Flow-Independent Dark-Blood Delayed Enhancement (FIDDLE)

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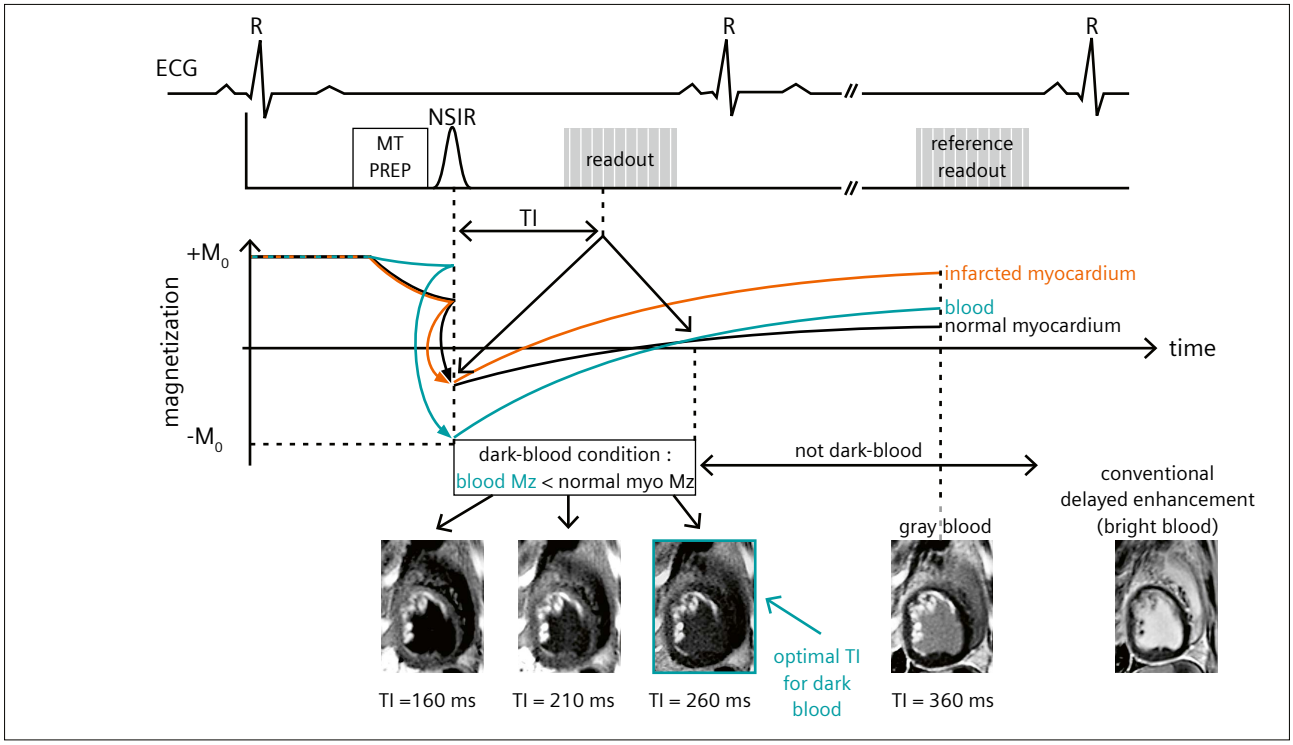
Abstract and key points

Delayed enhancement MRI is regarded as the imaging gold standard for the *in vivo* diagnosis of myocardial infarction. However, infarcted myocardium and ventricular blood pool possess similar signal intensities after contrast agent administration. Therefore infarcted myocardium immediately adjacent to the blood pool may not be detected in some cases. This problem is overcome in the flow independent dark-blood delayed enhancement (FIDDLE) technique[1] by improving the contrast between blood-pool and myocardium leading to an even higher accuracy in infarct detection than in conventional delayed enhancement. In this publication, we explain the mechanism behind creating contrast-enhanced dark-blood images with FIDDLE, and we give image examples in both ischemic and nonischemic heart disease patients.

[1]*The product is still under development and not commercially available yet. Its future availability cannot be ensured.*



1 Conceptual diagram of the FIDDLE sequence showing its core components: a tissue-signal-attenuating preparatory module, in this example using a series of magnetization transfer (MT) pulses (MT-prep); a non-selective inversion recovery (NSIR) pulse for imparting T1-weighting; a readout and reference readout for phase-sensitive IR (PSIR) reconstruction, and an inversion time (TI) which renders blood magnetization smaller than tissue magnetization (dark-blood condition). Even with TI outside the dark-blood condition (TI > 260 ms in this example), blood-pool signal is suppressed compared with conventional DE-MRI, improving the conspicuousness of infarcted myocardium. This is known as gray-blood imaging. ECG = electrocardiogram; M_0 = baseline longitudinal magnetization; M_z = blood or tissue magnetization.

The role of delayed-enhancement imaging in cardiac MRI

Cardiac MRI has emerged as a leading non-invasive imaging tool with a broad range of applications for cardiology. Much of the strength of cardiac MRI rests on its ability to differentiate healthy and diseased tissue using the delayed-enhancement MRI (DE-MRI) technique. The detection of myocardial damage is essential, as even small amounts of dead tissue are associated with a poor prognosis [1].

DE-MRI is regarded as the reference standard for the *in vivo* diagnosis of myocardial infarction (MI), owing in part to its high spatial resolution and excellent contrast between infarcted and normal myocardium. However, an important limitation is that the infarcted tissue and the ventricular blood pools possess similar signal intensities after contrast agent administration [2]. Hence, infarcted myocardium may be hidden if it is immediately adjacent to the blood pool, since there is poor delineation between bright tissue and bright blood. Thus, techniques that improve the contrast between blood-pool and adjacent myocardium were needed to improve the sensitivity of DE-MRI.

The evolution of dark-blood techniques

The development of dark-blood methods that provide blood-pool suppression after contrast agent administration required a break from conventional dark-blood techniques. Traditional dark-blood MRI [3, 4] depends upon the long T1 of blood (about 2 seconds at 3T) and sufficient blood flow between the dark-blood preparation and the data readout. The time between these two events allows inverted blood magnetization to recover to approximately zero and thus generate zero-blood signal, i.e. dark blood. However, after contrast media administration, the T1 of blood is greatly shortened, and thus the traditional method cannot be used to provide contrast-enhanced, dark-blood images.

Several approaches to improve discrimination of post-contrast blood-pool and infarcted myocardium have been proposed. Some are dependent on the motion of blood in the cavities, as either bulk flow [5, 6] or diffusion [7]. 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, i.e. those most in need of cardiac imaging.

Other techniques have been proposed that are not dependent on blood flow. For example, Kellman et al. [8] describe a multi-contrast technique that acquires two separate images: one T2-weighted and one T1-weighted image. Liu et al. [9] describe a technique that is similar but combines T1- and T2-weighting in a single image. Foo et al. [10] describe a dual inversion time subtraction method which uses two acquisitions, at a long and short inversion time, respectively, to improve the delineation between infarcted myocardium and ventricular blood-pool. Peel et al. [11] describe a dual IR prep module to suppress blood-pool signal. However, none of these flow independent techniques have been adopted into clinical routine, perhaps in part due to the increased time and complexity of image acquisition. All of these methods result in images in which blood-pool signal is reduced compared to conventional delayed enhancement, but still higher than viable myocardium. Therefore, an endocardial layer that is partially infarcted may still be difficult to distinguish from the blood-pool.

A new class of dark-blood techniques such as Flow-Independent Dark-blood DeLayed Enhancement (FIDDLE) were developed in 2011 [12] to overcome these limitations and allow simultaneous visualization of contrast-enhanced tissue and a dark blood pool [13–15]. FIDDLE generates these contrast-enhanced dark-blood images through a combination of

- a non-selective tissue signal-reducing preparation module,
- a non-selective inversion recovery (IR) pulse,
- a phase-sensitive IR (PSIR) reconstruction [16], and
- the selection of an inversion time (TI) such that blood magnetization is lower than tissue magnetization and infarct magnetization is higher.

The resulting PSIR images simultaneously show contrast enhanced tissue and dark-blood (Fig. 1). It is worth mentioning that the blood is not dark because it is 'nulled' as in traditional dark-blood magnitude images. Instead, it appears dark in FIDDLE images, because they are PSIR images and as such depict the smallest magnetization as the darkest, irrespective of its absolute value.

Also owing to the PSIR reconstruction, a precise TI is not needed to yield dark blood, rather a range of TIs can be used, as long as the magnetization of blood is lower than myocardium; see the FIDDLE images with a range of inversion times fulfilling the dark-blood condition in Figure 1. However, among these TI values, choosing the longest one results in the best infarct-to-myocardium contrast. Interestingly, selecting longer TI values in FIDDLE can create gray-blood images with still better infarct-to-blood contrast than traditional (bright-blood) delayed enhancement.

FIDDLE variants

FIDDLE was designed to be flexible and modular in order to accommodate different preparation pulses, execution order, and readout type. Note that FIDDLE refers to the core concept of combining a tissue signal-reducing preparation and an IR pulse, both of which are spatially non-selective and therefore flow-independent. Based on

the FIDDLE concept, segmented and single-shot implementations exist, and the latter can also be combined with motion compensation (MOCO) [17].

Magnetization Preparation Configuration

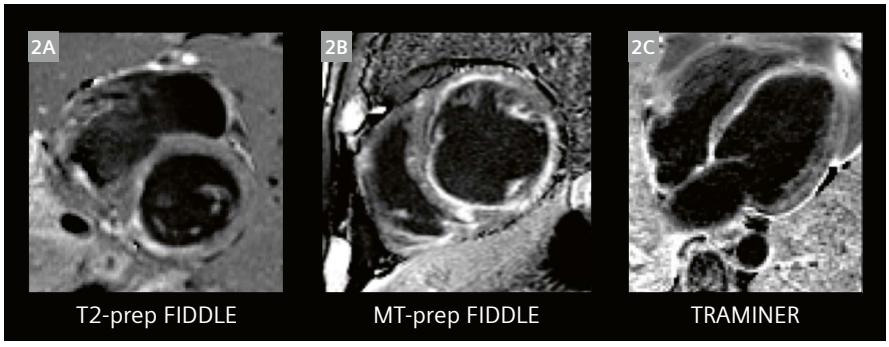
The position of the tissue signal-reducing preparation module relative to the IR pulse is flexible and can be placed before (prep-IR) or after the IR pulse (IR-prep). However, the IR-prep variant is more limited since the duration of the preparation module restricts the minimum inversion time that can be chosen. This constraint may not allow a short enough TI to result in a black-blood image, depending on the dose of contrast media given and the time elapsed after its administration.

The type of magnetization preparation is also flexible – the primary consideration is that the preparation module must attenuate tissue and blood to different degrees. Since its first description in 2011 [12] FIDDLE variants using a magnetization transfer (MT) preparation (MT-prep) [14], T2-preparation (T2-prep) [9], and an T2-rho preparation [15] have been employed. Examples of FIDDLE images with different preparation are shown in Figure 2.

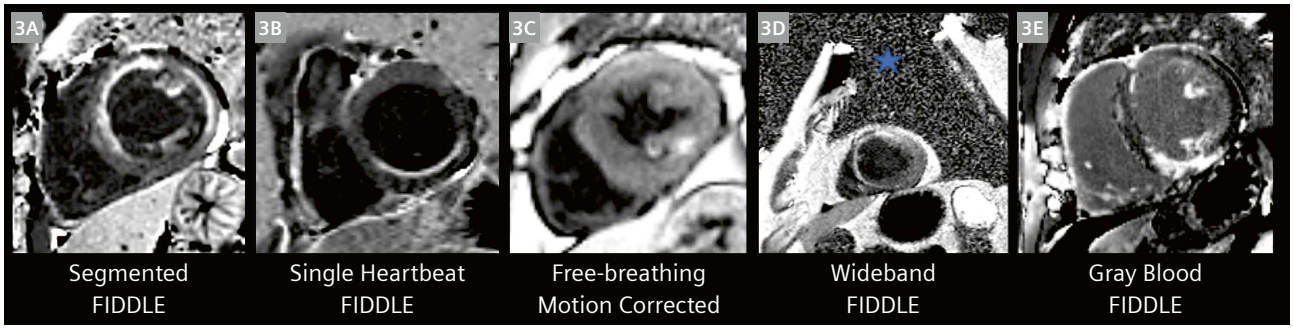
One common preparation for FIDDLE is MT-prep. An MT-prep employs a train of off-resonance MT pulses to saturate the macromolecular proton pool. This saturation is transferred to the main water pool resulting in a reduction in the detected magnetization that is proportional to the protein concentration of that tissue. The MT-prep variant of FIDDLE has been validated against histopathology in a canine model of MI and was shown to have higher diagnostic accuracy for the detection of MI in patients [14] than conventional DE-MRI.

T2-prep has also been shown to work well with FIDDLE. A T2-prep variant of FIDDLE combined with single-shot SSFP readout and motion correction to allow imaging during free breathing, demonstrated increased conspicuity of regions that were likely to represent subendocardial fibrosis [13] and demonstrated a higher rate of detecting hyperenhanced myocardium than conventional DE-MRI [18].

Yet another type of magnetization preparation for FIDDLE is the "T(Rho) And Magnetization Transfer And INvErsion Recovery" technique (TRAMINER) which creates separation between tissue and blood using a series of adiabatic BIR-4 pulses with a net flip angle of zero degrees. The BIR-4 pulses simultaneously impose T2-weighting due to the T2(Rho) relaxation in the spin-lock regime, and magnetization transfer contrast, both attenuating tissue magnetization while minimally affecting blood and effectively creating blood-tissue separation. TRAMINER has also been shown to result in a higher rate of detection of hyperenhanced myocardium compared with DE-MRI [15].



2 Clinical example images of different FIDDLE variants. **(2A)** T2-prep NSIR, **(2B)** MT-prep NSIR, and **(2C)** TRAMINER prep images all resulting in dark-blood images.



3 FIDDLE images (MT-prep NSIR) with different readout schemes: **(3A)** segmented acquisition, **(3B)** single-shot single heartbeat (reference and the MT-IR data readout occur in one heartbeat), **(3C)** free-breathing single-shot motion-corrected (MOCO), **(3D)** MT-prep wideband NSIR in a device patient, the blue star indicates the location of the device in the image, **(3E)** FIDDLE with a long TI to produce gray-blood images.

At the Duke Cardiovascular MR Center (DCMRC) we observed that MT-prep is superior to T2- preparation with regards to the homogeneity of the blood-pool. FIDDLE with T2-prep occasionally results in artifacts in the left atrial cavity, which appear to be secondary to non-uniform magnetization preparation, and this is particularly evident at 3T [18]. Additionally, unlike FIDDLE with MT-prep, FIDDLE variants with T2-prep can result in different blood suppression in the right versus the left ventricle. This is because deoxygenated blood in the right chamber has shorter T2 than the oxygenated blood in the left [18].

FIDDLE Imaging Variants

Its modular design allows FIDDLE to be adapted to a wide range of clinical settings. Figure 3 shows example images acquired with a selection of FIDDLE variants. All use off-resonance MT-prep.

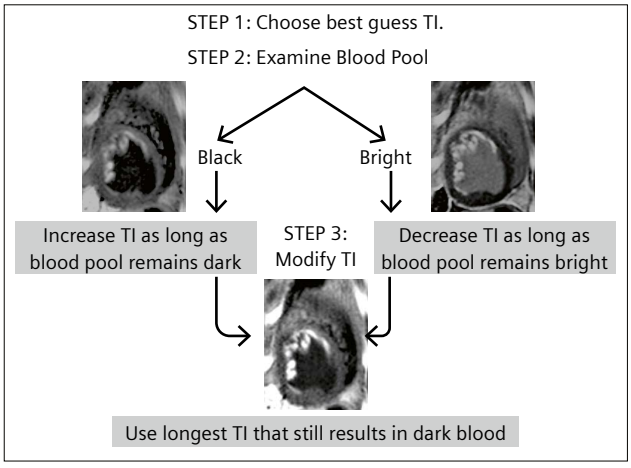
- **Segmented FIDDLE**: The most commonly used FIDDLE variant using a segmented, breath-held TrueFISP data readout combined with a MT-preparation (Fig. 3A). The segmented approach allows for high spatial and temporal resolution images to be acquired within a breath-hold. In patients who can hold their breath, this configuration provides the best diagnostic accuracy for assessment of myocardial damage.
- **Single-heartbeat FIDDLE**: For a fast overview of the entire heart or for patients who cannot hold their breath, FIDDLE has been implemented as single-shot TrueFISP technique (Fig. 3B). We use a single-heartbeat PSIR acquisition wherein reference- and IR-data are acquired in the same heartbeat [19]. This prevents spatial misregistration between the reference- and IR-data set, which can occur when running single-shot acquisitions with a trigger pulse of three during free breathing.
- **Motion-corrected, free-breathing, high spatial resolution FIDDLE**: A different free-breathing version of FIDDLE acquires multiple (usually eight) high spatial resolution single-shot images, which are motion-corrected and averaged together to improve signal-to-noise ratio (SNR) [17]. The motion correction algorithm corrects for in-plane motion between acquisitions and, similar to the single-heartbeat variant, reduces artifacts due to spatial misregistration (Fig. 3C).
- **Wideband FIDDLE for use with implanted cardiac devices**: This implementation uses a wideband (stretched adiabatic) IR pulse which provides a uniform inversion even in the presence of metal[2] (prosthetic valves, implanted cardiac devices, etc.) [20]. The MT-pulses are intrinsically robust towards poor B_0 homogeneity since they are applied off resonance. In addition, the wideband protocol is run with a GRE (FLASH) readout to reduce its sensitivity to metal (Fig. 3D).
- **Gray-blood FIDDLE**: If the inversion time is extended beyond that needed to fulfill the dark-blood condition (Fig. 1), a gray-blood image will result. While the blood-pool signal will be higher than that of normal myocardium, gray-blood imaging can still be helpful since blood-pool signal will be attenuated relative to conventional DE-MRI (Fig. 3E).

Clinical Implementation

From a breath-hold and clinical throughput standpoint, FIDDLE is essentially identical to conventional DE-MRI. No additional post processing or image registration is required, and all image reconstruction is completed at the time of image acquisition. The same dose of contrast media is used for FIDDLE compared to DE-MRI, and imaging can be performed at the same time-point after contrast agent administration. Moreover, spatial resolution, temporal resolution, and breath-hold duration (8–10 seconds) are also identical to DE-MRI. In other words, the implementation of FIDDLE can be regarded as a 'drag and drop' replacement for conventional DE-MRI.

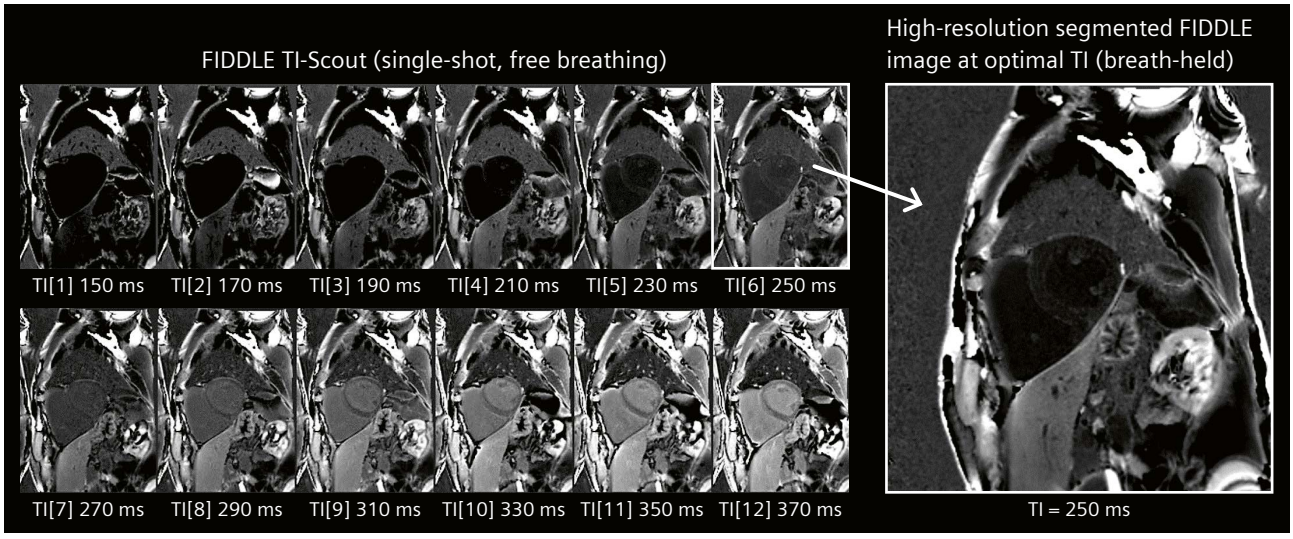
Setting the Inversion Time (TI)

Setting TI for FIDDLE is straightforward. One examines the image intensity of the blood-pool. If the blood-pool is not dark but gray or bright, TI needs to be reduced. If the blood-pool is dark, TI should be increased to the maximum value that still results in dark-blood. This algorithm is



4 Algorithm for manually setting TI of FIDDLE.

[2]*The MRI restrictions (if any) of the metal implant must be considered prior to patient undergoing MRI exam. MR imaging of patients with metallic implants brings specific risks. However, certain implants are approved by the governing regulatory bodies to be MR conditionally safe. For such implants, the previously mentioned warning may not be applicable. Please contact the implant manufacturer for the specific conditional information. The conditions for MR safety are the responsibility of the implant manufacturer, not of Siemens.*



5 A series of single shot FIDDLE images (PSIR by default) are acquired during a free breathing TI-scout scan. Each image has an increased TI compared with its predecessor (increments of 20 ms in this example). By exactly mimicking the magnetic evolution of the segmented sequence, the TI-scout creates single-shot images with the same image contrast as the segmented sequence for a given TI. The TI of the scout image showing optimal contrast (blood black and normal myocardium dark-gray) is plugged into the segmented sequence to obtain a segmented FIDDLE image with optimal contrast.

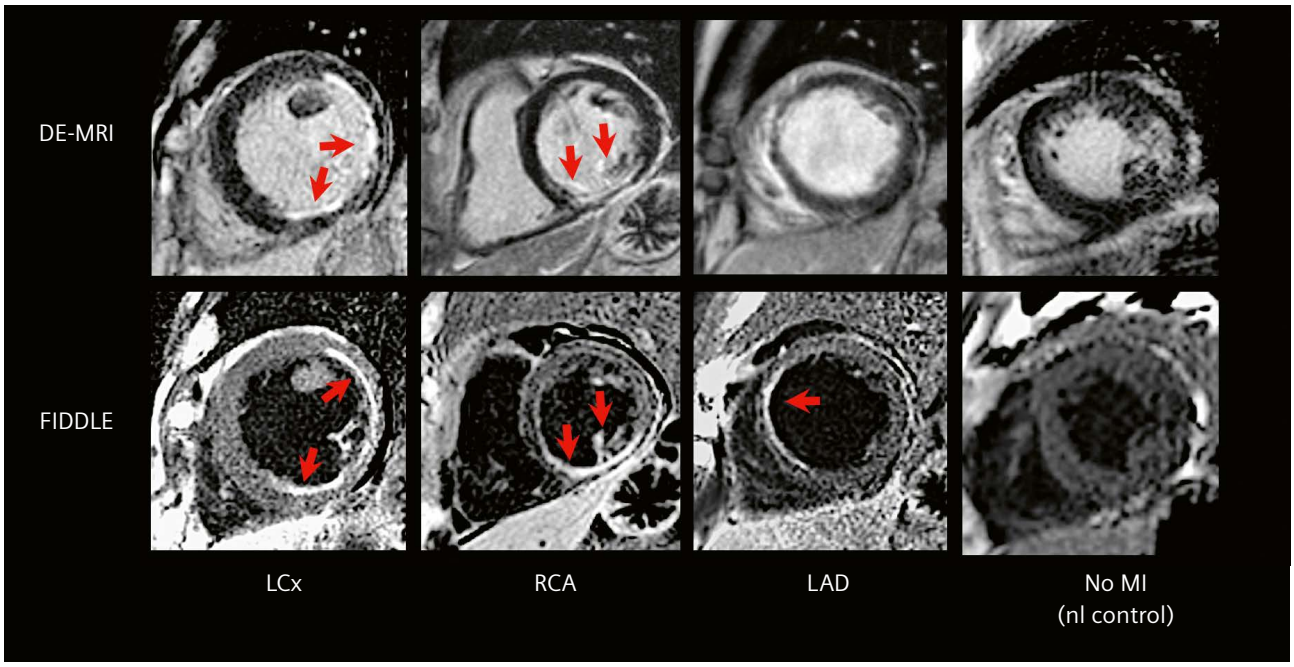
shown in Figure 4. For simplicity, our current practice is to use an initial TI that is purposely chosen to be too long (i.e. image is not dark-blood), and to incrementally reduce the TI until the dark-blood condition is fulfilled. Given its diagnostic performance and ease of use, FIDDLE has become a core component of the DCMRC clinical cardiac MR exam and is used daily at both 1.5 and 3T.
For new adopters of FIDDLE, a recently developed free-breathing FIDDLE TI-scout [21] allows one to find the optimal inversion time in a single-step and with high accuracy. Figure 5 shows a series of TI-scout images and the segmented FIDDLE image acquired with the TI found to be optimal by the scout. In contrast to the conventional TI-scout also known as Look-Locker sequence, the new TI-scout can also produce PSIR images, which are required for FIDDLE. Analogous to using the conventional TI-scout for DE-MRI the new TI-scout determines the TI at the time that it is run, but the optimal TI increases with time after contrast agent administration and TI should be continually adjusted.

Clinical scenarios and cases

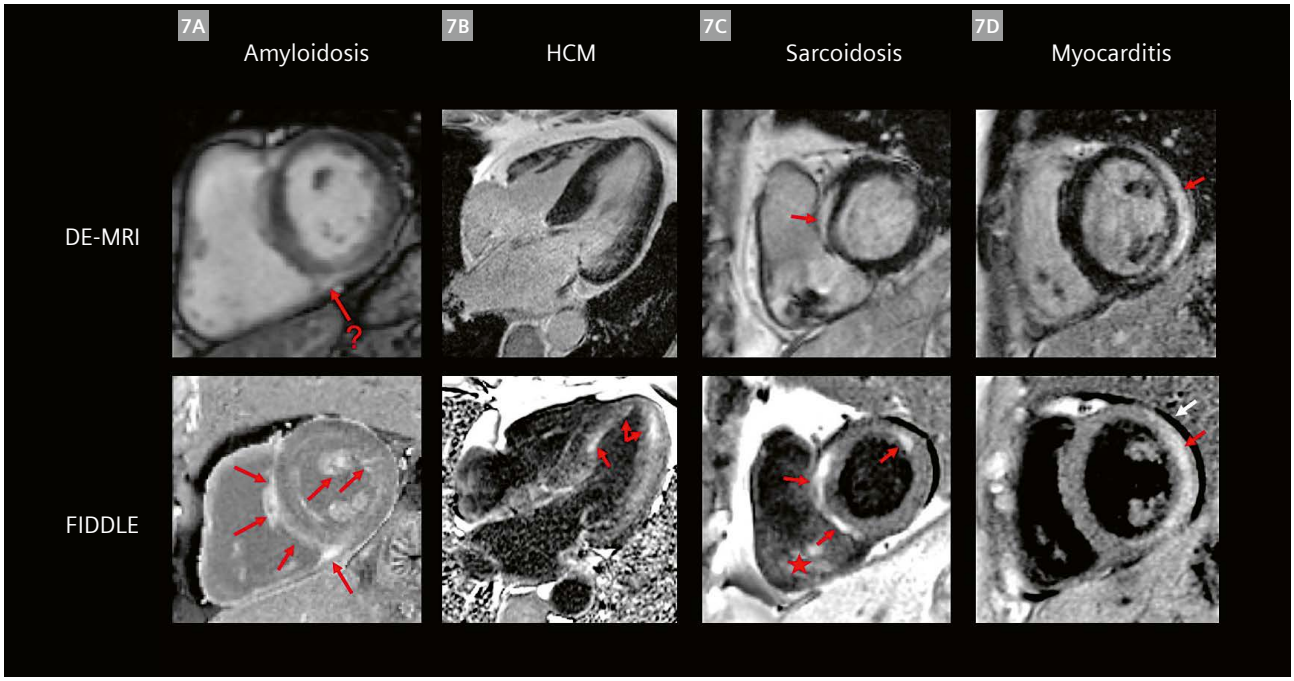
Myocardial Infarction
In a recent validation study, FIDDLE was shown to provide superior diagnostic performance for the detection of myocardial infarction (MI) compared with conventional DE-MRI [14]. Sensitivity and accuracy were significantly higher for FIDDLE compared to DE-MRI (96% vs. 85% and 95% vs. 87%, respectively). This improvement in diagnostic performance mainly came from improved detection of subendocardial infarctions, where the sensitivity of DE-MRI was only 80% compared to 98% for FIDDLE.

Although this result may suggest that the primary advantage of FIDDLE is in patients with small infarcts, this report also observed that some infarcts missed by DE-MRI were relatively large. Even when infarction was identified by DE-MRI, the data indicated that it was rare to visualize the entire length of the MI endocardial border, in contra-distinction to FIDDLE images for which the entire border was always visualized. Hence, infarct size measurements were more robust with FIDDLE than with DE-MRI; in comparison to pathology, there was reduced bias and smaller 95% limits-of-agreement with FIDDLE.

Figure 6 shows examples from four patients referred for myocardial viability assessment. In the first case, the patient had an occlusion of the left circumflex artery (LCx), and the hyperenhancement is well visualized on both the DE-MRI and FIDDLE images. In the next example, the infarct related artery was the right coronary artery (RCA), and while it is clear on DE-MRI that there is an infarct present in the inferior wall, the subendocardial border of the infarct is unclear. The third example is a patient with disease in the left anterior descending (LAD), which is difficult to identify on the conventional DE-MRI but is clearly visualized on the FIDDLE image. The final example is in a normal control patient with no CAD. In this case, a TrueFISP band in the anterior/anteroseptum gives a suggestion of hyperenhancement on the DE-MRI image, but the FIDDLE image clearly shows that there is no hyper-enhancement.



6 Comparison of conventional DE-MRI and FIDDLE images in patients with myocardial infarctions. The images are grouped by infarct-related artery (IRA): circumflex artery (LCx), right coronary artery (RCA), and left anterior descending (LAD). A control patient is shown on the right. See text body for details.



7 Example images in different nonischemic cardiomyopathies. In many of these cases, dark blood improves the appreciation of the location and extent of hyperenhancement. Red arrows indicate regions of hyperenhancement. In **7C**, the star indicates the RV lead from a cardiac device, which appears black on the conventional bright-blood DE-MRI, and bright on the FIDDLE image. In **7D**, the white arrow highlights that the PSIR reconstruction used with FIDDLE has the added benefit of rendering fluid (in this case a pericardial effusion) black, enabling better visualization of the epicardial surface.

Nonischemic Cardiomyopathy
There are no published comparisons of FIDDLE for the diagnosis of nonischemic cardiomyopathies (NICM). However, the DCMRC has used FIDDLE in nonischemic cardiomyopathy cases and found it to be equivalent, if not superior, to conventional DE-MRI. Figure 7 shows a series of example images in different nonischemic cardiomyopathies. In many of these cases, the suppression of the blood pool has allowed for improved appreciation of the location and extent of hyperenhancement.

Cardiac Amyloidosis
The first nonischemic cardiomyopathy (Fig. 7A) is cardiac amyloidosis. Cardiac amyloidosis (CA) can be challenging to image and as a result, studies on the prognostic value of DE-MRI in patients with CA have yielded inconsistent results [23]. A challenge in CA patients is that there is often global, diffuse hyperenhancement of the myocardium, which is why it can be difficult to appropriately set TI in DE-MRI to best visualize the abnormalities. FIDDLE mitigates this challenge as it uses a PSIR reconstruction and has a wide range of TIs over which the blood is suppressed, while providing differentiation of diseased and normal myocardium. In Figure 7A, the DE-MRI image does not clearly show any abnormal tissue, although there is a hint of possible hyperenhancement near the RV insertion site. However, the FIDDLE image depicts multiple areas of subendocardial hyperenhancement, as well as hyperenhancement of the RV side of the septum (see arrows).

Hypertrophic Cardiomyopathy
FIDDLE can also provide insight in cases of hypertrophic cardiomyopathy (HCM), where the hyperenhancement is diffuse and subendocardial, as is shown in Figure 7B. In this case, the DE-MRI image hints at possible diffuse disease along the lateral wall and apical septum, but the image characteristics are also similar to partial volume of trabeculations and blood pool. In the FIDDLE image, the blood pool is suppressed allowing the reader to clearly visualize the apical lateral hyperenhancement and the subendocardial mid-apical septal hyperenhancement (see arrows).

Cardiac Sarcoidosis
The suppression of the blood pool is particularly helpful in cases of cardiac sarcoidosis (CS), where the hyperenhancement is often on the RV side of the septum near the base of the heart. On conventional (bright-blood) DE-MRI images it can be challenging to differentiate LV outflow tract, RV blood pool and hyperenhancement in this setting, as is demonstrated in the CS case shown in Figure 7C. In the DE-MRI images, it is clear that there is hyperenhancement of the RV side of the anterior septum (see arrow), however it is ambiguous if the inferior septum is also hyperenhanced. On the FIDDLE image, it is clear that there is hyperenhancement of both the anterior and inferior septum, and there is also a small amount of hyperenhancement in the anterior lateral wall (see arrows). Also of interest, this is an example of wideband FIDDLE [20], the bright region in the RV blood pool (see star) is due to pacemaker leads.

Myocarditis
FIDDLE can also be used to identify regions of myocardial hyperenhancement in cases of myocarditis. In the example shown in Figure 7D, the hyperenhancement is well visualized on both the DE-MRI and FIDDLE images (see arrows). In the case of myocarditis, the suppression of the blood pool by FIDDLE does not provide a benefit over DE-MRI, however the PSIR reconstruction also renders the pericardial effusion black (see white arrow), allowing for a clearer visualization of the lateral epicardial border.

Conclusion

Despite the availability of an armamentarium of modern MRI techniques, the image-based diagnosis of myocardial disease can still be difficult. Finding new imaging methods that improve decision making, risk stratification, and management, is critical. The reduced variability associated with FIDDLE is expected to be important in clinical trials that employ infarct size as a surrogate endpoint. While studies have validated FIDDLE in patients with MI, FIDDLE provides a general approach to improve contrast-enhanced MRI 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, for example atrial fibrosis and aortopathies.

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