T1, T2, and Fat Fraction Cardiac MR Fingerprinting: Preliminary Clinical Evaluation

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Background: Dixon cardiac magnetic resonance fingerprinting (MRF) has been recently introduced to simultaneously provide water T1, water T2, and fat fraction (FF) maps.

Purpose: To assess Dixon cardiac MRF repeatability in healthy subjects and its clinical feasibility in a cohort of patients with cardiovascular disease.

Population: T1MES phantom, water-fat phantom, 11 healthy subjects and 19 patients with suspected cardiovascular disease.

Study Type: Prospective.

Field Strength/Sequence: 1.5T, inversion recovery spin echo (IRSE), multiecho spin echo (MESE), modified Look–Locke inversion recovery (MOLLI), T2 gradient spin echo (T2-GRASE), 6-echo gradient rewound echo (GRE), and Dixon cardiac MRF.

Assessment: Dixon cardiac MRF precision was assessed through repeated scans against conventional MOLLI, T2-GRASE, and PDFF in phantom and 11 healthy subjects. Dixon cardiac MRF native T1, T2, FF, postcontrast T1 and synthetic extracellular volume (ECV) maps were assessed in 19 patients in comparison to conventional sequences. Measurements in patients were performed in the septum and in late gadolinium enhanced (LGE) areas and assessed using mean value distributions, correlation, and Bland–Altman plots. Image quality and diagnostic confidence were assessed by three experts using 5-point scoring scales.

Statistical Tests: Paired Wilcoxon rank signed test and paired t-tests were applied. Statistical significance was indicated by *(P < 0.05).

Results: Dixon cardiac MRF showed good overall precision in phantom and in vivo. Septal average repeatability was ~23 msec for T1, ~2.2 msec for T2, and ~1% for FF. Biases in healthy subjects/patients were measured at +37 msec*/+60 msec*/ and ~8.8 msec*/~8 msec*/ when compared to MOLLI and T2-GRASE, respectively. No statistically significant differences in postcontrast T1 (P = 0.17) and synthetic ECV (P = 0.19) measurements were observed in patients.

Data Conclusion: Dixon cardiac MRF attained good overall precision in phantom and healthy subjects, while providing coregistered T1, T2, and fat fraction maps in a single breath-hold scan with similar or better image quality than conventional methods in patients.

Level of Evidence: 2.

Technical Efficacy Stage: 2.

QUANTITATIVE CARDIAC magnetic resonance imaging (MRI) parameter mapping is a promising diagnostic tool for early and accurate assessment of cardiovascular disease.1 Clinical recommendations and protocols for T1, T2, T2*, and extracellular volume (ECV) mapping of the heart were issued by the Society for Cardiovascular Magnetic

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Recent studies have demonstrated the diagnostic and prognostic potential of multiparametric cardiac magnetic resonance imaging (MRI). The updated Lake Louise criteria for myocardial inflammation considers T2 mapping to characterize myocardial edema as well as T1 or ECV mapping to assess nonischemic myocardial injury, whereas serial T1 and T2 mapping during chemotherapy treatment have been shown to enable early detection of myocardial damage. Conventionally, these parametric maps are acquired sequentially under multiple breath-holds. Joint parametric mapping techniques have been proposed to map simultaneously T1 and T2, or T1 and FF of the myocardium in a single acquisition. Magnetic resonance fingerprinting (MRF) has also been proposed as an attractive multiparametric mapping technique promising quantification of as many parameters as those included in the signal model. This is achieved with an acquisition and reconstruction framework that includes three main components: 1) a variable pulse sequence sensitized to the parameters of interest (eg, T1 and T2); 2) highly undersampled acquisition that introduces spatiotemporal incoherent aliasing artifacts; and 3) dictionary-based matching for multi-parametric map estimation. Cardiac MRF has been shown to provide simultaneous T1 and T2 mapping in a single breath-hold acquisition of ~16 seconds and has shown promising results in preliminary clinical evaluations. We have recently proposed a water-fat Dixon cardiac MRF approach that enables simultaneous myocardial water T1, water T2 and FF mapping in a single ~15 seconds breath-hold. This approach showed good T1, T2, and FF accuracy in phantoms and good agreement with conventional mapping techniques in a small cohort of healthy subjects.

The aims of this study were 1) to assess the repeatability of Dixon cardiac MRF measurements compared to conventional T1, T2, and proton density fat fraction (PDFF) sequences in phantom and a cohort of healthy subjects, and 2) to investigate the feasibility of using Dixon cardiac MRF to measure these parameters pre- and postcontrast injection and derive ECV in a pilot study in patients with diverse cardiovascular diseases.

Materials and Methods
The study was approved by the Institutional Review Board and written informed consent was given by all participants before imaging. All data were acquired on a 1.5T MR scanner (Ingenia, Philips, Best, The Netherlands; Software Release R5.1.7, Patch: KCLDcMRFv3) with a 28-channel cardiac coil.

Study Design
The study designs for the phantom, healthy subject, and patient studies are summarized in Fig. S1 and described hereafter. Acquisition parameters for all conventional and reference scans are summarized in Table S1 and further described in the Image Acquisition section.

PHANTOM STUDY. Data were acquired in a standardized T1/T2 phantom (T1MES) and an in-house built water-fat phantom. Inversion-recovery spin echo (IRSE), T2 multicine spin echo (MESE), and 6-echo gradient echo (GRE) PDFF were performed as reference measurements. Nine datasets were acquired (three datasets acquired consecutively per session repeated on three separate days) each containing MOLLI 5(3 s)3, T2-GRASE, 6-echo GRE PDFF, and Dixon cardiac MRF sequences. Sequence parameters are described on the Image Acquisition section and in Table S1. Measurements (Xp,r) acquired the same day p were considered dependent and used to obtain a first measurement of repeatability for each day, Rp(r) (Eq. (1)). Those acquired on separate days were considered independent and were used to provide a second measure of repeatability for each repetition r, Rr(r) (Eq. (2):

\[
R_d(p) = \frac{1}{n-1} \sum_{k=1}^{n-1} |X_{p,k} - X_{p,k+1}| \\
R_i(r) = \frac{1}{l-1} \sum_{k=1}^{l-1} |X_{r,k} - X_{r,k+1}| 
\]

where n = l = 3. Rp(r) measurements were averaged over all days to obtain the average dependent (Rd) repeatability measure. Rr(r) measurements were averaged over all repetitions to obtain the average independent (Ri) repeatability measure.

HEALTHY SUBJECTS’ STUDY. MOLLI 5(3 s)3, T2-GRASE, PDFF, and Dixon cardiac MRF mapping were acquired for 11 healthy subjects. Sequence parameters are described on the Image Acquisition section and in Table S1. Three datasets were acquired for each mapping technique in mid short axis (SA) view in a single scan session. The first two datasets were acquired consecutively (dependent scans). The subject was then removed from the scanner bore and repositioned, and the mid SA view was replanned before acquiring the third dataset to achieve an independent measurement. In this healthy cohort study, scans 1 and 2 were used to obtain a first measurement of repeatability (Rd) and scans 2 and 3 a second measure of repeatability (Ri).

PATIENTS’ STUDY. Twenty patients referred to a clinical MR scan for known or suspected cardiovascular diseases were enrolled in this study. Study exclusion criteria included patients with arrhythmia...
and MR-incompatible devices. One patient presented significant arrhythmias during the scan and was excluded from the study retrospectively (according to the study exclusion criteria), leading to 19 patients included in the analysis.

Native Dixon cardiac MRF, MOLLI, T2-GRASE, and PDFF sequences and postcontrast injection Dixon cardiac MRF and MOLLI sequences were acquired in the same single mid-ventricular SA slice. Patients received an injection of gadobutrol (0.15 mL/kg, Gadovist, Bayer, Leverkusen, Germany) as part of their routine clinical scan. MOLLI and Dixon cardiac MRF postcontrast acquisitions were performed more than 10 minutes after contrast injection. Routinely acquired additional scans included phase sensitive inversion recovery (PSIR) late gadolinium enhancement (LGE) images. Additional views (eg, 4-chamber, 2-chamber, or apical views) were acquired using Dixon cardiac MRF postcontrast in the case of pathology findings on PSIR LGE images. Sequence parameters are described in the Image Acquisition section and in Table S1.

Image Acquisition
Dixon cardiac MRF acquisition consists of 15 modules (with different inversion recovery and T2 magnetization preparation, one per heartbeat) performed in a single -15-second breath-hold, as previously described (Fig. 1). For the phantom study, Dixon cardiac MRF was acquired for a fixed heart rate of 60 bpm. In vivo, the second inversion pulse (nominal inversion time [TI] of 300 msec) was not feasible in subjects with heart rates higher than 90 bpm. In these cases the TI was set to its maximal attainable value. Acquisition parameters for Dixon cardiac MRF were: acquired spatial resolution 1.8 × 1.8 mm²; reconstructed spatial resolution 0.9 × 0.9 mm², slice thickness 8 mm; receiver bandwidth = 658 Hz/pixel; field of view (FOV) = 548 × 548mm²; first, second, and third echo times, TE1/TE2/TE3 = 1.6/3.53/5.47 msec; repetition time, TR = 7.5 msec; acquisition window of 217.5 msec, 435 radial spokes (29 per heartbeat) with 304 samples along the readout direction acquired in total for each echo time, acquisition time ~15 seconds. Identical heartbeat) performed in a single ~15-second breath-hold, as previous

Parameter Maps Reconstruction
Conventional T1 and T2 maps were reconstructed directly on the scanner. PDFF maps were reconstructed offline using Hernando et al’s graphcut method (ISMRM Fat-water toolbox v1). Dixon cardiac MRF results were reconstructed as described in earlier works, using a high-dimensionality undersampled patch-based (HD-PROST) reconstruction for each echo, a water-fat separation, a dictionary matching, and a FF estimation step. The Dixon cardiac MRF reconstruction framework was implemented in-house in MatLab (MathWorks, Natick, MA). The HD-PROST denoising step within the iterative reconstruction algorithm was implemented in C++.

The dictionary included slice profile and inversion efficiency corrections. It was generated for the following values ([lower value: step size: upper value]): [50:10:1400, 1430:30:1600, 1700:100:2200, 2400:200:3000] msec for T1 and [5:2:80, 85:5:150, 160:10:300, 330:30:600] msec for T2 using the extended phase graphs formalism.

Blood samples were not available for this study; thus, synthetic hematocrits (Hctsyn) were derived using the MOLLI left ventricular blood pool native T1 measurement (T1b(MOLLI)) and Eq. 3:

\[
\text{Hctsyn} = 922.6 \times \frac{1}{1 - \frac{1}{T1_{\text{nat}}(\text{MOLLI})} - 0.1668}
\]

Synthetic ECV maps were then generated (Eq. 4) for both MOLLI and Dixon cardiac MRF T1 maps using the same Hctsyn value:

\[
\text{ECV}_{\text{syn}} = (1 - \text{Hct}_{\text{syn}}) \times \frac{1}{T1_{\text{PC}} - \frac{1}{T1_{\text{nat}}} - \frac{1}{T1_{\text{bPC}}}}
\]

Where T1PC, T1nat, T1bPC, and T1b(MOLLI) are the postcontrast (PC) and native (nat) myocardial T1 maps and the native and postcontrast left ventricular blood (bnat and bPC) T1 measurements, respectively. The native and postcontrast T1 maps were cropped and rigidly coregistered (MatLab registration tools) before synthetic ECV estimation.

A synthetic fat-suppressed LGE image can be generated from the postcontrast Dixon cardiac MRF maps for comparison with the PSIR LGE images using the following equation (Eq. 5):

\[
S_{\text{LGE}} = M_{0,w} \left(1 - 2e^{-\ln 2 \frac{T1_{\text{PC}}}{\text{TIME}}} \right)
\]

where M0,w, T1PC, and T1b(MOLLI) are the postcontrast Dixon cardiac MRF water proton density map, water T1 map, and myocardial T1 measurement, respectively.

Image Analysis
In the phantom study, regions of interest (ROIs) were manually drawn (O.J., 3 years of experience in cardiac MR) for the nine datasets and all the phantom vials (17 vials). FF values were...
measured on all vials. T1 and T2 values were measured on the water-only vials (standardized T1/T2 phantom, nine vials).

For all healthy subjects, septal T1, T2, and FF values were measured using manually drawn ROIs (O.J., 3 years of experience in cardiac MR) in the middle of the septum for each method and the three repeated acquisitions.

In patients, native T1, native T2, FF, postcontrast T1, and ECV values were measured. All ROIs were larger than 20 voxels in size. A first group of measurements excluding the patient with diffuse amyloid deposition and paying attention to avoid abnormal LGE areas (N = 18 patients, L = 18 measurements, Group 1) were performed in the septum or remotely when necessary. Focal disease measurements and septal measurements in the case of diffuse disease were also performed, leading to a total of L = 22 measurements in N = 19 patients (analyzed as Group 2). Measurements of the left ventricular blood T1 pre- and postcontrast were obtained to compute the synthetic ECV maps for the 19 patients analyzed.

The patients’ native T1, native T2, FF, postcontrast T1, and synthetic ECV Dixon cardiac MRF and conventional maps were rated by three experienced clinicians (P-G.M., S.N., and R.H. with 14, 5, and 2.5 years of experience in cardiac MR, respectively) for overall image quality and diagnostic confidence independently, using two 5-point scoring scales. The scale for map quality was given by: 1: uninterpretable maps, 2: poor definition of edges, significant noise and/or residual artifacts, 3: mildly blurred edges, mild noise and/or residual artifacts, 4: slightly blurred edges, minor residual artifacts, 5: neglectable blurring or residual artifacts. For diagnostic confidence, the scale was given by: 1: no confidence, 2: slight confidence, 3: moderate confidence, 4: substantial confidence, 5: strong confidence.

**Statistical Analysis**

In phantom, mean biases, 95% confidence intervals (CIs; 1.96 standard deviation, SD), lines of best fit and coefficient of determination compared to reference IRSE, MESE, and conventional PDFF, as well as dependent and independent repeatability (Rd and Ri), are reported to assess the accuracy and precision of the different methods.

In healthy subjects, mean values, 95% CIs (±1.96 inter-subject SD) and repeatability (Rd and Ri) are reported for Dixon cardiac MRF and conventional mapping techniques. The intraclass correlation coefficients (ICC) between dependent (ICCd) and independent (ICCi) measurements as well as the coefficient of variation (CoV) between all repeated measurements are also reported.

In patients, Group 1 native measurements were compared to the healthy cohort measurements. Group 2 measurements with the proposed and conventional mapping techniques were compared using Bland–Altman and correlation plots.

Statistical analysis using two-tailed Student paired t-tests were performed to compare conventional and Dixon cardiac MRF mean measurements in healthy subjects and patients. Student paired t-tests were also used to compare dependent and independent repeatability in healthy subjects. All distributions compared using Student t-tests were tested positively for normality using a Shapiro–Wilk test. A paired Wilcoxon signed rank test was performed to assess statistically
significant differences between conventional and Dixon cardiac MRF scores for map quality and diagnostic confidence. Mean scores and interreader ICCs (ICC(A-k)) are reported for each parameter and method. All statistical tests were performed in MatLab and significant differences between methods are reported for *P < 0.05.

Results

Phantom Study

Metrics comparing conventional and Dixon cardiac MRF T1, T2, and FF measurements are reported in Table 1, an example phantom dataset is shown in Fig. S2, and all data points are shown in correlation plots in Fig. S3. Dixon cardiac MRF reported biases were −14 msec, −5.1 msec, and −0.7% for T1, T2, and FF, respectively, when compared to IRSE and MESE reference scans. The different metrics show Dixon cardiac MRF has higher accuracy than MOLLI, and comparable accuracy to T2-GRASE (<1 msec difference in bias) and to PDFF (<1% bias). Good Rd and Ri repeatability was observed for all methods (<7 msec, <4 msec, and < 1% for T1, T2, and FF respectively) showing comparable precision between Dixon cardiac MRF and conventional methods.

Healthy Subjects

The healthy subjects cohort included 11 subjects (four females, age: 30 /C6 12.8 years, BMI: 22.4 /C6 7.5 kg/m², nominal heartrate: 67 ± 12 bpm). Water T1, T2, and FF Dixon cardiac MRF maps and representative septal ROIs are shown in Fig. S4 for a representative healthy subject for the three-scan session. Mean, 95% CI, spatial variability (within ROI SD), repeatability (Rd and Ri), ICCs (ICCd and ICCi), and CoV for T1, T2, and FF measurements with Dixon cardiac MRF in comparison to conventional approaches are reported for the healthy cohort in Table 2. Average differences between the proposed and conventional methods were of 37 msec*, −8.8 msec*, and 0.4% (P = 0.46) for T1, T2, and FF, respectively. Tukey boxplots of the three separate Dixon cardiac MRF and conventional septal measurements for each parameter are shown in Fig. S5.

T1, T2, and FF Dixon cardiac MRF repeatability were measured at 20 msec, 2.2 msec, 0.7% for Rd and 23 msec, 2.2 msec, 1.0% for Ri. Corresponding average differences in repeatability compared to conventional techniques were of 4 msec, 1.1 msec, and − 0.9%* for Rd and −12 msec, 1.0 msec and − 0.8% for Ri. Corresponding boxplots and P-values are indicated in Fig. S6. Additionally, good overall agreement (ICCd and ICCi >0.7) between dependent and independent measurements was seen for Dixon cardiac MRF and T2-GRASE but not for MOLLI and PDFF.

Patient Study

Within the patient cohort (11 females, age: 53.4 ± 14.8 years old, BMI: 30.4 ± 7.5 kg/m², nominal heartrate: 72.4 ± 12.7 bpm), eight had no evidence of cardiovascular disease at MR, four had chronic ischemic cardiomyopathies, four had nonischemic dilated cardiomyopathies (including two cases with left bundle branch block and two cases with mild systolic dysfunction), one had cardiac amyloidosis, two had hypertrophic cardiomyopathy, and one had acute myocarditis. The patient with acute myocarditis was excluded from the analysis due to frequent supraventricular and ventricular ectopic beats leading to a total of 19 patients in the analysis.

Patients’ remote (Group 1) mean measurements and intersubject SD are reported for Dixon cardiac MRF and the corresponding conventional techniques (Table 3) and illustrated qualitatively with representative maps of a patient with no cardiac disease finding (Fig. 2). Statistically significant biases of 61 msec* for T1 (P < 0.001) and − 8.0 msec* for T2 (P < 0.001), while FF and additionally postcontrast T1 and synthetic ECV Dixon cardiac MRF measurements presented low (and not statistically significant) differences of −

| Phantom                        | Bias  | 95% CI (1.96SD) | Repeatability (dependent) | Repeatability (independent) |
|-------------------------------|-------|-----------------|---------------------------|-----------------------------|
| Dixon cardiac MRF T1 (msec)   | −14   | [−43:14]        | 0.9                       | 5.3                         |
| MOLLI (msec)                  | −77   | [−220:65]       | 4.8                       | 6.4                         |
| Dixon cardiac MRF T2 (msec)   | −5.1  | [−20:9.7]       | 0.7                       | 3.7                         |
| T2-GRASE (msec)               | −4.3  | [−17:8.4]       | 0.4                       | 3.9                         |
| Dixon cardiac MRF FF (%)      | −0.7  | [−2.9:1.4]      | 0.3                       | 0.7                         |
| PDFF (%)                      | N/A   | N/A             | 0.4                       | 0.7                         |

Table 1. Reported metrics for the assessment of dixon cardiac MRF, MOLLI 5(3 s)3, T2-GRASE, and PDFF measurements. Reported T1 and T2 metrics were averaged for all vials of the standardized T1/T2 phantom (nine vials), whereas FF metrics include both standardized T1/T2 and water-fat phantoms (17 vials). Mean bias and 95% confidence interval (1.96 SD) over nine repeated scans are reported for accuracy compared to reference IRSE, MESE, and PDFF scans. Dependent and independent repeatability (Rd and Ri) are reported to assess precision.
1.2% (P = 0.11), 6.4 msec (P = 0.17), and 0.8% (P = 0.19), respectively, when compared to conventional measurements (Table 3).

Map quality and diagnostic confidence assessment results are provided in Fig. 3. Average map quality scores were 3.9* (native T1), 4.7* (T2), 4.8* (FF), 4.1* (post-contrast T1), and 4.1* (synthetic ECV), respectively, using Dixon cardiac MRF and 3.4, 3.0, 4.4, 3.1, and 3.3 for conventional maps. Similarly, Dixon cardiac MRF showed higher diagnostic confidence average scores for all parameters compared to conventional methods (Fig. 3). Map quality and diagnostic confidence scores were statistically significantly better (P < 0.05) for all maps with Dixon cardiac MRF in comparison to conventional techniques.

Myocardial native T1, postcontrast T1, native T2, and ECV measurements (Group 2) and left ventricular blood native and postcontrast T1 measurements derived from MOLLI or Dixon cardiac MRF sequences were compared using the correlation and Bland–Altman plots in Fig. 4. Dixon cardiac MRF left ventricular blood T1 measurements also showed high correlation (r² > 0.99) with MOLLI measurements. Lower determination coefficients (r² = 0.45) were observed between T2 measurements.

Native T1, T2, postcontrast T1, and ECV are shown in Fig. 5 for both Dixon cardiac MRF and conventional techniques in a patient with subendocardial chronic infarct (infarction occurred ~1 year prior to the scan session and observed in the PSIR LGE images).

Postcontrast Dixon cardiac MRF T1, T2, and FF maps are shown in Fig. 6 for a patient who presented with myocardial infarction (~72 days prior to the scan session) and non-viable myocardium in the left anterior descending artery territory. No T2 increase, but a decrease in postcontrast T1 in the scar region compared to remote tissue was observed. No fat infiltration was detected. Additionally, a synthetic fat-suppressed PSIR LGE image generated from the Dixon cardiac MRF maps is shown in Fig. 6 for comparison with the clinical PSIR LGE image.

A patient with asymmetric left ventricular hypertrophy is shown in Fig. 7a. Additionally, the patient presented diffuse mid-wall myocardial fibrosis as observable in the postcontrast T1, ECV and LGE images (Fig. 7a). Dixon cardiac MRF findings in this patient were in agreement with those observed with conventional techniques, with higher average map quality (proposed: 3.9, conventional: 3.1) and diagnostic confidence scores (proposed: 4.2, conventional: 3.3) for Dixon cardiac MRF.

A patient with cardiac amyloidosis is shown in Fig. 7b. Dixon cardiac MRF and conventional maps showed elevated native T1 and ECV values over the whole left ventricle. Septal measurements reported for native T1 values were 1148 msec and 1128 msec and for ECV were 34.3% and 35% using Dixon cardiac MRF and MOLLI, respectively.
Discussion

Following initial technical developments, cardiac MRF is currently being investigated and compared to conventional sequences to assess its clinical value. Dixon cardiac MRF has been recently proposed to provide coregistered T1, T2, and FF measurements. This study investigated the bias and precision of Dixon cardiac MRF for myocardial tissue characterization in phantom and healthy subjects in comparison to conventional techniques and its preliminary clinical performance in a cohort of patients with suspected cardiovascular diseases.

Bias and Precision of Dixon Cardiac MRF

In a phantom study, Dixon cardiac MRF showed low biases for T1, T2, and FF measurements in comparison to reference spin echo and PDFF measurements. Biases were also reported for conventional MOLLI and T2-GRASE scans in comparison to the spin echo references. Comparable precision between Dixon cardiac MRF and conventional techniques were obtained in phantom, especially when looking at independent repeatability.

In healthy subjects, statistically significant differences in T1 and T2 were observed in comparison to MOLLI and T2-GRASE, consistent with previous cardiac MRF studies. Larger intersubject variations (larger 95% CIs) in healthy subjects were observed for Dixon cardiac MRF compared to conventional techniques. Dixon cardiac MRF showed good overall precision with slightly lower measured mean precision than T2-GRASE (although the results were not shown to be statistically significant), comparable precision to MOLLI.

Table 3. Healthy subjects’ (Native T1, T2, and FF) septum (n = 11 subjects × 3 Repetitions) and patients’ (n = 18) remote measurements (Native and Postcontrast) for Dixon cardiac MRF and conventional techniques. Reported values are expressed as mean value over all scans ± interscan standard deviation. P-values of the differences between conventional and Dixon cardiac MRF are reported for both cohorts.

|                     | Healthy subjects n = 33 (11x3) | Patients (remote) n = 18 |
|---------------------|--------------------------------|--------------------------|
|                     | Conventional                | Dixon cardiac MRF       | P   | Conventional          | Dixon cardiac MRF       | P   |
| Native T1 (msec)    | 1025 ± 33.3                  | 1062 ± 44.8              | <0.001 | 995 ± 29               | 1056 ± 32.6              | <0.001 |
| Native T2 (msec)    | 51.8 ± 1                     | 43.0 ± 2.5               | <0.001 | 52.1 ± 3.9             | 44.1 ± 5.2               | <0.001 |
| Fat fraction (%)     | −0.1 ± 1.4                   | 0.2 ± 2.5                | 0.46  | −0.7 ± 1.7             | −1.9 ± 2.4               | 0.11  |
| Postcontrast T1 (msec) | N/A                         | N/A                      |       | 445 ± 50.2             | 452 ± 55.5               | 0.17  |
| Synthetic ECV (%)   | N/A                          | N/A                      |       | 25.6 ± 2.6             | 26.4 ± 2.2               | 0.19  |

Figure 2: Native T1, native T2, postcontrast T1, and synthetic ECV for conventional techniques (top) and Dixon cardiac MRF (bottom) in a patient with no cardiac disease finding.
(no statistically significant differences), and slightly higher precision than PDFF \((P < 0.05)\) when comparing dependent scans. Similar results were obtained when comparing independent scans. Accuracy and repeatability of \(T_1\) and \(T_2\) measurements are comparable with recent findings comparing cardiac MRF and conventional MOLLI and \(T_2\)-prepared balanced steady-state free-precession techniques in a large cohort of healthy subjects.\(^{31}\)

**Dixon Cardiac MRF in Patients**

Dixon cardiac MRF was acquired in patients with suspected cardiovascular diseases amid a clinically indicated examination. Patients’ precontrast \(T_1\), \(T_2\), and FF average measurements and intersubject SD were comparable to those measured in healthy subjects leading to statistically significant differences in native \(T_1\) and \(T_2\) compared to conventional measurements. A lower determination coefficient was observed between methods for native \(T_2\) measurements. This may be explained due to remaining artifacts in \(T_2\) maps with poor image quality and the lower range of \(T_2\) values measured compared to phantom measurements, and will be further investigated.

Dixon cardiac MRF provided higher average map quality and diagnostic confidence scores when compared to those obtained with conventional methods. Representative results have been demonstrated in a variety of cases including no cardiac findings, myocardial infarction, hypertrophic cardiomyopathy, and amyloidosis. The same Dixon cardiac MRF sequence was used before and after contrast injection in this study. However, the pattern/duration of preparation pulses

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**FIGURE 3:** Boxplots comparing map quality and diagnostic confidence scores of three readers (14, 10, and 2.5 years of experience) in patients. Distributions of (a) map quality scores and (b) diagnostic confidence for Dixon cardiac MRF and conventional methods. Median (—), mean (o), 75% interquartile range (box), Tukey whiskers, and outliers (+) are shown. Average scores and interrater ICC are also indicated. Differences in mean scores were all statistically significant \((P < 0.05)\).
could be optimized for the mapping of lower postcontrast T1 values, similar to MOLLI, potentially leading to shorter scan times. This will be investigated in future studies.

A preliminary clinical study has previously reported statistically significant differences in postcontrast T1 and synthetic ECV measurements between MOLLI and non-Dixon cardiac MRF. These differences were not observed in this study and for postcontrast T1 measurements in two other studies. Differences in hardware, sequence acquisition schemes, and dictionary generation could be the cause of these discrepancies.

Limitations
In this study Dixon cardiac MRF precision was studied in a single center and on a single scanner. Further assessment of precision, through reproducibility studies between vendors and sites, should be investigated, as has been done for other quantitative parametric mapping methods and for cardiac MRF recently, to determine whether an absolute normal range could be determined.

Repeatability was studied in the septum of healthy subjects only. However, recently a segmental analysis of cardiac MRF maps also showed comparable precision when compared to conventional sequences in a large cohort of healthy subjects. Heart rate dependency for Dixon cardiac MRF measurements was not investigated in this study, although the results are expected to match previous cardiac MRF results (showing low heart rate dependency) due to the similar nature of the simulations.

The sample sizes (11 healthy subjects and 19 patients) are small, with some of the reported P-values being only slightly above the threshold of 0.05, which could result in statistically significant differences in larger cohorts.

MOLLI T1 maps were generated in-line on the scanner software; however, this software does not consider registration between single-shot T1 images and therefore may lead to residual motion artifacts in the maps due to imperfect breath-holding or varying heart rates. Motion compensation strategies were also not included for Dixon cardiac MRF. These strategies could be investigated in future works, similar to Ref. 37, to increase mapping robustness. Patients with arrhythmias were not included in this study. Additional improvements including prospective measures for arrhythmia rejection are necessary for application to arrhythmic patients and will be investigated in future work.

Negative fat fraction values were measured using both PDFF and Dixon cardiac MRF FF in phantom, healthy subjects and patients. These errors may be associated with the low amplitude of the measured fat fractions, T2* induced biases, and inaccuracies in phase estimation. The proposed framework could potentially be extended to additionally map T2* for iron content assessment, as recently shown for liver imaging.

In this study, Dixon cardiac MRF reconstructions were performed in MatLab on a Linux workstation with 8 Intel Xeon E5-2687W (3.1 GHz) and 252 GB RAM. It took ~2 hours (84 minutes for dictionary generation, 30 minutes for HD-PROST reconstruction, and 8.6 seconds for water-fat separation, matching, and fat fraction estimation) making it too long for adoption in clinical routine. The slice profile correction included 50 points along the slice profile. A large
FIGURE 5: Phase-sensitive inversion recovery late gadolinium enhanced (PSIR LGE) images (a), diagram of reported unviable segments (b), conventional maps (c), and Dixon cardiac MRF maps (d) in a patient with subendocardial chronic infarct (red arrow in PSIR LGE). Example ROIs drawn in the scar (red) and remote (black) areas are shown on the conventional T2 map. Water T1 (pre- and postcontrast), water T2, and synthetic ECV Dixon cardiac MRF values are in good agreement with conventional measurements.

FIGURE 6: Dixon cardiac MRF post contrast T1, T2, and FF maps, Dixon cardiac MRF synthetically derived fat suppressed LGE image and the clinical PSIR LGE image are shown for two-chamber (top row) and short-axis (bottom row) views in a patient with occlusion of the left anterior descending artery. Lower postcontrast T1 values and similar T2 values compared to remote myocardium in the scar region with no fat infiltration were observed, consistent with the chronic infarct clinical finding.
number of points along the slice profile were considered to ensure accurate profile correction; experiments without slice profile correction can greatly reduce dictionary generation times (1 minute, 40 seconds) but with decreased accuracy. The HD-PROST reconstruction included 15 conjugate gradient (CG) iterations within each of the six iterations of the Alternating Direction Method of Multipliers (ADMM) algorithm. Lower numbers of iterations for the reconstruction could be considered; preliminary experiments (not included here) with three CG iterations within each of the six ADMM iterations have been shown to reduce the reconstruction time to ~5 minutes with small impact on the final map quality; however, the impact in accuracy needs to be investigated. Additionally, recent developments for fast dictionary generation and fast MRF image reconstructions could be combined with Dixon cardiac MRF to enable clinically acceptable reconstruction times and will be investigated in the future.

Finally, no patients in this study presented myocardial infiltration. Dixon cardiac MRF thus needs to be investigated in a larger cohort of patients, including patients with myocardial infarction, where the presence of fat infiltration has high prevalence and prognostic value.

**Conclusion**

Dixon cardiac MRF provides repeatable $T_1$, $T_2$, and FF measurements in phantom and healthy subjects. The results in healthy subjects were consistent with previous cardiac MRF results. Dixon cardiac MRF showed promising preliminary clinical results, with higher expert scores than conventional sequentially acquired mapping techniques, but in a single
breath-hold and providing intrinsically coregistered maps. Future work will focus on improving the robustness and further assessing the performance of Dixon cardiac MRF in patients with diverse pathophysiologicals, such as fat infiltrations, inflammation, tumors, and/or myocardial infarctions.

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Informed Consent
This study was approved by the National Research Ethics Committee. All volunteers and patients provided written informed consent for participation in this study.

Conflict of Interest
T.S., P.K., and M.D. are employees of Philips. The other authors declare that they have no competing interests.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributions
O.J., G.C., P.G.M., and C.P. contributed substantially to the conception and design of the study. O.J. implemented the acquisition and reconstruction framework, acquired and analyzed the data, and wrote the main draft of the article. P.G.M. recruited the patients. P.G.M., R.H., and S.N. provided the expert scores. G.C., A.B., P.K., M.D., and T.S. contributed to the implementation of the acquisition and reconstruction framework. C.P., R.M.B., and D.R. acquired the necessary funding. All authors read, revised, and approved the final article.

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