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Objectives: Free-breathing 3-dimensional (3D) late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) techniques with high isotropic resolution and dark-blood contrast may optimize the delineation of myocardial scar patterns. The extended acquisition times required for such scans, however, are paralleled by a declining contrast agent concentration. Consequently, the optimal inversion time (TI) is continuously increasing. We hypothesize that a steadily increasing (dynamic) TI can compensate for this effect and can lead to improved blood nulling to optimize the dark-blood contrast.

Materials and Methods: Fifty consecutive patients with previous cardiac arrhythmias, scheduled for high-resolution 3D LGE MRI, were prospectively enrolled between October 2017 and February 2020. Free-breathing 3D dark-blood LGE MRI with high isotropic resolution (1.6 × 1.6 × 1.6 mm) was performed using a conventional fixed TI (n = 25) or a dynamic TI (n = 25). The average increase in blood nulling TI per minute was obtained from Look-Locker scans before and after the 3D acquisition in the first fixed TI group. This average increment in TI was used as input to calculate the dynamic increment of the initial blood nulling TI value as set in the second dynamic TI group. Regions of interest were drawn in the left ventricular blood pool to assess mean signal intensity as a measure for blood pool suppression. Overall image quality, observer confidence, and scar demarcation were scored on a 3-point scale.

Results: Three-dimensional dark-blood LGE data sets were successfully acquired in 46/50 patients (92%). The calculated average TI increase of 2.3 ± 0.5 ms/min obtained in the first fixed TI group was incorporated in the second dynamic TI group and led to a significant decrease of 72% in the mean blood pool signal intensity compared with the fixed TI group ($P < 0.001$). Overall image quality ($P = 0.02$), observer confidence ($P = 0.02$), and scar demarcation ($P = 0.01$) significantly improved using a dynamic TI.

Conclusions: A steadily increasing dynamic TI improves blood pool suppression for optimized dark-blood contrast and increases observer confidence in free-breathing 3D dark-blood LGE MRI with high isotropic resolution.

Key Words: cardiovascular diseases, myocardial infarction, magnetic resonance imaging, late gadolinium enhancement

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Late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) has been considered the reference standard for noninvasive assessment of myocardial scarring for 2 decades.[1–3] Its ability to depict areas of myocardial infarction from healthy myocardium is well established, making LGE a widely accepted component of standard cardiac MRI protocols. Clinical routine 2-dimensional (2D) bright-blood LGE breath-hold techniques, however, have their limitations in terms of spatial resolution and scar-to-blood contrast. The spatial resolution that can be obtained is intrinsically limited by the low signal-to-noise ratio, which may be further compromised in case of single-shot acquisitions required for patients with insufficient breath-holding.[4] Another important drawback of routine bright-blood LGE techniques is the high-intensity signal of the blood pool that hinders correct distinction of the scar-blood barrier and subsequently compromises image quality. As a result, the scar volume can be substantially underestimated or even completely obscured.[5]

Three-dimensional (3D) MRI acquisitions, which excite the entire 3D volume, benefit from intrinsically higher signal-to-noise ratio, enabling higher spatial resolution and acquiring thinner slices.[6] The poor contrast-to-noise ratio can be improved by using a dark-blood LGE method that suppresses the blood pool signal while maintaining high scar signal intensity.[7] This recently introduced method proved superior for the detection of (subendocardial) ischemic scar patterns in a cohort of 300 patients.[8] Ideally, this dark-blood contrast mechanism would be implemented in a free-breathing 3D acquisition to combine the increased scar-to-blood contrast with high isotropic spatial resolution. The prolonged acquisition times required for such scans, however, are accompanied by a progressive decline in contrast agent concentration in the blood pool. As a result, the ideal inversion time (TI) to null the blood pool and obtain dark-blood contrast gradually increases. In this study, we investigated the feasibility of a steadily increasing TI method to optimize blood pool nulling for improved dark-blood contrast during free-breathing 3D LGE acquisitions with high isotropic resolution. The degree of blood pool nulling, observer confidence, image quality, and scar demarcation (if present) were evaluated and compared with a conventional fixed TI method.

MATERIALS AND METHODS

Study Population

Fifty consecutive patients with ventricular arrhythmia who were scheduled for either implantable cardioverter-defibrillator implantation or ablation therapy, and referred for prior high-resolution 3D LGE MRI, were prospectively enrolled between October 2017 and February 2020. In the first 25 patients, free-breathing 3D dark-blood LGE with high isotropic resolution was performed with a conventional fixed TI. In the second 25 patients, the same 3D LGE sequence was performed with a steadily increasing dynamic TI mechanism that was installed using a

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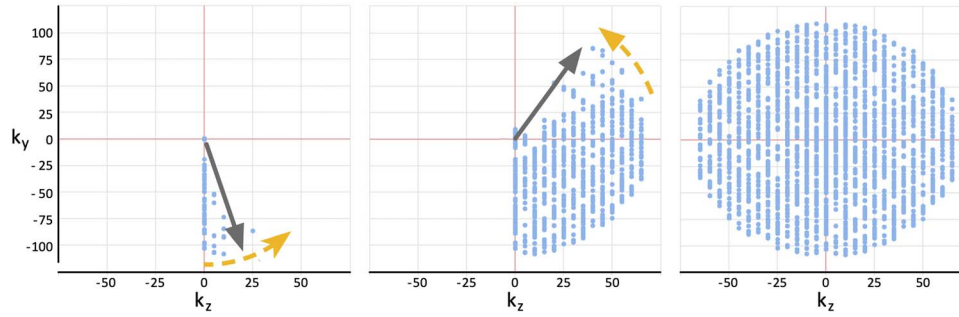

FIGURE 1. Schematic overview of the Cartesian k-space sampling strategy used for the 3D LGE sequence. Each blue dot represents a k-line in the third dimension (k_x). Every heartbeat, a selected number of k-lines are acquired from the center toward the periphery (representing a "spoke," indicated by the solid arrow). After every heartbeat, the spoke of k-lines that is acquired slowly rotates (dashed arrow). During the sequence, the spoke keeps rotating until a full data set is acquired. Note that for each heartbeat a single "center-out" spoke of k-lines is acquired, meaning that central k-space data are acquired during the entire sequence.

temporary software patch. Exclusion criteria included the standard MRI contraindications, a glomerular filtration rate less than 30 mL/min/1.73m^2, a known allergy to gadolinium-based contrast agents, and the presence of implanted cardiac devices. This study was approved by the local ethics committee (METC2019-1136) and was conducted according to the Declaration of Helsinki. All patients provided written informed consent.

MRI Protocol

All scans were performed on a 1.5-T MR system (Ingenia; Philips Healthcare, Best, the Netherlands). Localizer images, as well as left 2-chamber, 4-chamber, and short-axis cine images, were acquired to facilitate accurate planning of the 3D LGE sequence. Approximately 10 minutes after intravenous injection of 0.2 mmol/kg gadobutrol (Gadovist; Bayer Pharmaceuticals, Berlin, Germany), the 3D LGE sequence was started. The scan parameters for this electrocardiogram-triggered respirator-navigated 3D whole-heart phase-sensitive inversion recovery (PSIR) sequence with spoiled gradient-echo readout were as follows: echo time, 3 milliseconds; repetition time, 6.5 milliseconds; flip angle, 25 degrees; PSIR reference flip angle, 5 degrees; acquired resolution, 1.6 × 1.6 × 1.6 mm (reconstructed to 0.8 × 0.8 × 0.8 mm); compressed SENSE factor of 3; spectral presaturation with inversion recovery fat suppression; fat-water shift of 0.9 pixel; and respiratory navigator gating window, 5 mm. A commercially available Cartesian k-space sampling strategy was used that samples a radial "center-out spoke" of k-lines (in the third dimension) during every heartbeat (Fig. 1). Because only a part of the center of k-space is acquired every heartbeat, central k-space data are acquired during the entire sequence. Slices were acquired in the axial plane. The acquisition window was set in the diastolic resting period as observed in the earlier acquired 2- and 4-chamber cine images, with a maximum duration of 130 milliseconds. The dark-blood mechanism without using additional magnetization preparation has been described in prior studies.[7] In short, the TI is shortened to the point of left ventricular (LV) blood nulling (instead of myocardium). Combined with a PSIR reconstruction, a significant improvement in scar-to-blood contrast is accomplished, while maintaining excellent scar-to-myocardium discrimination.[7,9] Inversion time was defined as the time between the center of the inversion pulse and start of signal readout. The duration of these free-breathing 3D dark-blood PSIR LGE acquisitions with high isotropic resolution varied between 8 and 10 minutes, depending on the field of view, heart rate, acquisition window duration, and assuming 100% breathing efficiency. The given contrast dose is in accordance with local protocol and current international recommendations.[10]

In the fixed TI group, a Look-Locker (LL) scan was performed before the 3D LGE sequence to obtain the starting TI required for LV blood pool nulling. As standard practice, an empirically derived addition of 40 milliseconds was made to this initial TI to compensate for the contrast washout[11,12] (Fig. 2, left panel). This leads to an intermediate fixed TI that is well balanced between the TIs identified at the start and end of the free-breathing 3D LGE acquisition (Fig. 2, right panel). At the end, a second LL scan was performed. In all patients, the difference between the 2 TIs was divided by the time

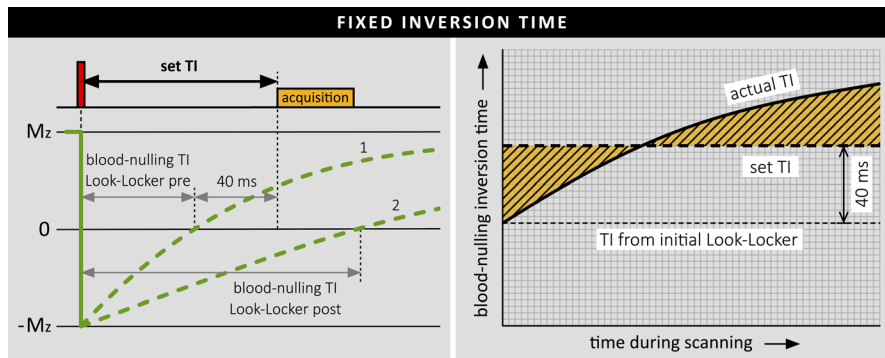

FIGURE 2. Overview of the fixed inversion time (TI) strategy used for conventional late gadolinium enhancement MRI. Left panel, The required blood nulling TI is obtained using a preceding Look-Locker scan and then increased by 40 milliseconds to compensate for the expected contrast washout during the 3D sequence. This results in an intermediate fixed TI that is well balanced between the TI required at the start (curve 1) and end of the scan (curve 2). Right panel, Although the (intermediate) fixed TI is well balanced within the range of required TIs during scanning, the set TI (dashed line) is significantly "off-target" with the actual TI (solid line) at the start and end of the scan. The marked areas between the curves (diagonally striped) indicate the "off-targetness" of the set TI with respect to the actual TI.

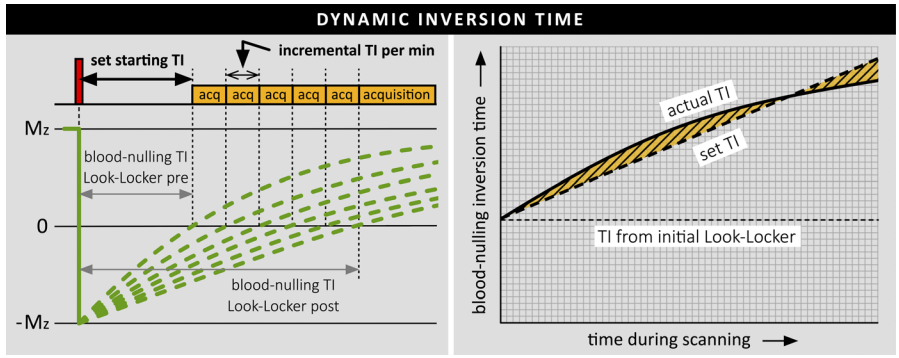

FIGURE 3. Overview of the novel dynamic inversion time (TI) strategy for improved blood nulling and optimized dark-blood contrast. Left panel, The blood nulling TI obtained from the preceding Look-Locker scan is directly set for the 3D sequence, but automatically increased every minute with the increment value as obtained from Look-Locker data from the fixed TI group. Right panel, Although the evolution of the actual TI is unknown and varies in patients, the "off-targetness" is always lower when using the dynamic TI mechanism compared with a conventional fixed TI. The marked areas between the curves (diagonally striped) indicate the "off-targetness" of the set TI (dashed line) with respect to the actual TI (solid line).

between the 2 LL scans to derive the average increase in TI (in milliseconds per minutes) for dynamic LV blood pool nulling.

In the dynamic TI group, the first LL scan was performed before the 3D LGE sequence to obtain the starting TI. This TI was subsequently automatically increased during the 3D LGE sequence by the previously calculated value (in milliseconds per minute) (Fig. 3). The increasing dynamic TI mechanism was not affected by breathing efficiency and/or heartbeat acceptance. At the end of the 3D LGE sequence, the second LL scan was performed to derive the actual increase in TI per minute for validation.

Image Analysis

The acquired 3D volume rendered 3 image types: magnitude images, corrected real/PSIR images, and PSIR reference images. The magnitude images were used to evaluate the degree of blood pool suppression because the signal intensity scale has a fixed zero point. In these images, regions of interest (ROIs) were drawn in the LV blood pool and evaluated using MATLAB (Version 2018b; The Mathworks, Natick, MA). The papillary muscles, chordae tendineae, and valve leaflets were excluded from these ROIs. The mean signal intensity of the blood pool was used as a measure for blood pool suppression. The standard deviation of mean blood pool signal intensities within each group was calculated to assess blood nulling consistency. Because dedicated noise scans without radiofrequency pulses could not be performed due to time restrictions, no signal-to-noise ratios were calculated. All data sets were presented blinded and in random order to an expert cardiovascular radiologist (S.G.) that scored these for overall image quality, observer confidence, and scar demarcation (if present) on a 3-point scale (1 = low, 2 = medium, 3 = high).

Statistical Analysis

Differences between the 2 groups were evaluated using the independent samples Student's *t* test (normally distributed data) or the nonparametric Mann-Whitney *U* test (nonnormally distributed data). Normality of data was evaluated using the Shapiro-Wilk test. In case normality of data was found, Levene test was performed to assess equality of variances. If unequal variances were indicated, a Welch *t* test/unequal variances *t* test was used rather than a (standard) equal variances independent samples Student's *t* test. All statistical tests were performed using SPSS Statistics (Version 26; IBM, Armonk, NY). Tests were 2-tailed, and *P* values less than 0.05 were considered significant. Results are expressed as mean ± standard deviation unless otherwise specified. No sample size calculation could be made for this feasibility study as the changes that might be achieved in the parameters of interest were unknown. Instead, a practical cohort size of 25 patients for each group was used.

RESULTS

Complete 3D dark-blood LGE data sets were successfully acquired in 46 (92%) of 50 patients. In 3 patients, the scan was terminated

TABLE 1. Baseline Characteristics of Study Cohort

	Fixed TI Group (n = 23)	*P*	Dynamic TI Group (n = 23)	Study Cohort (n = 46)
Sex, male (%)	15 (65)	0.31*	19 (83)	34 (74)
Age, median (range), y	63 (21–78)	0.57	59 (17–79)	61 (17–79)
Weight, kg	79.8 ± 15.1	0.20	86.0 ± 17.3	82.9 ± 16.4
Length, cm	174 ± 8	0.05	179 ± 8	177 ± 8
BMI, kg/m^2	26.2 ± 4.4	0.61	27.0 ± 5.6	26.6 ± 5.0
Heart rate, beats per minute	70 ± 13	0.17	65 ± 11	67 ± 12
eGFR, mL/min/1.73 m^2	73 ± 18	0.50	76 ± 15	74 ± 16
TI Look-Locker pre, ms	135 ± 19	0.33	142 ± 24	139 ± 22
TI Look-Locker post, ms	211 ± 26	0.92	210 ± 28	211 ± 27
Temporal TI increase, ms/min	2.3 ± 0.5	0.23	2.5 ± 0.5	2.4 ± 0.5

Results are expressed as mean ± standard deviation, unless otherwise specified.

*Fisher's exact test.

BMI, body mass index; TI, inversion time; eGFR, estimated glomerular filtration rate.

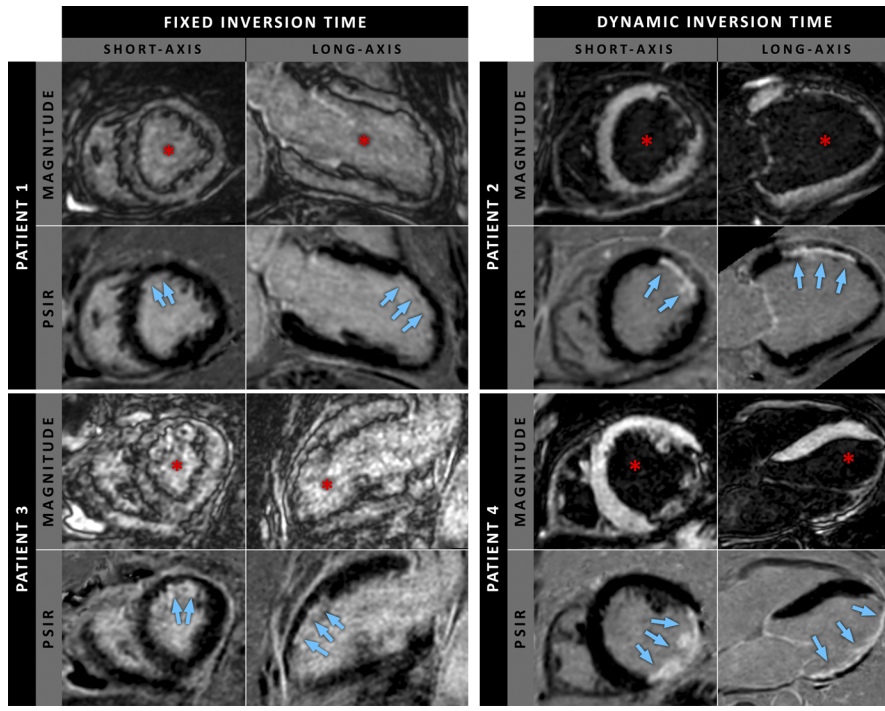

FIGURE 4. Magnitude and phase-sensitive inversion recovery (PSIR) images acquired in 4 patients using a 3D dark-blood late gadolinium enhancement MRI acquisition, 2 with a conventional fixed inversion time (TI) and 2 with a steadily increasing dynamic TI. For all patients, the TI was set for blood nulling. Note that the left ventricular blood pool in the magnitude images, marked by asterisks, was accurately nulled (appearing black) using the dynamic TI, which was not achieved using the fixed TI (appearing grayish). The PSIR images, used for clinical decision making, therefore show improved scar-to-blood contrast and superior scar visibility (marked by arrows) when using a dynamic TI.

prematurely due to the sudden onset of cardiac tachyarrhythmias (n = 2) or poor navigator efficiency (n = 1). In 1 patient, the TI was mistakenly set for myocardium instead of blood nulling. These 4 patients, 2 per group, were excluded from further analysis. Baseline characteristics of the study cohort (n = 46) are summarized in Table 1.

In the fixed TI group, the preceding LL scan was performed at 9 ± 1 minutes after contrast injection, showing an optimal blood nulling TI of 135 ± 19 milliseconds. After the 3D acquisition, the LL scan indicated a blood nulling TI of 211 ± 26 milliseconds. The increase of 76 ± 18 milliseconds demonstrates that the empirically derived addition of 40 milliseconds to the obtained starting TI led to an intermediate fixed TI that was well balanced between the TIs identified at the start and end of the 3D LGE scan. Taking the average time between the LL scans of 34 ± 11 minutes into account, a temporal TI increase of 2.3 ± 0.5 ms/min was calculated for the dynamic blood nulling mechanism. In the dynamic TI group, the initial LL scan was performed 9 ± 2 minutes postinjection, rendering an optimal blood nulling TI of 142 ± 24 milliseconds. After the 3D acquisition, the LL scan revealed a blood nulling TI of 210 ± 28 milliseconds, resulting in a TI increase of 2.5 ± 0.5 ms/min for adequate blood nulling (interscan interval, 28 ± 8 minutes). No significant differences were found in the average increase per minute between the 2 groups ($P = 0.23$).

The mean blood pool signal intensities in the dynamic TI group were significantly reduced by 72% (70.8 vs 251.6 a.u., $P < 0.001$; Fig. 4) compared with those in the static TI group, indicating improved blood nulling. The standard deviation of mean blood pool signal intensities (for each group) was reduced by 76% in the dynamic TI group (20.3 vs 84.4 a.u.; Fig. 5), indicating superior blood nulling consistency. The sizes of the drawn ROIs (all >600 voxels) were similar in both groups ($P = 0.53$).

Observer confidence and overall image quality were significantly increased when using a dynamic TI compared with a fixed TI ($P = 0.02$ for both). Nineteen cases showed high observer confidence using a dynamic TI, compared with 12 cases using a fixed TI (Fig. 6). In the subgroup of cases with myocardial scar (14 fixed TI group, 17 dynamic TI group), scar demarcation was significantly improved using a dynamic TI ($P = 0.01$) (Fig. 4).

DISCUSSION

The present feasibility study demonstrates the superiority and improved consistency of a steadily increasing dynamic TI for optimized

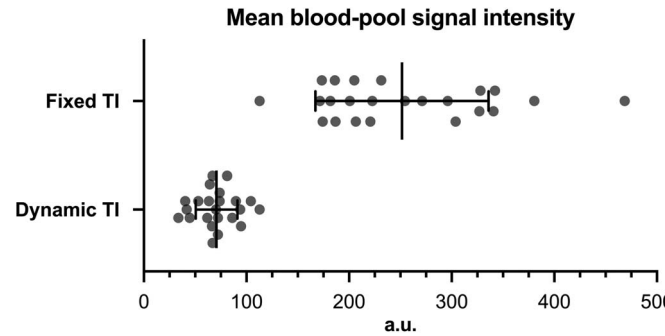

FIGURE 5. Boxplot of the blood pool signal intensities asmeasured on the magnitude images acquired using the conventional fixed TI and steadily increasing dynamic TI. On average, the images aqcuired using a dynamic TI showed a significant reduction of 72% in blood pool signal intensity (ie, improved blood pool nulling) compared with the images acquired using a conventional fixed TI (70.8 vs 251.6 a.u., P < 0.001). The standard deviation in blood pool signal intensity within each group was reduced by 76%in the dynamic TI group compared with the conventional fixed TI group (20.3 vs 84.4 a.u.), indicating improved blood nulling consistency for the dynamic TI.

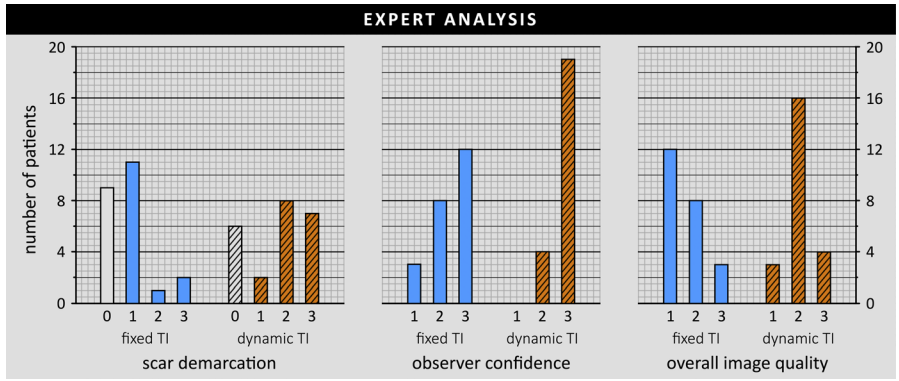

FIGURE 6. Bar graph of the expert analysis on scar demarcation (left panel), observer confidence (center panel), and overall image quality (right panel) scored for both groups using a 3-point scale (1 = low, 2 = medium, 3 = high). Note that the "0" bars for scar demarcation indicate the number of patients with absence of scar tissue.

LV blood pool suppression during free-breathing 3D LGE acquisitions with high isotropic resolution, compared with a conventional fixed TI. The resulting dark-blood contrast led to improved scar demarcation, observer confidence, and overall image quality.

For almost 20 years, fixed TIs have been used to null the signal intensity of viable myocardium in 2D LGE MRI. More recently, fixed TIs have been used for blood pool nulling[7] and infarct nulling.[13] Such fixed TIs are suitable for short 2D breath-hold acquisitions, where the TI can be adjusted immediately before each acquisition. For longer free-breathing 3D whole-heart acquisitions with high isotropic resolution, however, such fixed TIs will increasingly differ from the appropriate TI, resulting in inaccurate nulling of the tissue of interest. Although the PSIR mechanism can partly compensate for small deviations in TI, large differences will build up over prolonged scan durations and cause unexpected and inconsistent signal intensities, resulting in degraded image quality and poor scar-to-blood contrast.

To mitigate this problem, tens of milliseconds are usually added to the starting TI to reach an intermediate fixed TI.[11,12] At the beginning and end of these acquisitions, however, the chosen fixed TI value is substantially off target (Fig. 2). To save scan time and avoid problems with off-target TIs, free-breathing 3D LGE protocols that sacrifice on slice thickness (usually 2–4 mm) have been used.[11,12,14] This, however, results in nonisotropic voxels and therefore poor multiplanar reconstruction possibilities. More recently, highly accelerated 3D acquisitions and reconstruction techniques have been proposed that can acquire high isotropic resolution in just a few minutes.[15] Although such techniques are promising for specific applications, these are less suitable for inversion recovery LGE sequences, often require offline reconstruction afterward, and are not widely available in clinical settings yet.[16] In this study, a readily available steadily increasing TI mechanism was implemented that aims to compensate for the continuous contrast washout to obtain accurate blood pool nulling during the entire scan duration. As a result, consistent dark-blood contrast and high isotropic resolution can be simultaneously acquired in free-breathing 3D LGE acquisitions without requiring patient-dependent adjustments. This dynamic TI mechanism differs from the dynamic TI mechanisms proposed to reduce sensitivity to RR interval variations in patients with cardiac arrhythmias.[17,18]

Clinical benefits of the combined high isotropic resolution and optimized dark-blood contrast reside in the improved detection and visualization of thin subendocardial scar patterns. The importance of accurate scar detection is underlined by a recent study by Antiochos et al,[19] which showed that, compared with recognized myocardial infarction patients, those with unrecognized myocardial infarction were less likely to receive guideline-directed medical therapies and presented an increased risk of heart failure hospitalization. Subtle areas of scarring may remain unrecognized or inaccurately assessed because of the thick 8 to 10 mm slices routinely acquired or by the poor scar-to-blood contrast acquired using conventional bright-blood LGE methods. The improved scar demarcation and observer confidence, achieved by the dynamic TI mechanism in this study, is a promising step toward improved detection and qualification of complex ventricular scar architectures. Further benefits include the improved ability to detect microstructural fibrosis important for patients with presumed idiopathic ventricular fibrillation and the ability to perform accurate multiplanar reconstructions for assessment of papillary muscle scar (see Video, Supplemental Digital Content 1, http://links.lww.com/RLI/A589 which demonstrates the accurate multiplanar reconstruction possibilities using 3D dark-blood LGE MRI with high isotropic resolution). This may pave the way for improved diagnostic accuracy and prognosis, and more personalized treatment of patients with ventricular tachyarrhythmias.

Limitations

Although this dynamic TI mechanism is promising, there are limitations that need to be addressed. First, the interindividual variability of renal clearance and respiratory efficiency may affect the actual per-patient periodic increase for optimal blood pool nulling TI. Despite these uncertainties, blood suppression was improved and more consistent for the dynamic TI group compared with the fixed TI group, even when using the same TI increase of 2.3 ms/min for all patients in the dynamic TI group. Second, a linear increase in TI over time was assumed, whereas this does not fully reflect the more complex clearance of gadolinium-based contrast agents and associated T_1 relaxation rates that mainly determine the required TI for accurate blood pool nulling. We anticipate these effects to have minor impact during the clinically relevant acquisition times in patients with normal renal function. Third, the used commercially available 1-dimensional respiratory navigator, which limits data acquisition to quiescent periods of the breathing cycle, makes the efficiency of this free-breathing sequence highly patient dependent, and leads to unpredictable scan durations (28 ± 9 minutes in this study). Although alternative forms of respiratory motion correction have been proposed in the past, these have not been made widely available by the vendors yet.[20,21] Vendors should therefore focus on translating more advanced respiratory motion correction strategies to the clinic. Finally, because all scans were performed as routine workup, every patient underwent high-resolution 3D LGE MRI only once. The combination of scan duration and contrast washout did not allow for performing both TI methods during the same scan, hindering a direct comparison in scar assessment for this feasibility study. Future research should therefore focus on scar quantification using both methods and include patients with various cardiac pathologies.

CONCLUSIONS

The use of a steadily increasing dynamic TI improves LV blood suppression and consistency for optimized dark-blood contrast in free-breathing 3D LGE acquisitions with high isotropic resolution. The use of a dynamic TI led to improved scar demarcation, observer confidence, and overall image quality. The combination of high isotropic resolution and optimized dark-blood contrast provides a promising diagnostic tool for improved myocardial scar assessment.

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