OBJECTIVES This study introduced and validated a novel flow-independent delayed enhancement technique that shows hyperenhanced myocardium while simultaneously suppressing blood-pool signal.

BACKGROUND The diagnosis and assessment of myocardial infarction (MI) is crucial in determining clinical management and prognosis. Although delayed enhancement cardiac magnetic resonance (DE-CMR) is an in vivo reference standard for imaging MI, an important limitation is poor delineation between hyperenhanced myocardium and bright LV cavity blood-pool, which may cause many infarcts to become invisible.

METHODS A canine model with pathology as the reference standard was used for validation (n = 22). Patients with MI and normal controls were studied to ascertain clinical performance (n = 31).

RESULTS In canines, the flow-independent dark-blood delayed enhancement (FIDDLE) technique was superior to conventional DE-CMR for the detection of MI, with higher sensitivity (96% vs. 85%, respectively; p = 0.002) and accuracy (95% vs. 87%, respectively; p = 0.01) and with similar specificity (92% vs. 92%, respectively; p = 1.0). In infarcts that were identified by both techniques, the entire length of the endocardial border between infarcted myocardium and adjacent blood-pool was visualized in 33% for DE-CMR compared with 100% for FIDDLE. There was better agreement for FIDDLE-measured infarct size than for DE-CMR infarct size (95% limits-of-agreement, 2.1% vs. 5.5%, respectively; p < 0.0001). In patients, findings were similar. FIDDLE demonstrated higher accuracy for diagnosis of MI than DE-CMR (100% [95% confidence interval (CI): 89% to 100%] vs. 84% [95% CI: 66% to 95%], respectively; p = 0.03).

CONCLUSIONS The study introduced and validated a novel CMR technique that improves the discrimination of the border between infarcted myocardium and adjacent blood-pool. This dark-blood technique provides diagnostic performance that is superior to that of the current in vivo reference standard for the imaging diagnosis of MI.

Even when the diagnosis of MI is known, assessment of the size, location, and transmural extent of infarction is important for patient management decisions, such as whether to undergo coronary revascularization, resynchronization therapy, or cardioverter-defibrillator insertion (2).
Delayed enhancement cardiac magnetic resonance (DE-CMR) is considered the in vivo reference standard for imaging MI, given its ability to generate high resolution spatial maps of infarcted and viable myocardium. Accordingly, it is being used increasingly in clinical practice and in randomized trials evaluating novel MI treatments, to provide a measure of therapeutic efficacy (2).

One important limitation of DE-CMR, however, is that infarcted myocardium and the left ventricle (LV) blood-pool are often hyperenhanced to a similar degree following administration of contrast agent (3). Hence, infarcted myocardium may be hidden when immediately adjacent to the LV cavity because there is poor delineation between bright tissue and bright blood-pool. This may explain why a recent multicenter trial evaluating the performance of DE-CMR demonstrated that up to 21% of infarcts may be missed in select patient cohorts (i.e., those with non-Q-wave chronic MI) (4).

Conventional “black-blood” CMR techniques provide improved delineation of tissue by suppressing signal from adjacent blood-pool (5). However, these techniques depend upon the long $T_1$ (longitudinal relaxation time) of blood (~2 s at 3-T) and sufficient blood flow within this time period to generate black-blood images. Hence, conventional techniques are not designed to work after contrast administration (which greatly shortens blood $T_1$) and cannot be used to provide contrast-enhanced, black-blood images of tissues.

In this study, we introduced a novel flow-independent dark-blood delayed enhancement (FIDDLE) technique that allows visualization of tissue contrast enhancement while simultaneously suppressing blood-pool signal. We validated FIDDLE in an animal model of MI and demonstrated its clinical performance in patients.

**METHODS**

**FLOW-INDEPENDENT DARK-BLOOD DELAYED ENHANCEMENT.** The pulse sequence timing diagram and evolution of longitudinal magnetization for different primary tissue components are shown in Figure 1 (6,7). The primary components are: 1) a preparatory module that affects the magnetization of myocardium differently than blood; 2) an inversion-recovery pulse (IR); 3) phase-sensitive reconstruction; and 4) an inversion time (TI) selected such that blood magnetization is less than tissue.

Because the magnetization of blood ($M_0$) is made more negative than normal myocardium (i.e., blood $M_z <$ myocardial $M_z$; aka, black-blood condition), phase-sensitive reconstruction renders blood in the cardiac chambers darker than myocardium by remapping the magnetization to positive-only values. As a result, a precise TI is not needed to make the blood black, rather, a range of TIs can be used, as long as the magnetization of blood is more negative than that of myocardium (Figure 1).

**PILOT STUDY.** Theoretically, any pulse that affects the magnetization of myocardium differently than blood can be used as the initial preparatory module (8). We chose a magnetization transfer (MT) module and performed a pilot study prior to the main investigation in a canine model. The pilot study involved 2 parts: first, empirical data were acquired in vivo to characterize the effects of the MT preparation (MT-PREP) module on the magnetization of normal myocardium, infarcted myocardium, and blood-pool; and second, the data from these in vivo experiments were used to simulate the effects of TI on the signal intensity of these tissues.

For the pilot in vivo experiments, the animal preparation was the same as that for the main study (details below) but performed in a separate cohort of canines. Imaging was performed 15 min after intravenous administration of gadoversetamide (0.15 mmol/kg), using an MT-PREP module (a train of gaussian radiofrequency pulses each of which is 5.12 ms in duration) that was immediately followed by a single-shot steady-state free-precession (SSFP) readout. The effects of MT-PREP train length (1 to 20 repetitions in steps of 1), flip angle (20° to 90° in steps of 50°), and off-resonance frequency (200 to 1,500 Hz in steps of 100 Hz) on tissue magnetization were measured.

Simulations were then performed using Matlab software (MathWorks, Natick, Massachusetts). The effects of readout pulses, diffusion, and imperfections in the inversion pulse were assumed to be negligible. Longitudinal magnetization following the MT-PREP and IR pulse for a given tissue species ($a$) as a function of time ($t$) was expressed as:

$$M_a(t) = M_{0,a} - \left[MT_{\text{eff}} + M_{0,a}\right]\exp(-t/T_{1,a})$$

(Equation 1)

where $M_{0,a}$ is the equilibrium magnetization of each tissue species, $MT_{\text{eff}}$ is the signal immediately after the MT-PREP (based on the canine data), and $T_{1,a}$ is the $T_1$ of the species, $T_1$ values of 410 ms, 630 ms, and

**ABBREVIATIONS AND ACRONYMS**

- **CNR** = contrast-to-noise ratio
- **DE-CMR** = delayed enhancement cardiac magnetic resonance
- **FIDDLE** = flow-independent dark-blood delayed enhancement
- **MT-PREP** = magnetization transfer preparation
- **IR** = inversion recovery
- **LV** = left ventricle
- **$M_0$** = baseline longitudinal magnetization
- **SAR** = specific absorption rate
- **SNR** = signal-to-noise ratio
- **SSFP** = steady state free precession
- **$T$** = Tesla
- **$T_1$** = inversion time
- **$T_1,a$** = $T_1$ of the species
- **$a$** = tissue species

**Figure 1**

Figure 1 of myocardium differently than blood; 2) an preparatory module that affects the magnetization of normal myocardium, infarcted myocardium, and blood-pool; and second, the data from these in vivo experiments were used to simulate the effects of TI on the signal intensity of these tissues.
440 ms for infarct, normal myocardium (myo), and blood, respectively, were used assuming typical conditions for delayed enhancement imaging at 3-T (9). Following phase-sensitive reconstruction, and assuming the black-blood condition (\(M_{\text{blood}}[t] \leq \min\{M_{\text{myo}}[t], M_{\text{infarct}}[t]\}\)), the signal of normal myocardial tissue (or infarcted tissue) normalized to equilibrium magnetization was calculated as:

\[
FIDDLE_{\text{myo/or infarct}}(t) = \frac{M_{\text{myo/or infarct}}(t) - M_{\text{blood}}(t)}{M_{0,\text{myo/or infarct}}};
\]

(Equation 2)

**CANINE PROTOCOL OVERVIEW AND PATHOLOGY.** Following optimization of the MT-PREP module in the pilot study, the diagnostic performance of FIDDLE was assessed by using pathology as the reference standard. For both the pilot and main investigations, the same canine model of MI was used. MI was produced by occluding the left anterior descending coronary artery or the left circumflex artery (obtuse marginal branch) under sterile conditions after a thoracotomy was performed. To investigate a wide range of infarct sizes and transmurality, we used a range of occlusion times (40 to 90 min), followed by reperfusion (10). As a point of reference, a 40-min occlusion in the canine model led to a sub-endocardial infarct that averaged 38% transmurality (11). The care and treatment of canines followed the Position of the American Heart Association on Research Animal Use (12). The protocol was approved by the Duke University Institutional Animal Care and Use Committee.

Following CMR, the heart was removed, and the infarcted region was confirmed using histochemical staining (13).
Cardiac magnetic resonance was performed over a range of time points following MI to test whether infarct age might affect the performance of FIDDLE. The range was 2 days to 7 months, with 14 scanned within the first 2 weeks, and 8 after 2 weeks (median 14 weeks). Images were acquired using a 3-T Verio model (Siemens, Malvern, Pennsylvania) during ventilated breath holds. DE-CMR and FIDDLE were performed immediately after one another in random order, using matched parameters (e.g., slice thickness: 7 mm; in-plane spatial resolution: 1.2 x 1.0 mm; temporal resolution: 180 ms; TR: 2 R-R intervals; breath hold time: 8 to 10 s) 15 min after intravenous administration of gadoversetamide (0.15 mmol/kg).

A segmented, IR gradient-echo sequence was used for DE-CMR, with TI manually selected to null signal from normal myocardium (4). FIDDLE consisted of an MT-PREP module and IR pulse, followed by a segmented SSFP readout (TE: 1.36 ms; flip angle: 50°; bandwidth: 975 Hz/pixel; average: 2). Parameters for the MT-PREP module were selected based on the findings from the pilot study (train length: 19; flip angle: 500°; offset frequency: 800 Hz). The TI was manually selected to render blood black and maximize image contrast between infarcted and normal myocardium. This was performed by selecting the longest TI (typically, 200 to 280 ms) that still resulted in black-blood. A complete short-axis stack of DE-CMR and FIDDLE images were obtained.

Pathology slices were registered with CMR images by using myocardial landmarks. Pathology, FIDDLE, and DE-CMR studies were read separately, blinded to other data. Window and level for CMR images were preset so that noise was still detectable and infarcted regions were not over-saturated (14). The presence of MI was determined by visual inspection. Images were also examined to determine whether the entire length of the infarct subendocardial border could be distinguished from the adjacent blood-pool. Infarct size (%LV mass) was measured by planimetry of the stack of short-axis pathology and CMR images. The transmural extent of infarction was expressed as the percentage of myocardial sector area on a slice-by-slice basis (10). Measurements were performed at our core laboratory, which undergoes regular audits and testing for quality assurance (e.g., inter- and intraobserver agreement of infarct size demonstrated a bias of 1.0% and -0.1%, respectively, with a standard deviation of differences of 2.6% and 0.8%, respectively).

Patients presenting with a history of MI were recruited prospectively. The diagnosis of MI was based on the Universal Definition. Patients <18 years of age or with a history of multiple infarcts were excluded. Consecutive patients who underwent coronary angiography during admission for MI in whom the culprit infarct-related artery was clearly identified and who agreed to participate were enrolled. The control group consisted of subjects with no known coronary disease and with low probability for developing disease over the next 10 years (lowest Framingham risk score: 1% for women, 2% for men) (15). All participants gave written informed consent, which was approved by the Duke University Institutional Review Board.

The CMR protocol was the same as that in the canine study, and the same sequences were used at similar settings. However, to test the generalizability of FIDDLE, one-half of the patients were scanned at 3-T and one half at 1.5-T. FIDDLE and DE-CMR were performed using matched parameters (at 3-T the slice thickness was 6 mm; in-plane spatial resolution: 1.7 x 1.3 mm; temporal resolution: 180 ms; TR: 2 R-R intervals. At 1.5-T, the slice thickness was 8 mm; in-plane spatial resolution: 1.9 x 1.4 mm; temporal resolution: 180 ms; TR: 2 R-R intervals). FIDDLE incorporated 2 averages; however, the breathhold time was the same as for DE-CMR (~8 to 10 s) because FIDDLE used an SSFP readout with twice the k-spaces per segment (59 vs. 29, respectively). The MT-PREP parameters at 3-T (train length: 19; flip angle: 500°; offset frequency: 800 Hz) and at 1.5-T (train length: 19; flip angle: 500°; offset frequency: 600 Hz) were similar.

Images were obtained 15 min after intravenous administration of gadoversetamide (0.15 mmol/kg) in multiple short-axis (every 10 mm throughout the LV) and 3 long-axis views. CMR analysis was the same as that for canines, and FIDDLE and DE-CMR were interpreted independently, masked as to patient identity and clinical information. Additionally, CMR images were scored on a 17-segment model to determine the infarct locations. Coronary angiograms, in patients with MI, were read blinded to all other information and analyzed in order to localize the perfusion territory of the infarct-related artery on a 17-segment model (4). CMR localization of infarction was categorized as correct or incorrect based upon the match with the infarct-related artery perfusion territory on coronary angiography, as previously described (4).

Specific Absorption Rate. All scans were performed under strict adherence to U.S. Food and Drug Administration guidelines for specific absorption rates (SAR) (<4 W/kg averaged over the whole body for any 15-min period). The vendor calculated
whole-body SAR was collected from the Digital Imaging and Communications in Medicine (DICOM) header.

**CONTRAST-TO-NOISE RATIO.** A separate group of patients, all with a clearly identifiable infarct on conventional DE-CMR, were recruited in order to measure infarct-to-normal myocardium contrast-to-noise ratio (CNR). Both FIDDLE and DE-CMR images were obtained and then reconstructed directly in signal-to-noise ratio (SNR) units (16). CNR was calculated by subtracting the SNR from manually drawn regions of interest on the SNR scaled image reconstructions.

**STATISTICAL ANALYSIS.** Continuous data are presented as mean ± SD or as median and interquartile range as appropriate. McNemar’s test was used to compare the diagnostic performance of methods. Linear regression analysis was used to compare the relationships between infarct size by CMR and pathology, accounting for measurements from the same subject. Bland-Altman analysis was performed to assess the agreement between CMR and pathology measurements but modified to use the pathology measurements as the reference. Statistical tests were 2-tailed. A p value <0.05 was considered significant. SAS software (Cary, North Carolina) was used to perform analyses.

**RESULTS**

**PILOT STUDY.** The effects of the MT-PREP parameters on in vivo tissue signal were measured in 8 canines with 1-week-old MIs. Increasing train length, increasing flip angle, and decreasing off-resonance frequency reduced signal intensity for all tissues (Figure 2A). However, the effect was substantially increased for myocardium compared with that for blood. Differences between normal and infarcted myocardium were negligible.

These data were then used to model the signal behavior of FIDDLE (Figure 2B). These simulations showed 1) blood-pool signal is nulled (i.e., black-blood condition is met) over a wide range of MT-PREP train lengths and TIs (Figure 2B, red arrows); 2) infarct signal was high over a wide range, leading to large differences in signal between infarcted myocardium and blood; and 3) when blood-pool signal was nulled, longer TIs led to increased signal differences between normal and infarcted myocardium.

**CANINES.** The performance of FIDDLE was assessed in 22 canines. Data from all canines surviving surgery were included. Examples of in vivo CMR are shown in Figure 3A. In subjects 1 to 3, hyperenhanced regions are visible on DE-CMR and appeared to match the infarcted regions by pathology (Figure 3A, blue arrows). In subjects 4 and 5, the exact borders between hyperenhanced myocardium on DE-CMR and the bright LV cavity blood-pool were not always clear. In contradistinction, for all 5 subjects, hyperenhanced regions are clearly visible on FIDDLE, and the complete borders are easily distinguished from adjacent blood-pool and normal myocardium (Figure 3A). Moreover, the shape and contour of hyperenhancement on FIDDLE closely resembled the infarcted regions by pathology.

Figure 3B shows comparisons in 1 subject at multiple short-axis locations. Pathology demonstrated a small subendocardial infarct involving the inter- and the posteromedial papillary muscle, spanning from the base to the apex. The infarct is clearly depicted by FIDDLE but is poorly visualized by DE-CMR on many short-axis locations.

Table 1 summarizes the diagnostic performance of FIDDLE and DE-CMR for the diagnosis of MI compared to that of pathology (n = 136 slices). Overall, sensitivity and accuracy for FIDDLE (96% and 95%, respectively) were higher than those for DE-CMR (85% and 87%, respectively). Specificity was similarly high for both. When only pathology slices with ≥25% transmural infarction were considered (n = 87), sensitivity and accuracy remained high for FIDDLE and were again significantly higher than that for DE-CMR (sensitivity: 98% vs. 80%; accuracy: 95% vs. 85%; p ≤ 0.02 for both). Specificity remained 92% for both.

There was no relationship between infarct age and diagnostic performance of FIDDLE. Accuracy was 93% for MI ≤2 weeks old and 97% for MI >2 weeks old (p = 0.35). In infarcts that were identified by both techniques, the entire length of the endocardial border between infarcted myocardium and adjacent blood-pool was visualized in 100% for FIDDLE compared with 33% for DE-CMR. There was no evidence of “slow blood flow” artifacts in the LV cavity in any of the FIDDLE images.

On a per-subject basis, infarct size by FIDDLE (r = 0.99) and DE-CMR (r = 0.98) were highly correlated with infarct size by pathology (Figure 4A). Bland-Altman analyses demonstrated that the level of agreement was high for both comparisons with pathology (Figure 4B). However, DE-CMR showed a small but significant bias (−1.1%; p = 0.001), whereas, FIDDLE showed no bias (−0.01%; p = 0.38). Additionally, 95% limits-of-agreement were larger for DE-CMR (−3.9%, 1.6%) compared with FIDDLE (−1.1%, 0.9%).
**PATIENTS.** We enrolled 31 subjects (20 with MI, 11 normal controls), all of whom successfully completed CMR studies. No subject was excluded based on poor image quality. The SAR for FIDDLE was 0.76 W/kg at 1.5T and 1.97 W/kg at 3T, and there were no issues with exceeding FDA SAR constraints in any patient.

**Table 2** shows the baseline clinical characteristics. Among patients with MI, 10 were imaged ≤2 weeks post MI, and 10 were imaged >2 weeks post MI (median: 24 weeks). In all 20 patients with MI, the infarcted region on FIDDLE matched the perfusion territory of the infarct-related artery identified by x-ray coronary angiography. There was no evidence of “slow blood flow” artifacts in the LV cavity in any of the FIDDLE images.

**Figure 5A** shows typical images in MI patients in whom both FIDDLE and DE-CMR clearly depicted infarcted regions. **Figure 5B** shows images in 5 patients (n = 3 with MI, n = 2 control patients without MI) in whom the diagnosis of MI was ambiguous on DE-CMR. With FIDDLE, patients with MI were easily distinguished from the controls.
Overall, the diagnostic performance in patients was similar to that observed in canines (Table 1), and there were no differences between the findings at 3-T (n = 15) and those at 1.5-T (n = 16). Accuracy was higher for FIDDLE than DE-CMR (100% vs. 84%, respectively). Also, there were trends toward higher sensitivity (100% vs. 85%, respectively) and higher specificity (100% vs. 82%, respectively).

The CNR between infarct and normal myocardium was measured in 11 additional patients, all of whom had a clearly identifiable infarct on DE-CMR. At 1.5-T, the mean CNRs for DE-CMR and FIDDLE were 11.0 ± 5.8 and 9.5 ± 3.5, respectively, reflecting an average 14% loss for FIDDLE. At 3-T, CNRs were 11.3 ± 4.1 and 10.1 ± 2.6, respectively, representing an average 10% loss.
In this study, we introduced FIDDLE, a new CMR technique that allows visualization of myocardial tissue contrast enhancement while simultaneously rendering the blood-pool black. FIDDLE was characterized in simulations and validated in a canine model of MI, with direct reference to pathology. The clinical performance of FIDDLE was demonstrated in patients with documented MI and known coronary artery anatomy. FIDDLE provided diagnostic performance superior to that of conventional DE-CMR, the current in vivo reference standard for the imaging diagnosis of MI.

<table>
<thead>
<tr>
<th>TABLE 1 Diagnostic Performance of FIDDLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Subjects</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Canines</td>
</tr>
<tr>
<td>DE-CMR</td>
</tr>
<tr>
<td>FIDDLE</td>
</tr>
<tr>
<td>p value</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>DE-CMR</td>
</tr>
<tr>
<td>FIDDLE</td>
</tr>
<tr>
<td>p value</td>
</tr>
</tbody>
</table>

Values n/total; % (95% CI).

DE-CMR = delayed enhancement cardiac magnetic resonance; FIDDLE = flow-independent dark-blood delayed enhancement.

DISCUSSION

Figure 4

(A) Linear regression and (B) Bland-Altman plots demonstrating higher correlation and better agreement with FIDDLE. See text for details. LV = left ventricle; other abbreviations as in Figure 1.
TABLE 2  Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>MI Patients (n = 20)</th>
<th>Normal Controls (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56 ± 14</td>
<td>32 ± 11</td>
</tr>
<tr>
<td>Females</td>
<td>8 (40)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (60)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (70)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>8 (40)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>ECG at MI admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>13 (65)</td>
<td>-</td>
</tr>
<tr>
<td>Non-ST-segment elevation</td>
<td>7 (35)</td>
<td>-</td>
</tr>
<tr>
<td>Troponin T, ng/mL*</td>
<td>7.6 (4.0–11.9)</td>
<td>-</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>10 (50)</td>
<td>-</td>
</tr>
<tr>
<td>LCx</td>
<td>7 (35)</td>
<td>-</td>
</tr>
<tr>
<td>RCA</td>
<td>3 (15)</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n (%), or median (interquartile range). *Troponin I was used in the diagnosis of acute MI in 4 patients.

In canines, sensitivity and accuracy were significantly higher for FIDDLE, whereas specificity was excellent for both techniques. Findings were similar in patients, where FIDDLE had a diagnostic accuracy of 100% versus 84% for DE-CMR.

FIDDLE overcomes an important intrinsic limitation of conventional DE-CMR. Because infarcted myocardium and adjacent blood-pool have comparable T1 values following contrast media administration (9), image intensities are often similar on DE-CMR (3). As a result, distinguishing hyperenhanced infarcted tissue from bright blood-pool may be difficult, unless the infarct is fully transmural or nearly so. This may explain why the diagnostic performance of DE-CMR is reduced in some cohorts, such as patients with non-Q-wave MI who are more likely to have infarcts that are subendocardial (4). Consistent with this notion, in the current study, when only subendocardial infarcts were considered, the sensitivity of DE-CMR dropped to 80%, whereas it remained high for FIDDLE at 98%.

Although this may suggest that the primary advantage of FIDDLE is in patients with small infarcts, we observed that some infarcts missed by DE-CMR can be relatively large. An example of such a case is shown in patient 9 (Figure 5B), who had an infarct size of 14% of LV mass as measured by FIDDLE. This demonstrates that an infarct can be extensive in the circumferential direction but still be subendocardial and missed by DE-CMR.

Even when infarction was identified by DE-CMR, the data indicate that it was rare to visualize the entire length of the MI endocardial border, in contradistinction to FIDDLE images for which the entire border was always visualized. Hence, infarct size measurements were more robust with FIDDLE than with DE-CMR; in comparison to pathology, there was reduced bias and smaller 95% limits of agreement with FIDDLE.

Several approaches for improving the discrimination of blood-pool and infarcted myocardium have been proposed. Some are dependent on the motion of blood in the LV cavity, either as bulk flow or diffusion (17). These techniques are limited in that “slow blood flow” artifacts, which are bright and difficult to distinguish from subendocardial infarction, are likely to occur in patients with ventricular dysfunction. Unlike these approaches, FIDDLE uses a novel method which is not dependent on the movement of blood. In the current study, there was no evidence of “slow blood flow” artifacts in any of the FIDDLE images, including long-axis views. Nonetheless, it should be noted that inhomogeneities in B1 (applied radiofrequency field) and B0 (static magnetic field) may affect the uniformity of dark-blood preparation, particularly at 3-T.

Other techniques have been proposed that are not dependent on blood flow. Liu et al. (18) described a technique that combined $T_2$ and $T_1$ weighting to improve the delineation between infarcted myocardium and ventricular blood-pool. Peel et al. (19) described a method that used a dual IR prepulse to suppress blood-pool signal. Although contrast between infarcted myocardium and blood-pool may be improved with these techniques, the level of blood suppression may be minimal. Unlike FIDDLE, none of these methods produced black-blood images. Specifically, these methods resulted in images in which blood-pool signal was higher than viable myocardium, hence, an endocardial layer that is partially infarcted may still be difficult to distinguish from blood-pool.

FIDDLE was designed to be flexible and modular in order to accommodate different preparation pulses, execution orders, and readout types. Since its first description by our group in 2011 (6), some pilot studies with variants of FIDDLE have been reported (8,16,20). Muscogiuri et al. (20) used a $T_2$-rho-PREP variant of FIDDLE and reported that this technique detected more patients with infarction than DE-CMR in patients with suspected MI. They speculated that one possible benefit of a $T_2$-rho-PREP over an MT-PREP was that the latter may have high energy requirements. However, with the sequence described herein, we did not encounter this problem. There
were no issues with exceeding SAR constraints in any of the patients scanned at 1.5-T or 3-T.

Kellman et al. (16) described a T2-PREP variant of FIDDLE, albeit the order of the T2- and IR preparations were reversed. This variant also combines single-shot SSFP readout with motion correction in order to allow imaging during free-breathing. In a pilot study of 30 patients in which 1 slice location was imaged per patient, with both dark-blood and bright-blood techniques, they reported that the conspicuousness of subendocardial fibrosis was improved by dark-blood imaging. Unfortunately, there was no reference standard for the diagnosis of fibrosis; hence, the diagnostic accuracy of dark-blood imaging was not assessed. In comparison, the current study is the first to validate dark-blood delayed enhancement imaging.

**FIGURE 5** Patient Examples of FIDDLE and DE-CMR

- **A** Clearly delineated infarct on DE-CMR and FIDDLE
  - Patient 1
  - Patient 2
  - Patient 3
  - Patient 4

- **B** Ambiguous DE-CMR that is resolved with FIDDLE
  - Patient 5
  - Patient 6
  - Patient 7
  - Patient 8
  - Patient 9

(A) Images obtained in 4 patients in whom the infarct is clearly delineated on both FIDDLE and DE-CMR images. Notably, there are no “slow flow” artifacts in any of the short- or long-axis FIDDLE images. (B) Images obtained in 3 patients with MI and 2 controls. In patients 5 and 6, there is possibly anteroseptal wall hyperenhancement on DE-CMR (red arrows). However, FIDDLE shows no hyperenhancement and correctly identifies patient 6 as a normal control. In patients 7 and 8, FIDDLE identifies the fact that patient 8 is a normal control. In patient 9, FIDDLE clearly demonstrates not only a subendocardial infarct in the anterior wall but also extension into the inferoapical wall (blue arrows). IRA = infarct-related artery; LAD = left anterior descending; LCx = left circumflex; MI = myocardial infarction; RCA = right coronary artery.
imaging (of any type) directly in comparison with a pathology-based reference standard. Additionally, high diagnostic accuracy was verified in patients, and imaging in patients was performed at both 1.5-T and 3-T field strengths to increase the generalizability of the findings.

Recently, our group compared a T₂-PREP variant of FIDDLE with MT-PREP FIDDLE (8). We observed that T₂-PREP FIDDLE was more likely to result in artifacts in the left atrial cavity, which appeared to be secondary to nonuniform magnetization preparation, particularly at 3-T. Additionally, T₂-PREP FIDDLE occasionally resulted in different levels of blood-pool suppression in the right versus left-sided cardiac chambers. This is because deoxygenated blood in the right-sided chambers has shorter T₂ than the oxygenated blood in the left-sided chambers. Although these findings suggest potential advantages with MT-PREP, these are only preliminary data; further investigation is needed.

From an efficiency standpoint, FIDDLE is essentially identical to DE-CMR. No additional post-processing or image registration is required, and image reconstruction is completed at the time of image acquisition. The same dose of contrast medium is used, and imaging can be performed at the same time point after contrast administration. Moreover, spatial resolution, temporal resolution, and breath-hold duration (8 to 10 s) were identical in this study. In other words, the implementation of FIDDLE reported herein was designed to be a “drag-and-drop” replacement for conventional DE-CMR.

Additionally, setting the TI for FIDDLE is straightforward. One examines the image intensity of the blood-pool: if the blood-pool is not black, the TI needs to be reduced; whereas, if the blood-pool is black then the TI should be increased to the maximum value that still results in black-blood. Generally, 1 to 2 scout images are sufficient to find the optimal TI, but nonetheless, this is a limitation that can lengthen scan time. Given its diagnostic performance and ease of use, FIDDLE has become a core component of our clinical CMR examination, and we are currently using it daily at both 1.5- and 3-T.

There are several implications of our study. Our data suggest that, even in the modern era, the imaging diagnosis of MI can be difficult and that new methods may improve decision making, risk stratification, and management. Moreover, the data suggest that the most important source of variability in infarct size measurements by DE-CMR is the uncertainty in identifying the border between infarction and LV blood-pool. The reduced variability associated with FIDDLE is expected to be important in clinical trials that use infarct size as a surrogate endpoint. In the current study, patients with known MI were enrolled in order to validate FIDDLE. In the future, studies in patients with suspected rather than clinically confirmed MI will be needed. It should be noted that FIDDLE provides a general approach to improve contrast-enhanced imaging of tissue pathology by separating parenchymal contrast enhancement from blood-pool enhancement. Hence, the technique may have broad applicability in visualizing other pathologies throughout the heart and cardiovascular system (e.g., atrial fibrosis, aortopathies, and others). This will need to be evaluated in future investigations.

CONCLUSIONS

Our results demonstrate that FIDDLE provides diagnostic performance superior to that of the current in vivo reference standard for the imaging diagnosis of MI.

ADDRESS FOR CORRESPONDENCE: Dr. Raymond J. Kim, Duke Cardiovascular Magnetic Resonance Center, Duke University Medical Center, DUMC-3934, Trent Drive, Durham, North Carolina. E-mail: raymond.kim@duke.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: FIDDLE, a novel flow independent dark-blood delayed enhancement CMR technique, is described and validated in comparison with pathology in an animal model of myocardial infarction. Comparisons with conventional delayed enhancement CMR, the current in vivo reference standard for imaging myocardial infarction, demonstrated that FIDDLE has higher diagnostic accuracy and provides more accurate infarct size measurements. Findings were replicated in patients, where FIDDLE also showed higher accuracy than delayed enhancement CMR for the diagnosis of myocardial infarction.

TRANSLATIONAL OUTLOOK: Future studies will further elucidate the role of FIDDLE in identifying infarction, fibrosis, or scarring in patients with coronary artery disease and non-ischemic cardiomyopathies. FIDDLE may provide a new avenue to explore pathologies involving the right ventricle, atria, and other tissues where blood pool enhancement may mask tissue enhancement, as well as improve the quantification of infarct size, which is an important surrogate endpoint in clinical trials.
REFERENCES


KEY WORDS cardiac magnetic resonance, diagnosis, infarct size, myocardial infarction