Therefore, fmVTI requires prior acquisition of a T_1 map, but unlike VTI it does not require the TI reference scan.

2.2.1. Target blood M_z

The target blood M_z is calculated before the initial R-wave trigger of the sequence, using the following equations:

$$TI_{null}^{myo} = T_1^{myo} \left(\ln 2 - \ln \left(1 + e^{\frac{-meanRRinterval}{T_1^{myo}}} \right) \right) \quad (3)$$

$$TI_{null}^{blood} = T_1^{blood} \left(\ln 2 - \ln \left(1 + e^{\frac{-meanRRinterval}{T_1^{blood}}} \right) \right) \quad (4)$$

$$M_z^{bloodTarget} = 1 - e^{\frac{-TI_{null}^{myo} - TI_{null}^{blood}}{T_1^{blood}}} \quad (5)$$

where *meanRRinterval* is an estimate of the mean R-R interval during free-breathing, provided by the scan operator. T_1^{myo} and T_1^{blood} are the normal myocardial T_1 and LV blood T_1 , respectively, as measured by the operator from a T_1 map acquired immediately before starting the fmVTI 3D LGE scan. TI_{null}^{myo} and TI_{null}^{blood} are the estimated TIs required to null normal myocardium and blood, respectively. $M_z^{bloodTarget}$ is the target blood M_z .

2.2.2. Modelling and TI calculation

Bloch simulations are performed within the pulse sequence after each R-wave trigger to model the M_z evolution of normal myocardium and blood over the entire sequence history, to calculate the TI required to achieve the target blood M_z for the imminent sequence cardiac cycle. Before the first R-wave trigger, the blood and normal myocardial M_z are assumed to equal 1 (*i.e.* thermal equilibrium). A linear iterative search is then performed from short to long TI, to determine which TI will deliver a blood M_z closest to the target blood M_z . For each iteration, the ECG trigger delay is also adjusted to ensure a consistent data segment start time across all the iterations. As with the VTI method, complete M_z inversion is assumed since the inversion pulse is adiabatic. Having determined the TI to be applied in the current cardiac cycle, the normal myocardial and blood M_z for this cycle are then calculated for the chosen TI. Next in the sequence is the series of imaging slab-excitation pulses, each followed by the physical repetition time TR in which a spoiled gradient-echo line of k-space is sampled. The model applies the imaging flip angle and calculates the M_z recovery during the time between each imaging excitation. The blood and myocardial M_z are then stored to be used in the calculation in the next sequence repeat, which occurs after the next R-wave trigger. The delay between the final imaging flip angle and the next R-wave trigger is included in the modelling.

3. Materials and methods

In this work we compared the image quality of the VTI and fmVTI methods via patient scans and numerical phantom simulations.

3.1. Patient scans

In total, 28 patients were included in this study, each undergoing one scanning session. All scans were performed under local ethics approval, using Siemens 1.5 T Avanto Fit and Aera scanners (Siemens Healthineers, Erlangen, Germany). After acquisition of other requisite clinical scans, including approximately 15–20 min of conventional 2D LGE after injection of approximately 0.1 ml/kg of gadolinium-based contrast agent (gadobutrol, 0.1 mmol/kg body weight), two 3D LGE scans were applied during each session: 1) VTI and 2) fmVTI. To mitigate the possibility of bias from contrast agent washout, the order of the two 3D LGE scans was varied across the patients. Overall, equal patient numbers

were scanned with VTI first ($n = 14$) or second ($n = 14$).

The 3D LGE sequence parameters were as follows: inversion-recovery segmented 3D spoiled gradient-echo, fat saturation pre-pulse, transverse image volume, field of view: 380 mm $\times$ 427.5 mm, matrix size: 256 $\times$ 288, centre-out k-space ordering for primary (k_y) and secondary (k_z) phase-encoding, imaging flip angle: 20°, TE = 1.49 ms, echo spacing = 3.4 ms, 37 k-space lines per segment (segment duration = 125.8 ms), segment start time adjusted to the diastolic pause for each patient (avoiding the atrial contraction), 4 cardiac cycles required to acquire all necessary k_y lines of a k_z plane, spatial resolution: 1.5 mm $\times$ 1.5 mm $\times$ 4.0 mm, through-plane over-sampling = 10–12.5% (depending on the chosen number of slices), 36–44 slices (reconstructed to 0.7 mm $\times$ 0.7 mm $\times$ 2.0 mm, 72–88 slices), single R-wave ECG-gating, crossed-pairs navigator respiratory-gating with a CLAWS respiratory-gating algorithm [28]. The diaphragm navigator was obtained by a spin-echo formed at the intersection of sagittal 10 mm slice-selective 90-degree excitation, with tilted 10 mm selective sagittal-coronal 180-degree refocusing. While some blood is inverted by this and enters the atria, the 3D LGE sequence in this work used a previously published correction method to mitigate the effect of this on the signal [29]. Parallel data acquisition was performed using GRAPPA [30] with acceleration factor 2 for the primary phase-encode only, and 24 reference lines (integrated into each acquired cardiac cycle). Depending on whether the VTI or fmVTI algorithm was selected, additional sequence parameters were entered to the scanning protocol before starting each 3D LGE scan, as described below.

3.1.1. Variable TI

As in the previous VTI work [12] and the theory section of this work (Section 2.1), normal myocardial T_1 was derived from the T_{1ref} required to null normal myocardium with a conventional 2D breath-hold LGE reference scan performed immediately before the VTI 3D LGE. A mid-ventricular short axis slice was selected, with ECG gating typically on every 3rd cardiac cycle. The reference scan was repeated as necessary, adjusting T_{1ref} until normal myocardium was nulled. T_{1ref} was then entered into the VTI 3D LGE sequence protocol, along with the reference scan repeat time sufficiently long for strong T_1 -recovery (for fast heart-rates, 3 or 4 $\times$ mean R-R interval as judged by the operator), where the mean R-R interval was estimated from the ECG display.

3.1.2. Fully-modelled VTI

The fmVTI algorithm requires the following input parameters: blood T_1 , normal myocardial T_1 and mean R-R interval. To obtain T_1 measurements, a T_1 map was acquired immediately before the fmVTI 3D LGE, using a vendor (MyoMaps, Siemens Healthineers, Erlangen, Germany) single-breath-hold single-slice 11-heartbeat Modified Look-Locker (MOLLI) sequence as previously optimised for post-Gadolinium T_1 ranges. The MOLLI acquisition parameters were: 2D, ECG-gated, mid-ventricular short axis, three inversion pulses (4(1)3(1)2 protocol), TE = 1.13 ms, matrix slice = 256 (frequency-encoding) $\times$ 144 (phase-encoding), field of view: 360 mm $\times$ 270 mm, in-plane interpolated spatial resolution = 1.4 mm $\times$ 1.4 mm, slice thickness = 8 mm, flip angle = 35°, GRAPPA parallel acquisition with acceleration factor 2 and 36 reference lines. Regions of Interest (ROIs) were drawn in the LV blood and the normal myocardium of the ventricular septum, taking the mean T_1 of each. The mean R-R interval was either estimated from the ECG display or set using the average R-R interval ('Nominal Interval') stored with the images from a clinical non-LGE anatomical 3D scan obtained earlier in the session.

3.2. Numerical phantom simulations

Further simulations based on the real patient R-R records of the above scans were planned as follows, with the aim of measuring from patient scans the magnetisation impact of fmVTI specifically, as opposed to the *in vivo* scans where the impact of magnetisation variations would

be conflated with other sources of phase-encode ghosting such as respiratory motion.

Using the timing and phase-encode ordering of each patient 3D LGE scan by VTI and by fmVTI, Bloch simulations were performed in MATLAB (The MathWorks, Natick, Ma) to simulate the signal intensity and ghosting in a 3D numerical phantom. The phantom portrayed three cylinders with axes parallel to the partition-encoding (slices) direction and stacked in the anterior-posterior (A-P) direction, where each cylinder represented either normal myocardium, blood, or scar. All the slices had similar phantom contents: cross-sections of the three cylinders, each of 37 mm diameter. Since the cylinders extended through all the slices, the cylinder lengths were determined by the number of slices acquired. For example, to simulate a scan of 44 slices with 4 mm slice thickness the cylinder lengths were effectively 44 $\times$ 4 mm = 176 mm.

The M_z evolution for each patient scan was generated for each tissue type, using sequence parameters (see below), real patient R-R intervals and the respiratory gating phase-encode order indices. The simulation parameters matched those used for the patient 3D LGE scans, including the following general parameters for all patients: scar $T_1 = 310$ ms, k_y lines per data segment = 37, in-plane GRAPPA acceleration factor = 2, GRAPPA kernel size = 3 $\times$ 4, echo spacing = 3.4 ms, imaging flip angle = 20°, no simulated image noise. Patient-specific parameters for fmVTI: measured myocardial T_1 , measured blood T_1 , number of acquired partitions, TIs, and trigger delays. Patient-specific parameters for VTI: estimated myocardial T_1 , estimated blood T_1 , T_{1ref} estimated repeat time, initial protocol TI, initial protocol trigger delay, and initial protocol TR.

For the fmVTI simulations, the myocardial and blood T_1 were taken from the MOLLI ROI measurements made in each patient before starting the fmVTI 3D LGE. For VTI, myocardial T_1 was derived from the reference scan T_{1ref} as in the patient scanning. However, for VTI the blood T_1 was not known, so it was estimated using the ratio of the VTI and fmVTI myocardial T_1 s:

$$T_{1}^{blood_VTI} = T_{1}^{blood_fmVTI} \left(\frac{T_{1}^{myo_estimated_VTI}}{T_{1}^{myo_fmVTI}} \right) \quad (6)$$

where $T_{1}^{myo_estimated_VTI}$ is the myocardial T_1 estimated from T_{1ref} , $T_{1}^{myo_fmVTI}$ and $T_{1}^{blood_fmVTI}$ are the measured myocardial and blood T_1 values used for the fmVTI scan, and $T_{1}^{blood_VTI}$ is the blood T_1 used by the VTI algorithm. Scar $T_1 = 310$ ms was chosen for both algorithms, to represent a typical relaxation time of enhanced myocardium in LGE.

The simulated M_z values at each TI were applied as weights to each phase-encoded line of each of the three separate phantom tubes in numerical k-space. The phantom raw datasets were then added together, generating 3D raw datasets for each patient's VTI and fmVTI scans, and the 3D image volume was reconstructed using a GRAPPA parallel imaging [30,31] framework [32] (4 simulated coil sensitivity profiles, 2D neighbourhood weight estimation without regularisation). Coil channels were combined using the sum-of-squares, producing magnitude images for subsequent ROI analysis.

3.3. Image analysis

3.3.1. Patient image ROI signal

ROIs were drawn on the centre slice of each image series, measuring the mean ROI magnitude for the LV blood (avoiding papillary structures, typical ROI diameter 17 mm) and normal myocardium (ventricular mid-septum, typical ROI extent = 25 mm $\times$ 4 mm).

3.3.2. Patient image quality scores

An experienced observer performed blinded randomised grading of each 3D LGE image series, grading twice in terms of 1) left atrial wall clarity and 2) total ghosting severity. A 4-point qualitative grading scheme was used for each of the two metrics, regardless of the presence or absence of disease. Greyscale windowing was applied to achieve

approximately consistent greyscale contrast across all image series and the left ventricular myocardium was ignored. Scoring criteria for left atrial wall clarity were as follows: 0 = non-diagnostic (left atrial wall completely unclear), 1 = poor (greater than ~50% obscured), 2 = fair (less than ~50% obscured), 3 = good (clear imaging of left atrial wall). Scoring criteria for total ghosting: 0 = non-diagnostic (extreme ghosting), 1 = poor (severe ghosting), 2 = fair (moderate ghosting), 3 = good (mild/no ghosting). Wilcoxon tests were used to compare the scores from the two dynamic TI algorithms.

3.3.3. Numerical phantom simulations: signal and ghosting

ROIs were drawn to measure the signal and ghosting of the three tissue types represented by the phantom. To measure the image magnitude of each tissue type, an ROI was drawn in the central slice of the three numerical phantom tubes. To quantify ghosting from each tube, an ROI was drawn in the free space either side of each tube, along the primary phase-encoding direction (*i.e.* right-left in the displayed images). The ghosting ROIs were extended through the slice-direction (partition phase-encoding), obtaining a total ghosting value for each tissue variety (each tube) for each 3D LGE scan. For each ROI, the mean value was used for subsequent analysis.

3.4. Statistical analysis

Significance tests were performed to compare all the metrics from the VTI and fmVTI methods. All tests were performed using the in-built statistical package in MATLAB (The MathWorks, Natick, Ma). To determine the appropriate significance test, an Anderson-Darling normality test was first applied to each metric, with $p > 0.05$ interpreted as an indicator of normally-distributed data. A two-tailed paired *t*-test was applied for metrics passing the normality test, whereas a paired Wilcoxon signed rank test was used for non-normal metrics.

4. Results

4.1. Patient characteristics

All 28 patients were included in all the analyses presented. The overall patient characteristics were: age (mean $\pm$ Standard Deviation (SD)): 45 ± 18 years, weight: 79 ± 18 kg, 8 female, 20 male. No significant difference was found in age ($p > 0.1$) or weight ($p > 0.9$) between the patients scanned with fmVTI first or second. A balanced gender distribution was found between patients scanned with fmVTI first or second.

4.2. Patient scan ROIs

For fmVTI compared to VTI, there was a significant increase in the mean signal of the normal myocardium (VTI (mean $\pm$ standard deviation): 30 ± 10 , fmVTI: 35 ± 11 , $p < 0.01$) but not the blood (VTI: 70 ± 24 , fmVTI: 75 ± 20 , $p > 0.1$). The ROI measurements by VTI and fmVTI for each patient are plotted vertically against the R-R interval variability (horizontal axis) during each 3D LGE scan, as shown in Fig. 2.

4.3. Image quality scoring

For the quality scoring, no significant difference was observed for the left atrial wall clarity (VTI: 2.0 ± 1.0 , fmVTI: 1.8 ± 1.0 , $p > 0.1$) or the total ghosting (VTI: 1.9 ± 1.0 , fmVTI: 2.0 ± 1.0 , $p > 0.7$). Fig. 3 displays example images for each scoring level of the left atrial wall clarity assessments. Figs. 4 and 5 show example images for the qualitative scoring of total ghosting, with Fig. 4 representing the full greyscale range and Fig. 5 showing a consistently brightened greyscale window to highlight ghosting.

Fig. 6 displays a side-by-side comparison of images from the VTI and fmVTI methods, from the same patient cases as the examples of left atrial

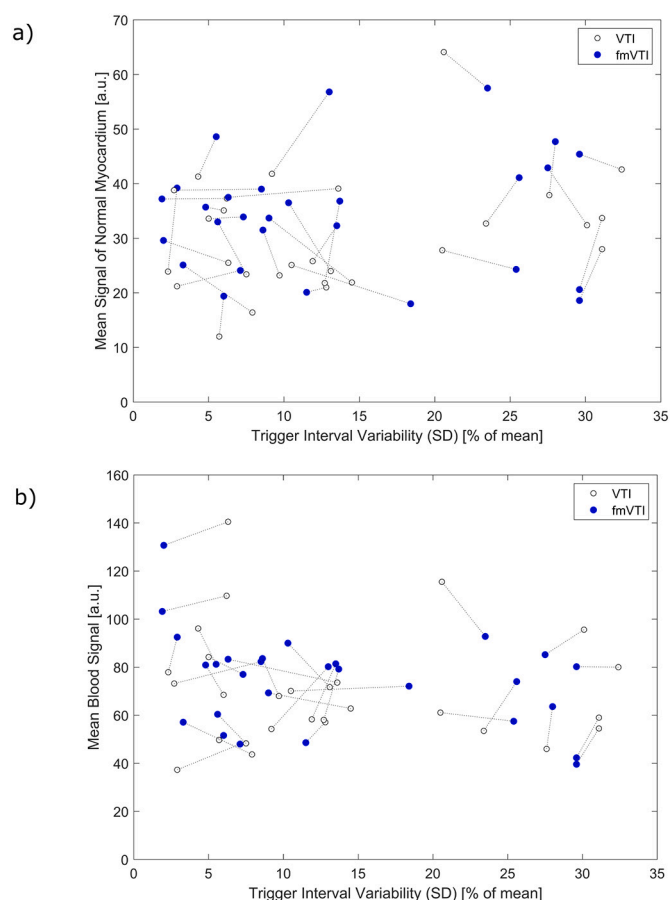


Fig. 2. Patient image ROIs: tissue signal versus trigger interval variability, for (a) normal myocardium and (b) blood. Lines link scans for each patient.

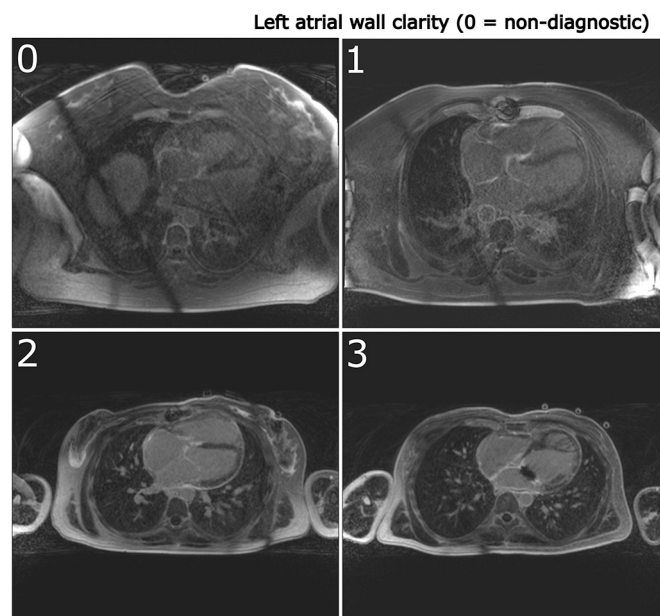


Fig. 3. Example patient image (centre slice) for each scoring level for left atrial wall clarity (0 = non-diagnostic). The purpose of this figure is to provide context for the left atrial wall clarity scores and demonstrate how each scoring level relates to visible image quality.

wall clarity in Fig. 3. Fig. 7 is similar to Fig. 6 but for the ghosting

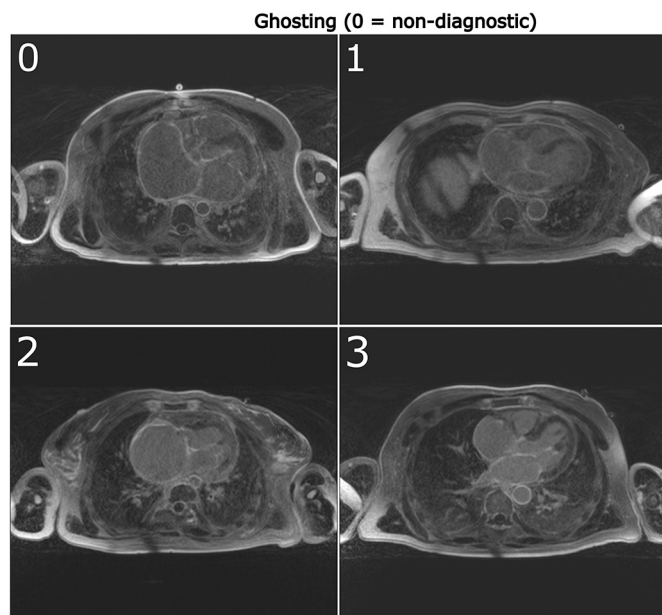


Fig. 4. Example patient image (centre slice) for each ghosting scoring level (0 = non-diagnostic), using the full greyscale range of each image. The purpose of this figure is to provide context for the ghosting scores, demonstrating how each scoring level relates to visible ghosting.

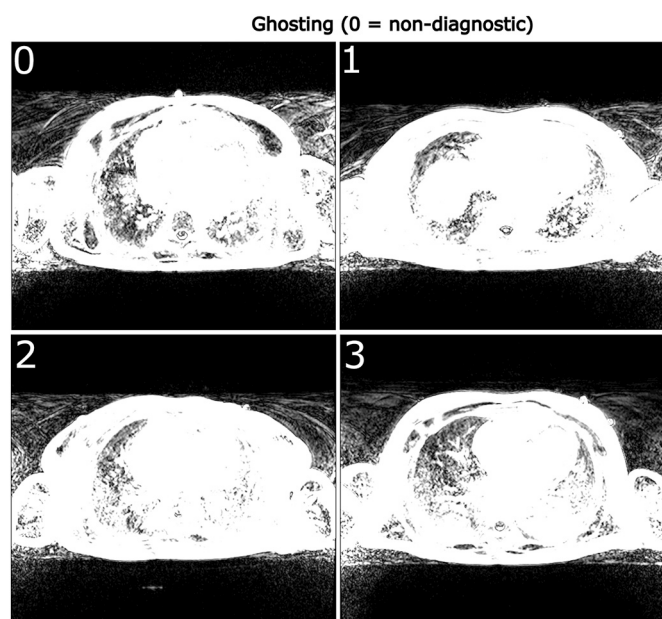


Fig. 5. Example patient image (centre slice) for each ghosting scoring level (0 = non-diagnostic), using a consistent low greyscale window to highlight ghosting in the free space. The purpose of this figure is to provide context for the ghosting scores, demonstrating how each scoring level relates to visible ghosting in the free space.

examples in Figs. 4 and 5. Fig. 8 contains the same image data as Fig. 7 but with greyscale windowing to highlight ghosting.

Fig. 9 plots the image quality scores for the VTI and fmVTI scans on each patient, against the R-R interval variability.

4.4. Numerical phantom simulations

4.4.1. Tissue mean magnitude

The numerical phantom simulations showed no significant

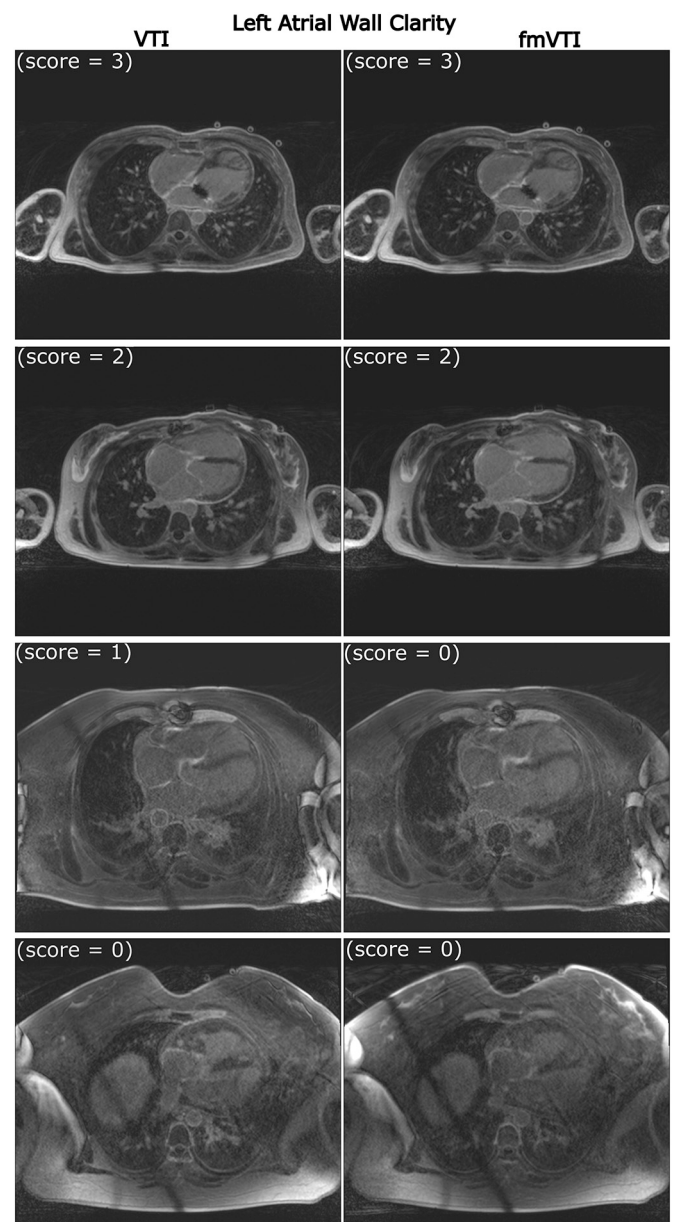


Fig. 6. Comparison of images from the VTI and fmVTI methods (centre slice) for the four example patients from the left atrial wall clarity examples in Fig. 3. Left atrial wall clarity scores are included for reference. The *in vivo* comparison of VTI and fmVTI will likely have been dominated by altered patterns of respiratory ghosting and washout changes in signals.

difference in mean myocardial signal (VTI: 3200 ± 1600 , fmVTI: 2800 ± 1000 , $p > 0.2$) or scar signal (VTI: 23000 ± 3400 , fmVTI: 24000 ± 4500 , $p > 0.07$). There was a significant increase in the mean blood magnitude (VTI: 8200 ± 3800 , fmVTI: 9400 ± 3700 , $p < 0.001$). Fig. 10 plots the simulation mean measurements for each patient, against the R-R interval variability.

4.4.2. Ghosting

A significant increase in myocardial ghosting measurements was found for the fmVTI algorithm compared to VTI (VTI: 170 ± 420 , fmVTI: 500 ± 690 , $p < 0.001$), with a significant decrease in blood ghosting (VTI: 410 ± 710 , fmVTI: 68 ± 40 , $p < 0.0005$) and for scar ghosting (VTI: 830 ± 1300 , fmVTI: 510 ± 730 , $p < 0.02$). Fig. 11 plots the results for each patient, against the R-R interval variability.

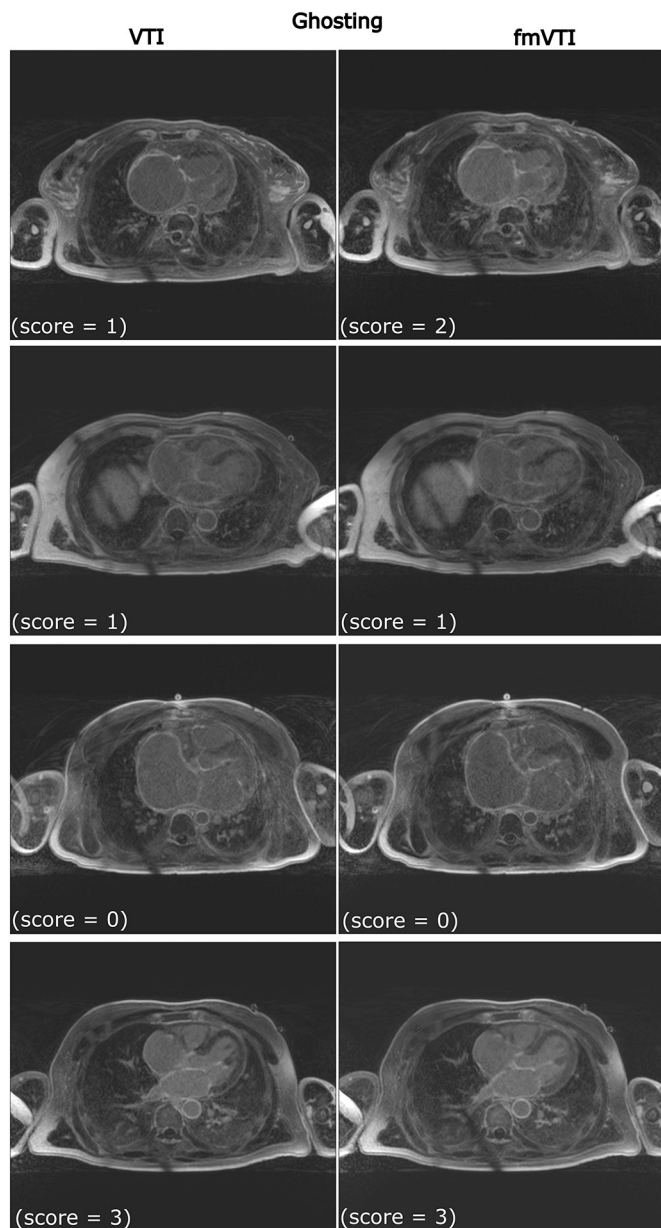


Fig. 7. Comparison of images from the VTI and fmVTI methods (centre slice) for the four example patients from the ghosting examples in Figs. 4 and 5. Ghosting scores are included for reference. The *in vivo* comparison of VTI and fmVTI will likely have been dominated by altered patterns of respiratory ghosting and washout changes in signals.

5. Discussion

An *in vivo* comparison of two variable TI 3D LGE methods was performed to explore their effectiveness against R-R interval variability, with accompanying numerical phantom simulations.

5.1. Patient scans

The patient scans showed a small but significant increase in the signal of normal myocardium for fmVTI compared to VTI, which of course is not an aim of fmVTI but a consequence of its algorithm. No significant change was shown for the blood signal. No effect of this change in normal myocardial signal was reflected in the image quality scores, where no significant change was observed for left atrial wall clarity or total ghosting.

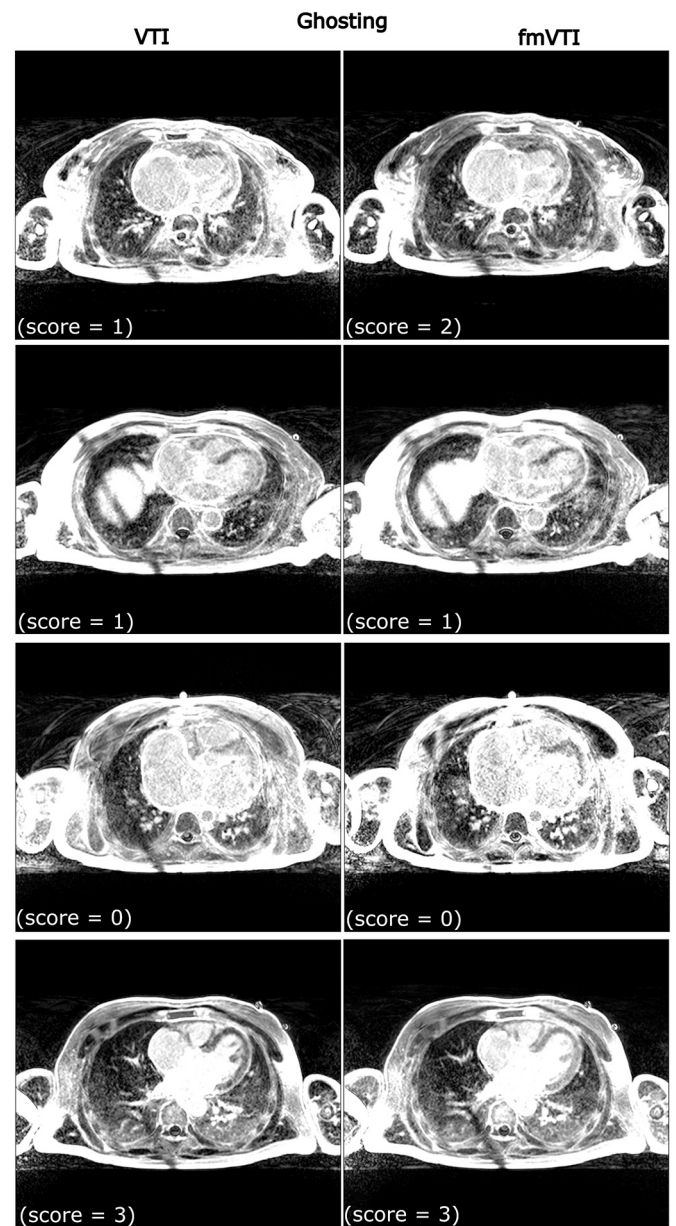


Fig. 8. Comparison of images from the VTI and fmVTI methods (centre slice) for the four example patients from the ghosting examples in Figs. 4, 5, and 7. Ghosting scores are included for reference. Greyscale windowing has been applied to highlight ghosting in the free space. The *in vivo* comparison of VTI and fmVTI will likely have been dominated by altered patterns of respiratory ghosting and washout changes in signals.

As expected, the plots of image quality scores demonstrate greater left atrial wall clarity for patients with lower trigger interval variability, due to reduced magnetisation variability. This trend was more subtle for the total ghosting scores, potentially due to additional ghosting from other sources such as respiratory motion.

5.2. M_z simulations

The simulations derived from patient R-R intervals aimed to elucidate any improvement in magnetisation handling by fmVTI compared to VTI.

The simulations reported a significant change in blood signal but showed no change for normal myocardium or scar tissue. The difference in blood signal level was not considered important, as the targets of the

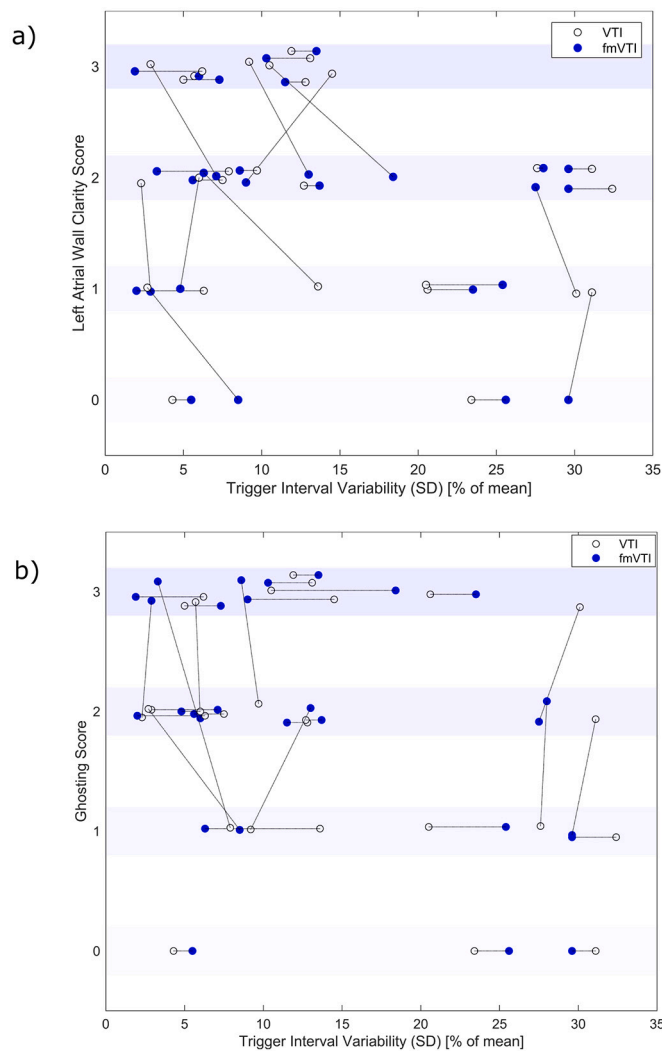


Fig. 9. Patient image quality scores (0 = non-diagnostic) versus trigger interval variability, for (a) left atrial wall clarity and (b) total ghosting. Lines link scans for each patient.

fmVTI method were the clarity of small features and the ghosting level, which are both associated with M_z variability.

A large variation in simulation ghosting was observed across the patients. The increase in simulated myocardial ghosting by fmVTI compared to VTI was expected because normal myocardium was not the target of the fmVTI method. Myocardial ghosting appeared to be greater for higher trigger interval variability, particularly for the fmVTI results. The reduction in simulation blood ghosting by fmVTI compared to VTI provided a strong indication of correct implementation of the algorithm. The fmVTI algorithm successfully kept blood ghosting close to zero for all cases. Despite the significant decrease in simulated blood ghosting by fmVTI compared to VTI, the fmVTI method delivered no change for the *in vivo* image quality scores. This was likely to have happened because other sources of error may have dominated the *in vivo* measurements, particularly respiratory motion artefacts, as these were all free-breathing navigator-gated acquisitions with each scan experiencing different patterns of respiratory motion. Furthermore, the CLAWS respiratory gating algorithm uses the respiratory motion pattern to determine the phase-encode ordering. Inconsistent intra-patient breathing patterns could be the cause of the high blood ghosting observed for some simulated VTI cases. For example, three of the simulated VTI datasets exhibited exceptionally high blood ghosting when compared to the corresponding fmVTI results. Although scar tissue was not targeted in

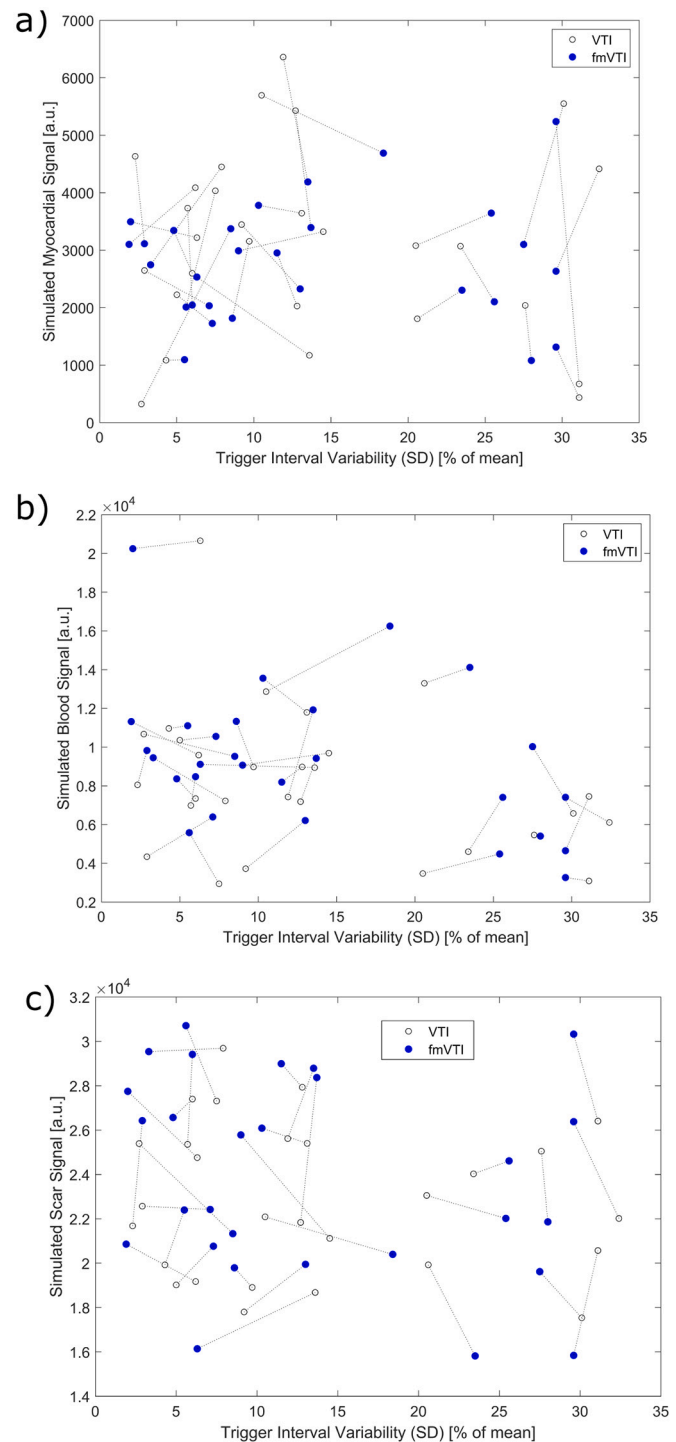


Fig. 10. Numerical phantom simulations. Tissue signal versus trigger interval variability, for (a) normal myocardium, (b) blood and (c) scar. Lines link scans for each patient.

the fmVTI method, the simulations also showed a reduction in scar ghosting by fmVTI compared to VTI. This could have been because the scar T_1 values tended to be in a range similar to that of blood. The cases with greatest scar ghosting had relatively high trigger interval variability.

To null normal myocardium with the fmVTI algorithm, the target M_z for normal myocardium was set as zero. The algorithm has the capability to target a non-zero normal myocardial M_z instead, which would have allowed the target myocardial M_z to be sufficiently positive to avoid

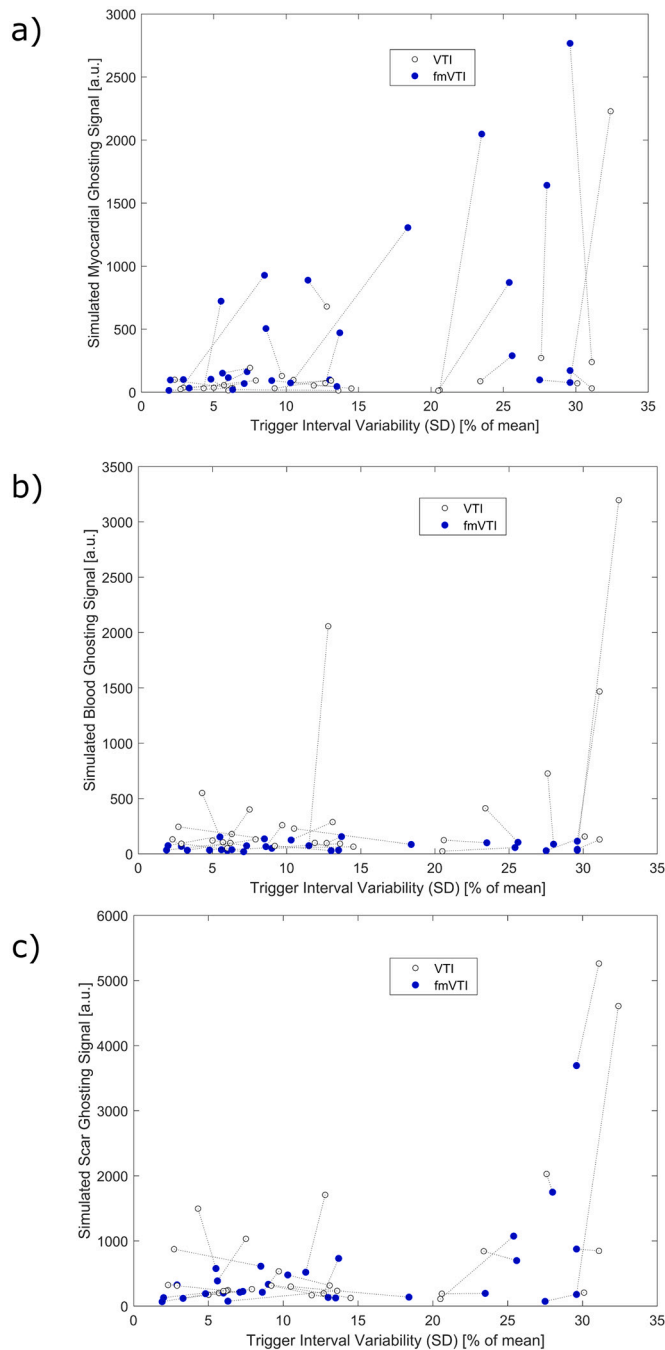


Fig. 11. Numerical phantom simulations. Ghosting signal *versus* trigger interval variability, for (a) normal myocardium, (b) blood and (c) scar. Lines link scans for each patient.

myocardial M_z fluctuations around zero. Such phase-polarity changes may be a greater cause of phase-encode ghosting than magnitude changes of uniform polarity. Providing the myocardial signal is close to zero, this phase-variation will be of weak amplitude, meaning subsequent artefacts may be close to the noise level. However, the risk of phase inversions across the phase-encoded data dimensions because of fmVTI, and indeed even VTI, may need further investigation.

The demonstrated VTI and fmVTI strategies for 3D LGE pulse sequence improvement could be applied to other clinical MRI methods to improve image quality in the presence of arrhythmia, such as those designed to achieve dark [33] or grey blood [34,35] to facilitate scar detection.

5.3. Limitations

All patient scans were performed within a routine clinical environment. Ideally B_1^+ variations across the heart would be mapped before the fmVTI 3D LGE and used to input the exact (*i.e.* averaged over most of the heart) excitation flip angle into the fmVTI algorithm calculations. However, due to clinical constraints it was not possible to include a B_1^+ -mapping scan in the protocol. Further, the variation in B_1^+ across the heart could not be accounted for, necessitating some form of spatial averaging.

The mean R-R interval as input to fmVTI was either estimated from the ECG display during free-breathing or from the recorded average (“nominal”) interval of a free-breathing scan obtained earlier in the clinical protocol. However, patients with arrhythmia inherently have a variable R-R interval, causing the average R-R interval to change between the time used for estimation and the duration of the fmVTI 3D LGE scan. This could lead to an inappropriate target blood M_z , which would worsen the myocardial nulling and increase myocardial ghosting. Although the VTI algorithm does not directly require a mean R-R interval, it does use an estimation of mean R-R from the ECG display during the breath-hold reference scan to estimate myocardial T_1 , thereby making it indirectly sensitive to changes in mean R-R interval between the reference scan and the free-breathing 3D LGE scan. Ideally, the mean R-R interval would be calculated automatically for each patient in an objective manner and as recently as possible before each 3D LGE. An improved strategy would have such information recorded automatically and sent into each sequence, to avoid mistakes and approximations. Unfortunately, for this work it was not possible to modify the clinical system or interrupt the clinical workflow for this purpose.

The aim of fmVTI is to maintain blood M_z consistency based on fully-modelled prior magnetisation history. However, blood entering the 3D slab will not have experienced the partial saturation of the spoiled gradient echo data segment acquisition. Therefore, the fmVTI algorithm is partially invalid for this newly-arriving blood, requiring some considerations of where this blood will typically enter the 3D LGE slab and how many cardiac cycles it may take to reach relevant cardiac chambers. Such blood will usually have experienced the non-selective inversion-pulse history far enough back in time, given that the scans are post-Gadolinium administration and the blood T_1 is in the region of 500–600 ms. Most of the pulmonary blood is in the transverse imaging slab, but one might predict some failure of fmVTI for blood in the Inferior Vena Cava (IVC) and Superior Vena Cava (SVC), perhaps even for blood entering the right atrium, which might require further investigation. The impact of the navigator on blood entering the heart was addressed in the Methods section. It would be difficult to predict the minor effect of such residual imperfections in the correction, which were assumed negligible.

It would be desirable to estimate the number of patients required to reach confidence in the statistical test conclusions, such as the comparison of image quality between VTI and fmVTI. However, we believe such power calculations are more feasible for clinical research, where a method’s reproducibility is already known or can be estimated from previous work where the method has been used. We are unaware of such data for standard fixed TI or VTI methods. Repeated scans are difficult to obtain for VTI and fmVTI as they are convoluted by Gadolinium-Based Contrast Agent (GBCA) washout, respiratory variability, or are difficult to justify ethically if performed by repeated sessions requiring extra GBCA injections.

5.4. Future work

As previously mentioned in this work, it is likely that respiratory motion contributed to the overall ghosting, therefore influencing the image quality scores. Future work could investigate the relationship between the image quality scores and R-R interval variation, as well as the relationship between image quality and the respiratory motion pattern.

Clearly the patient studies were limited largely to non-AF and future work would apply this in more patients with AF. Further research would incorporate B_1^+ mapping to ensure optimal application of the fmVTI method in each patient. Furthermore, a more objective and preferably entirely automatic update of the mean R-R interval input to the 3D LGE scans would reduce the chance of operator errors and approximations that may have degraded these results.

The phase-encode ordering takes no account of M_z history. While this was governed by the respiratory algorithm (CLAWS), in future work it might also account for the M_z in its choice of which phase-encoded lines to obtain in the imminent cardiac cycle.

6. Conclusions

The simulation results indicate that the fmVTI method reduced ghosting when compared to the VTI method, due to reduced M_z variability in the blood signal. However, no *in vivo* reduction of ghosting was observed in the patient studies available. Sources of phase-encode ghosting and blurring appeared to dominate and obscure this finding.

Author statement

General statement from the authors: The authors thank the reviewers for generously using their time and expertise to provide feedback on the submitted manuscript. The reviewers' comments are included in the response document, where each comment has a response from the authors. A small number of additional revisions are described at the end of the document. The authors have also provided a revised manuscript, one plain copy and one copy with changes highlighted.

Ethics approval and consent to participate

All patients scanned for this work gave informed written consent in accordance with local research ethics approval (consent form reference code: 10/H0701/11).

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CRediT authorship contribution statement

Jack J. Allen: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – original draft, Visualization. **Jennifer Keegan:** Conceptualization, Methodology, Software, Supervision, Funding acquisition. **George Mathew:** Investigation. **Miriam Conway:** Investigation. **Sophie Jenkins:** Investigation. **Dudley J. Pennell:** Resources. **Sonia Nelles-Vallespin:** Supervision. **Peter Gatehouse:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Sonya V. Babu-Narayan:** Investigation, Resources.

Declaration of Competing Interest

The authors declare there are no known competing interests to declare with regards to this article.

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