INTRODUCTION

In the past decade, there has been tremendous interest in developing and clinically applying MRI techniques for quantitatively mapping relaxation times in the myocardium.\textsuperscript{1-3} Myocardial T\textsubscript{1} and T\textsubscript{2} mapping can be used to discriminate between a range of different cardiomyopathies.\textsuperscript{4} T\textsubscript{1} mapping can be used to detect diffuse and focal fibrosis,
and can also be used to calculate extracellular volume fraction that is altered in many cardiomyopathies, while $T_2$ mapping is most commonly used to assess myocardial edema and inflammation.\textsuperscript{5–7} For some diseases, a combination of $T_1$ or $T_2$ mapping provides the most diagnostic power, for example, to detect myocarditis.\textsuperscript{8,9}

The most clinically used quantitative techniques enable $T_1$ or $T_2$ mapping as separate scans. For $T_1$ mapping, the MOLLI has been the most widely used due to its relatively high precision.\textsuperscript{10,11} There is less consensus regarding the optimal $T_2$ preparation balanced steady-state free precession ($T_2$-SSFP) have been used extensively.\textsuperscript{12–14} In recent years, there has been a growing interest in simultaneous $T_1$ and $T_2$ mapping techniques for the myocardium.\textsuperscript{15–22} Some of this work has been based on the MR fingerprinting (MRF) paradigm.\textsuperscript{23–25} MRF involves devising a pulse sequence which yields different magnetization evolution patterns for tissues with different $T_1$ and $T_2$ (but it could also include other quantities), and find the best match between the measured signal and a simulated dictionary with known $T_1$ and $T_2$. Typically, such dictionary-based fingerprinting schemes rely on heavily undersampled spiral or other non-Cartesian trajectories,\textsuperscript{26–28} where a measurement on the magnetization evolution time-curve is obtained from each aliased spoke. However, dictionary-based parameter mapping may also be combined with a Cartesian trajectory, in which case fewer time-points along the magnetization evolution curve can be used for dictionary matching, only those corresponding to the acquisition of the k-space center.\textsuperscript{29} The advantage of using Cartesian as opposed to spiral sampling is lower susceptibility to $B_0$-inhomogeneity, no signal aliasing and simplified reconstruction. Therefore, a Cartesian sampling strategy for dictionary-based $T_1$ and $T_2$ mapping may be more readily incorporated into a clinical setting.

The purpose of this work was to implement and perform initial optimization on a new dictionary-based technique for myocardial $T_1$ and $T_2$ mapping using Cartesian sampling. The proposed simultaneous $T_1$ and $T_2$ mapping technique (termed Multimapping) was tested in phantoms, healthy subjects, and patients with cardiovascular disease.

2 | METHODS

2.1 | Multimapping pulse sequence design

The proposed Multimapping pulse sequence consists of 10 single-shot images, electrocardiograph (ECG)-triggered to the mid-diastolic rest period, and incorporating inversion and $T_2$ preparation ($T_2$-prep) pulses to introduce $T_1$ and $T_2$ sensitization, respectively. The image acquisition consists of a balanced steady-state free precession (SSFP) sequence with Cartesian sampling. Imaging parameters for all experiments and simulations are: FOV = 320 × 320 mm, spatial resolution = 2 × 2 mm, slice thickness = 10 mm, nominal flip angle = 50°, bandwidth = 1076 Hz/pixel, TR = 2.3 ms, TE = 1.2 ms, SENSE factor = 2, linear profile order. Ten startup RF pulses are used with linearly increasing flip angles. An adiabatic inversion pulse is used with an assumed inversion efficiency of 0.94 for the in vivo experiments,\textsuperscript{30} corresponding to an inversion angle of 160°. For the $T_2$-prep module, hard 90° tip down and up pulses are used with four adiabatic refocusing pulses in between.

The timings of the inversion and $T_2$-prep pulses may be optimized to improve $T_1$ and $T_2$ sensitivity. Specifically, using more inversion pulses with different delays may increase sensitivity to different $T_1$, while using more $T_2$-prep with different TEs may yield better $T_2$ sensitivity. To provide some preliminary optimization in this regard, Multimapping pulse sequences with different pre-pulse settings were implemented and evaluated, the details of which are provided in Supporting Information Section 1, which is available online. The optimized Multimapping pulse sequence is illustrated in Figure 1, consisting of inversion pulses in cycles 1 and 5, and $T_2$-prep modules in cycles 8, 9, and 10 with different TEs of 30, 50 and 70 ms, respectively.

2.2 | Image post-processing, dictionary generation, and feature extraction

The Multimapping post-processing steps are summarized in Figure 1. The Multimapping dictionaries (denoted as [lower value: step size: upper value]) are generated by simulating the pulse sequence using the extended phase graph (EPG) framework for ranges of $T_1$, $T_2$, and $B_1$. The R-R intervals are recorded for each scan and, along with the patient-specific trigger delays, used to simulate a subject-specific dictionary. Unlike previous similar dictionary-based cardiac mapping techniques, which uses spiral or radial sampling to measure the transverse magnetization ($M_{xy}$) for each RF-pulse in the mid-diastolic acquisition window, here a Cartesian trajectory is used which results in a single $M_{xy}$ measurement per cardiac cycle. As a result, only the simulated $M_{xy}$ for the corresponding center of k-space acquisition in the cardiac cycle is used for the dictionary. To avoid the “curse of dimensionality,”\textsuperscript{16} which results in extremely long dictionary generation times, the RF
$B_1^+$ field ($B_1$) is first estimated using a relatively coarse grid for $T_1$ [500:100:1500] and $T_2$ [40:30:140] and a $B_1$ range of [0.5:0.05:1]. The estimated $B_1$ is calculated as the mean $B_1$ in a manually selected region of interest (ROI) in the ventricular septum and is used as input for the more highly resolved (HR) $T_1$ and $T_2$ dictionaries. These dictionaries that are only partially resolved for $T_1$ and $T_2$ are generated separately, where each dictionary contain a HR and a coarsely resolved (CR) parameter, to reduce dictionary generation time. For the in vivo experiments, the partially resolved $T_1$ dictionary ($T_1$ Dict$_{PR}$) has a $T_1$ range of [200:1:2500] and $T_2$ range of [20:30:150], and the partially resolved $T_2$ dictionary ($T_2$ Dict$_{PR}$) has a $T_1$ range of [200:50:2500] and $T_2$ range of [1:1:150]. The $T_2$ and $T_1$ time-steps for the $T_1$ Dict$_{PR}$ and $T_2$ Dict$_{PR}$, respectively, were empirically determined to provide a reasonable trade-off between short processing time and low quantification error, using in vivo data from three healthy subjects. Details on this optimization are provided in Supporting Information Section 2. For the phantom experiments, the dictionary has a $T_1$ range of [1:10:2500] and $T_2$ range of [1:4:400]. MATLAB scripts for the dictionary generation and feature extraction can be downloaded from github, including example Multimapping source images from one healthy subject (https://github.com/Multimapping/Matlab_files).

Prior to dictionary matching, in vivo images are motion corrected using non-linear image registration to

![Figure 1](https://github.com/Multimapping/Matlab_files)
minimize respiratory or cardiac-induced motion. The motion correction (MoCo) procedure consists of a total variation regularization algorithm implementation with default parameters. A second processing step performs phase sensitive correction on the acquired images to determine the polarity of the signal. Dictionary matching is then performed using the dot product between the dictionary entries and the motion and polarity corrected images, similar to previous dictionary-based techniques.

2.3 | MRI experiments

All experiments were performed on a Philips 1.5T Ingenia scanner (Philips Healthcare, Best, The Netherlands) with a 28-channel cardiac coil. All subjects provided written informed consent, and the study was approved by the local ethics committee. Imaging parameters for all experiments are outlined in the Multimapping pulse sequence section. Images were reconstructed on the scanner and transferred to an offline workstation with an Intel Core i7-8565U (1.80 GHz) processor and 16Gb RAM for post-processing using MATLAB (The MathWorks, Natick, MA). With this setup, the B1 dictionary took approximately 10 s to generate, and T1 DictPR and T2 DictPR approximately 13 min in total.

2.3.1 | Phantom studies

The International Society for Magnetic Resonance in Medicine/National Institute of Standards and Technology (ISMRM/NIST) phantom was scanned to evaluate any heart-rate dependency. Multimapping scans were performed with different heart-rates, from 40 bpm to 120 bpm with 20 bpm increments, to determine any heart-rate dependency. Reference T1 and T2 values were obtained using inversion recovery spin echo (IRSE) for T1, and multi-echo spin echo (MESE) for T2. Imaging parameters for the reference scans were: 2 × 2 mm spatial resolution, 10 mm slice thickness, eight TIs from 50 to 2000 ms, 7000 ms TR for the IRSE experiment, and eight echoes with TR/TE/ΔTE = 7000/15/15 ms for the MESE experiment. Only vials with T1 and T2 values within physiologically relevant ranges (50 ms to 2200 ms for T1, and 5 to 400 ms for T2) were considered. To evaluate agreement between reference T1 and T2 values in the phantom and those measured with Multimapping, correlation coefficients (R²) and normalized RMS errors (NRMSE) were calculated.

Repeatability of the in vitro T1 and T2 quantification was assessed by performing a second Multimapping phantom experiment (Scan 2) 2 mo after the experiments described in the previous paragraph. For this experiment, only a simulated heart rate of 60 bpm was performed and compared to the corresponding scan with the same simulated heart rate in the previous phantom experiments (Scan 1). Multimapping T1 and T2 values were compared between Scan 1 and Scan 2 by calculating R² and Bland-Altman analysis.

2.3.2 | In vivo experiments

In vivo experiments were performed in 16 healthy subjects (11 male, age: 30 ± 5.3 years, heart rate: 65 ± 6.4 bpm), one patient with dilated cardiomyopathy (47-year-old male, heart rate: 61 bpm) and two patients with acute myocarditis (one 49-year-old female, heart rate: 44 bpm; one 41-year-old female, heart rate: 58 bpm). A Multimapping slice was acquired in mid-ventricular short axis view in all subjects. Additionally, 5(3b)3 MOLLI was acquired for comparison of T1 values, while T2bSSFP with four different T2 weighting (0, 23, 46, and 70 ms TEs, three pause cardiac cycles between each image) was acquired to compare T2 values. Both MOLLI and T2bSSFP were acquired in the same mid-ventricular short-axis location as the Multimap slice with identical imaging parameters, apart from the flip angle, which was 35° for MOLLI and T2bSSFP. MOLLI used an adiabatic inversion pulse, identical to the one used for Multimapping, while the T2prep module for T2bSSFP was also the same as the one for Multimapping. Vendor-provided online curve fitting algorithms were used for parameter estimation of both MOLLI and T2bSSFP. To assess in vivo intra-scan repeatability, Multimapping, MOLLI, and T2bSSFP were repeated in six of the healthy subjects in the same scan session, waiting approximately 10 min between the acquisitions.

The Multimapping B1 maps were validated in three healthy subjects in which B1 mapping was performed using the single-shot dual refocusing echo mode (DREAM) technique, in addition to the Multimapping technique. Details of the B1 mapping validation experiments are provided in Supporting Information Section 3.

To compare Multimapping parameter maps to MOLLI and T2bSSFP, ROIs were manually drawn in the T1 and T2 maps according to the six mid-ventricular segments of the American Heart Association (AHA) model. Additionally, measurements were performed across the entire mid-ventricular slice. Differences in mean values and SDs (spatial variability) were analyzed using pair-wise t-tests with significance threshold of p < 0.05.

To investigate the influence of the B1 correction, T1 and T2 maps generated using B1 estimated from an ROI in the septum were compared to maps generated without correction (B1 = 1). This comparison was performed by calculating the sum of squared differences (SSD) between
the measured and the simulated signal with and without B₁ correction. B₁ was measured in the six AHA segments to evaluate homogeneity across the slice. The B₁ analysis was performed for all healthy subject datasets.

3 | RESULTS

3.1 | Phantom

Multimapping phantom measurements (Figure 2) showed good agreement with reference values for both T₁ and T₂. There did not appear to be noticeable systematic errors in general for Multimapping T₁ or T₂ for the different heart-rates, although T₂ values above 120 ms were higher compared to reference values for heart-rates of 100 and 120 bpm. The R² between T₁ and T₂ estimated using Multimapping compared to reference values was above 0.99 for all simulated heart rates. The T₁ NMRSE was largest for the heart rate of 40 bpm at 4.2% with a range of 0.5% to 11.5%. The T₂ NMRSE was largest for the heart rate of 120 bpm at 11.9% with a range of 2.4% to 32.9%. The T₁ and T₂ NMRSE and ranges for all simulated heart rates are summarized in Supporting Information Table S1.

Repeatability assessment of Multimapping T₁ and T₂ quantification yielded a R² of more than 0.99 with no significant bias (T₁ bias = −1.1 ms, T₂ bias = −1.2 ms). The correlation and Bland-Altman plot from the phantom repeatability experiments are shown in Supporting Information Figure S7.

3.2 | In vivo

Segment-wise B₁ measurements for all 16 healthy subjects are shown in Supporting Information Figure S8. The mean ± SD relative B₁ across all segments and subjects was 0.60 ± 0.04 and the mean SD for each subject (intra-subject relative B₁ variability) was 0.02. An example demonstrating the usefulness of B₁ correction for Multimapping is shown in Figure 3. The figure shows in vivo T₁ and T₂ maps from one healthy subject incorporating B₁ measured in the septum, with lower difference between measured and simulated signal compared to no B₁ correction (B₁ = 1). The mean ± SD SDD of the simulated and measured magnetization (in Mxy/M₀) for the myocardium in the healthy subjects using B₁ correction was 0.0035 ± 0.0012, significantly smaller than for no B₁ correction (0.010 ± 0.0022; p < 0.0001). Without B₁ correction the mean T₁ across all 16 healthy subjects was 1128 ± 20 ms and T₂ was 57.5 ± 3.4, significantly higher than with B₁ correction (T₁ = 1114 ± 14 ms, p < 0.01; T₂ = 47.1 ± 1.3 ms, p < 0.01).

Multimapping T₁ and T₂ maps generated with and without respiratory MoCo are shown in Supporting Information Figure S9 from the healthy subject with the largest respiratory motion amplitude. Representative Multimapping T₁ and T₂ maps for two healthy subjects are shown in Figure 4, along with MOLLI and T₂bSSFP for comparison. Comparable image quality between the Multimapping images and reference techniques can be observed. Bullseye plots of the group mean T₁ and T₂ measurements for the healthy subjects are shown in Figure 5, including segmental and global measurements. Group-wise mean T₁ for the healthy subjects in the entire slice was significantly higher using Multimapping (T₁ = 1114 ± 14 ms) compared to MOLLI (T₁ = 991 ± 26 ms; p < 0.01). Furthermore, group-wise mean Multimapping T₂ (47.1 ± 1.3 ms) was significantly lower compared to T₂bSSFP for the entire slice (T₂ = 54.7 ± 2.2 ms; p < 0.001). Bland-Altman plots of the myocardial T₁, blood T₁ and myocardial T₂ for the entire slice from Multimapping, MOLLI and T₂bSSFP are shown in Figure 6. Bullseye plots of the T₁ and T₂ mean spatial variability for Multimapping and reference techniques are shown in Figure 7. There was no difference in T₁ spatial variability between Multimapping (63.5 ± 12.8 ms) and MOLLI (66.1 ± 15.4 ms) for the entire slice (p = 0.62). However, T₂ spatial variability was significantly lower for Multimapping (5.8 ± 1.0 ms) compared to T₂bSSFP (8.4 ± 2.0 ms) for the entire slice (p < 0.01). A Multimapping source image, T₁ and T₂ map for one healthy subject are shown in Supporting Information Figure S10. Although T₁ and T₂ are homogeneous across the myocardium, quantification differences, particularly for T₂, can be observed for peripheral subcutaneous fat.

Bland-Altman plots comparing the repeated Multimapping, MOLLI and T₂bSSFP scans in six healthy subjects, for the six AHA segments (and left ventricular blood pool for T₁), are shown in Figure 8. All techniques yielded biases less than 1 ms between the repetitions. However, the 95% limits of agreement were smaller for Multimapping T₁ (−24.7 to 26.3 ms) compared to MOLLI (−34 to 32.3 ms), and Multimapping T₂ (−1.6 to 1.6 ms) compared to T₂bSSFP (−2.9 to 2.4 ms).

T₁ maps, T₂ maps, and late gadolinium enhancement (LGE) images from the patient with dilated cardiomyopathy are shown in Figure 9. Septal T₁ and T₂ from the Multimap (which overlaps with a region of LGE) was increased in this patient compared to the values in the cohort of healthy subjects. Increased T₁ but not T₂ was measured with the reference techniques, although the T₁ increase was more modest compared to the difference measured with Multimapping. Multimaps, reference maps, and LGE images for the 49-year-old patient with acute myocarditis (Figure 10) reveal an area of acute inflammation in the anterior segment. Multimapping T₁ in
this area was 1373 ms, compared to 1111 ms in the inferolateral segment without enhancement. Corresponding MOLLI $T_1$ was 1267 ms in the anterior segment, and 1004 ms in the inferolateral segment. Multimapping $T_2$ was 72.9 ms and 46.4 ms in the anterior and inferolateral segments, respectively. Corresponding $T_2$ bSSFP $T_2$ was 82.5 ms and 57.3 ms, respectively. Multimaps, LGE, and short tau inversion recovery (STIR) images for the 41-year-old patient with acute myocarditis are show in Supporting Information Figure S11. In this patient, the $T_1$ and $T_2$ values were significantly increased globally. However, due to the diffuse and global nature of the disease in this patient, myocardial contrast agent uptake was relatively difficult to appreciate in the $T_1$-weighted LGE images, while the $T_2$-weighted STIR images also yielded an apparent constant signal that was only borderline pathological (signal intensity ratio of myocardium versus skeletal muscle = 2.0).
DISCUSSION

In this work, the single-shot Cartesian Multimapping technique was proposed for simultaneous myocardial $T_1$ and $T_2$ mapping using dictionary matching. Multimapping yields generally accurate $T_1$ and $T_2$ times independently of the heart rate, as demonstrated in the phantom study. Studies in healthy subjects showed consistently different $T_1$ and $T_2$ values between Multimapping and reference techniques, although particularly for $T_1$ this is to be...
expected due to the known bias of MOLLI, which underestimates $T_1^{11,38}$

Inversion pulses and $T_2$ prep modules are frequently used for myocardial mapping techniques to provide $T_1$ and $T_2$ sensitization, respectively. The configuration of these pulses may be modified and optimized to increase accuracy and precision.$^{30,39}$ A number of Multimapping embodiments were investigated in simulations and in
vivo, all restricted to 10 cardiac cycle acquisitions, but with different inversion and T$_2$prep settings. There was a good agreement between simulation and in vivo results, showing that the highly T$_1$ sensitized approach fared better for T$_1$ quantification, while T$_2$ quantification suffered. Conversely, sensitizing primarily for T$_2$ yielded good T$_2$ quantification at the expense of T$_1$. The “balanced” approach with two inversion pulses and three
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T2prep modules appears to provide a good tradeoff between T1 and T2 quantification error. Nevertheless, this small optimization study was limited in scope and extent. Further experiments, using a more exhaustive range of Multimapping embodiments should be considered, which could also include using different or varying (between images) flip angles.

An assumption of the proposed Multimapping approach is that the B1 field is homogeneous and can be represented by an ROI in the septum. Evaluation of B1 across the healthy subjects scanned in this study and using a reference B1 mapping technique suggests this is a valid assumption, with little variation across the left ventricle. However, the inter-subject B1 variability was significant.
and approximately twice as large as the intra-subject variability, which justifies the use of a subject-specific $B_1$ determination rather than an empirically determined $B_1$ for all subjects. Incorporating subject-specific $B_1$ in the proposed fashion, as a pre-processing step, reduces the computational complexity of the dictionary matching, keeping the generation times low while avoiding overfitting the data and reducing precision. However, further studies are required to evaluate if this approach is valid in a more varied cohort of subjects, across vendor platforms, and importantly at different field strengths. Field inhomogeneity is typically more pronounced at 3T and an alternative strategy may be needed to ensure accurate quantification. Furthermore, the need for manual interaction to define the septal $B_1$ measurement is an obvious limitation of the technique, but one that could be solved using automation. Signal variations caused by $B_0$ inhomogeneities were also not considered in this work. The bSSFP technique used for Multimapping image acquisition is sensitive to $B_0$ field inhomogeneities, which may affect quantification. This was seen particularly in the image periphery, where $B_0$ is less homogeneous and $T_2$ quantification of subcutaneous fat yielded differences of approximately 40% (Supporting Information Figure S10). However, myocardial $T_1$ and $T_2$ did not suffer noticeably from such spatial variability, as very similar $T_1$ and $T_2$ were measured across the myocardium in the healthy subjects. Again, $B_0$ inhomogeneity is likely a greater source of errors.
at 3T, and strategies to mitigate against this should be considered, such as including B0 in the dictionary matching or using a spoiled gradient echo readout.

The emphasis of this work has been to develop a dictionary-based cardiac parameter mapping technique, similar to previously proposed cardiac MRF, but without the requirement for complex and time-consuming post-processing. This may potentially lower the barrier for clinical adoption of simultaneous multi-parametric mapping. Previous efforts in cardiac parameter mapping (particularly T1 mapping) have resulted in standardized imaging parameters with the aim of producing comparable quantification across platforms, and this could be readily translated to Multimapping, which uses a nearly identical Cartesian bSSFP image acquisition scheme. A long-standing challenge in conventional T1 and T2 mapping, where mapping is performed as separate scans, is the relatively large inter-subject variability of the quantification. Although some of this variability may be attributed to factors such as age, sex, or even hydration status,41,42 T1 mapping may be confounded by T2 effects, particularly if bSSFP readouts are used, and, vice-versa, T2 mapping can be confounded by T1 differences in tissue.43 An advantage of simultaneous T1 and T2 mapping such as Multimapping is that these confounders are minimized as they are both included in the signal model. This may explain why the inter-subject variability of both T1 and T2 for Multimapping was lower than for the reference in vivo techniques.

Although the mean Multimapping T1 of 1114 ms was higher than for MOLLI, it is still just under 100 ms shorter than reported values in what are considered accurate techniques, such as SASHA or SAPPHIRE at 1.5T.44,45 Correction for sources of systematic errors, such as slice profile correction, may yield T1 values in a similar range and will be the focus of future work. Nevertheless, the in vivo precision of Multimapping for quantifying myocardial T1, as indicated by the spatial variability, was comparable to MOLLI, which is considered the most precise of the widely used T1 mapping methods.11 There are several factors that influence the precision of a cardiac T1 mapping method, including which kind of pre-pulse is used (inversion or saturation) and how many source images are used for the curve-fitting or dictionary-matching procedure.11,46–48 In both these aspects, MOLLI and Multimapping are very similar, which could explain the near equivalence in T1 precision. For T2, there was a significant difference in mean values between Multimapping and the reference technique of -7.6 ms. There is less consensus regarding the true T2 for healthy myocardium at 1.5T, which ranges from approximately 46 to 58 ms, depending on the technique or vendor used.49–52 However, for previous comparable cardiac MRF techniques, T2 values in the range of 41 to 45 ms have been reported,28,53–55 which is lower than the T2 observed with Multimapping of 47.1 ms. Compared to T2 bSSFP, Multimapping produced T2 maps with significantly less spatial variability. Similar as for T1 mapping, T2 precision for T2 bSSFP is related to the number of source images used, which is typically limited by the need for long waiting times to allow for near complete T1 recovery between image acquisitions.56 The lower spatial variability of Multimapping T2 may be explained by the use of more images for the mapping procedure. While T2 bSSFP only used 4 source images for the fitting, 10 images were used for Multimapping. Even if only three cardiac cycles were preceded by T2-preparation to increase T2 sensitization in the Multimapping pulse sequence, the bSSFP readout itself provides T2/T1 contrast, which is exploited by the dictionary-based Multimapping technique but not with T2 bSSFP.57

The ability of Multimapping to detect pathological changes in T1 and T2 was demonstrated in three patients: one with dilated cardiomyopathy and two with acute myocarditis. In all cases, a significant increase in T1 and T2, well above the healthy ranges, was observed. This finding is consistent with previous studies using mapping techniques in these patient cohorts.58–60 Although a similar increase was also found using the reference techniques in both patients with acute myocarditis, T2 bSSFP did not find a significant T2 increase in the patient with dilated cardiomyopathy compared to the healthy subjects. Further studies are ongoing in patients with various cardiovascular diseases to compare Multimapping parameter values to clinical reference techniques and values obtained in healthy controls.

Long dictionary generation times are a significant impediment to the integration of dictionary-based techniques into the clinical workflow.25 To limit dictionary generation times while providing T1 and T2 maps with high parameter granularity, an approach using partially resolved dictionaries was proposed in this study. Comparison with a reference dictionary showed that this can be a practical solution to this problem, as T1 and T2 maps could be generated on a standard computer without optimized Matlab code within minutes, with excellent agreement for T2 and good agreement for T1 in the myocardium. Note, that this evaluation specifically considered native T1 and T2 for myocardium and may not be directly extended to tissues with other T1 and T2 values.

The proposed Multimapping technique shares similarities, but also has important differences compared to recent cardiac MRF techniques.27,28 Like cardiac MRF, inversion pulses, and T2-preparation are combined in the same pulse sequence and are the primary sources of T1 and T2 sensitization, respectively. However, Multimapping does not suffer from the signal aliasing that is intrinsic to
non-Cartesian MRF, which has some important implications. The number of data points that can be used to match measurements to simulations for each dictionary entry is smaller for the proposed Cartesian approach by nearly two orders of magnitude (10 measurements for Multimapping versus approximately 1000 for conventional cardiac MRF). Although the number of acquired images could be increased to mitigate against overfitting, this would either increase the breath-hold duration or require the use of free-breathing acquisition strategies. An advantage of avoiding signal aliasing in the measurements, particularly for cardiothoracic and abdominal application, is that tissue outside the ROI such as subcutaneous fat does not degrade the measurements. Solutions to this problem for cardiac MRF have relied on non-Cartesian multi-echo acquisition strategies that lower the acquisition efficiency and require more complicated reconstruction algorithms. A Cartesian dictionary-based technique similar to Multimapping, proposed by Kvernby et al., uses a simplified Bloch equation formulation that is limited to spoiled gradient echo readouts and has a SNR penalty compared to the bSSFP readout used in this study. Another comparable Cartesian dictionary-based technique using EPG simulations was recently proposed for T2 mapping of the prostate which uses a segmented k-space acquisition but demonstrates the feasibility of this approach. Finally, a dictionary-based Cartesian approach for myocardial T1 and T2 mapping was recently proposed by Milotta et al. using EPG simulations to generate the dictionaries. However, that study used a spoiled gradient echo, segmented k-space trajectory acquired during free breathing, which combines data across multiple cardiac cycles that are subject to variability and susceptible to cardiac and respiratory motion artifacts. Conversely, the proposed approach uses a bSSFP single-shot trajectory acquired in a breath-hold, where the inversion delays and timings are tailored and specific to each image to account for heart rate variability or arrhythmia.

This study has several limitations. Only a small number of healthy subjects and a few patients were included in this study to demonstrate proof-of-concept. Larger studies in healthy subjects and patients with cardiovascular disease are required to establish quantification ranges to discriminate between healthy and diseased myocardium. A very limited in vivo intra-scan repeatability evaluation was performed in this study and a more extensive evaluation, including reproducibility and inter-scan repeatability, is required to comprehensively assess its clinical potential. Although the reference techniques included in this study, MOLLI and T1-bSSFP, may be considered the most clinically used and relevant, there are alternative mapping techniques that provide improvements in accuracy or precision, which may be more appropriate reference techniques to assess these important quantification error metrics. The phantom used for in vitro experiments covers a wide range of T1 and T2, including those of pre- and post-contrast myocardium and blood. However, the phantom does not include the specific T1/T2 (~1200/50 ms) combinations found in the myocardium, which may have implication for assessing the accuracy of myocardial T1 and T2 quantification. In vitro studies using phantoms with similar T1/T2 combinations as the myocardium will be performed in the future. Correction for confounders, such as slice profile, inversion imperfections, or B1, were not considered in this work. Previous studies using MRF have demonstrated how this may be incorporated into the dictionary to improve accuracy at the expense of increasing dictionary generation times. Although this could improve the accuracy of the technique, it may also reduce precision. This consideration, in addition to the desire to limit the dictionary generation time to a short duration, was the rationale for only including T1 and T2 in the main dictionaries. Further work will explore if accuracy can be increased without compromising on precision or post-processing durations, for example, by using machine learning.

5 | CONCLUSIONS

Multimapping allows simultaneous T1 and T2 mapping of the myocardium with a Cartesian trajectory, demonstrating good agreement with reference techniques in vitro and promising in vivo image quality and parameter quantification results. The post-processing time could be significantly reduced by generating partially resolved T1 and T2 dictionaries, and the Multimapping approach for acquisition and post-processing is well-suited for integration into clinical routine. Further studies using Multimapping in healthy subjects and patients with cardiovascular disease are warranted.

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DATA AVAILABILITY STATEMENT

To support the findings of the manuscript, all MATLAB source code for generating the Multimapping dictionaries and feature extraction are available at https://github.com/Multimapping/Matlab_files, including example Multimapping source images for one healthy subject.

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REFERENCES

1. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2 and extracellular volume: a consensus statement by the society for cardiovascular magnetic resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging. J Cardiovasc Magn Reson. 2017;19.

2. Lota AS, Gatehouse PD, Mohiaddin RH. T2 mapping and T2* imaging in heart failure. Heart Fail Rev. 2017;22:431-440.

3. Radenkovíc D, Weingärtner S, Rickett S, Moon JC, Captur G. T1 mapping in cardiac MRI. Heart Fail Rev. 2017;22:415-430.

4. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: a comprehensive review. J Cardiovasc Magn Reson. 2016;18.

5. Ferreira VM, Piechtnik SK, Robson MD, Neubauer S, Karamitsos TD. Myocardial tissue characterization by magnetic resonance imaging: novel applications of T1 and T2 mapping. J Thorac Imaging. 2014;29:147-154.

6. Hamlin SA, Henry TS, Little BP, Lerakis S, Stillman AE. Mapping the future of cardiac MR imaging: case-based review of T1 and T2 mapping techniques. Radiographics. 2014;34:1594-1612.

7. Mavrogeni S, Apostolou D, Argyriou P, et al. T1 and T2 mapping in cardiology: “mapping the obscure object of desire.” Cardiology (Switzerland). 2017;138:207-217.

8. Puntmann VO, Zeiher AM, Nagel E. T1 mapping in cardiac MRI. Heart Fail Rev. 2017;19.

9. Pan JA, Lee YJ, Salerno M. Diagnostic performance of extracellular volume, native T1, and T2 mapping versus Lake Louise criteria by cardiac magnetic resonance for detection of acute myocarditis a meta-analysis. Circ Cardiovasc Imaging. 2018;11.

10. Messroghli DR, Radjenovic A, Kozerke S, Higgins DM, Sivananthan MU, Ridgway JP. Modified look-locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. Magn Reson Med. 2004;52:141-146.

11. Kellman P, Hansen MS. T1-mapping in the heart: accuracy and precision. J Cardiovasc Magn Reson. 2014;16.

12. Sprinkart AM, Luetkens JA, Träber F, et al. Gradient Spin Echo (GraSE) imaging for fast myocardial T2 mapping. J Cardiovasc Magn Reson. 2015;17.

13. Huang TY, Liu YJ, Stempfer A, Poncelet BP. T2 measurement of the human myocardium using a T2-prepared transient-state trueFISP sequence. Magn Reson Med. 2007;57:960-966.

14. Baeßler B, Scharrersmütz B, Stenhag C, Schnackenburg B, Mainz D, Bunck AC. Cardiac T2-mapping using a fast gradient echo spin echo sequence - First in vitro and in vivo experience. J Cardiovasc Magn Reson. 2015;17.

15. Hermann I, Kellman P, Demirel OB, Akçakaya M, Schad LR, Weingärtner S. Free-breathing simultaneous T1, T2, and T2+ quantification in the myocardium. Magn Reson Med. 2021;86:1226-1240.

16. Christodoulou AG, Shaw JL, Nguyen C, et al. Magnetic resonance multiscan for motion-resolved quantitative cardiovascular imaging. Nat Biomed Eng. 2018;2:215-226.

17. Akçakaya M, Weingärtner S, Basha TA, Roujol S, Bellm S, Nezafat R. Joint myocardial T1 and T2 mapping using a combination of saturation recovery and T2-preparation. Magn Reson Med. 2016;76:888-896.

18. Blume U, Lockie T, Stehning C, et al. Interleaved T1 and T2 relaxation time mapping for cardiac applications. J Magn Reson Imaging. 2009;29:480-487.

19. Marty B, Coppa B, Carlier PG. Fast, precise, and accurate myocardial T1 mapping using a radial MOLLI sequence with FLASH readout. Magn Reson Med. 2018;79:1387-1398.

20. Santini F, Kavel-Boehm N, Greiser A, Bremerich J, Bieri O. Simultaneous T1 and T2 quantification of the myocardium using cardiac balanced-SSFp inversion recovery with interleaved sampling acquisition (CABIRIA). Magn Reson Med. 2015;74:365-371.

21. Qi H, Bustin A, Cruz G, et al. Free-running simultaneous myocardial T1/T2 mapping and cine imaging with 3D whole-heart coverage and isotropic spatial resolution. Magn Reson Imaging. 2019;63:159-169.

22. Guo R, Chen Z, Herzka DA, Luo J, Ding H. A three-dimensional free-breathing sequence for simultaneous myocardial T1 and T2 mapping. Magn Reson Med. 2019;81:1031-1043.

23. Ma D, Gulani V, Seibertlch N, et al. Magnetic resonance fingerprinting. Nature. 2013;495:187-192.

24. Cruz G, Jaubert O, Botnar RM, Prieto C. Cardiac magnetic resonance fingerprinting: technical developments and initial clinical validation. J Cardioviol Rep. 2019;21.

25. Liu Y, Hamilton J, Rajagopalan S, Seibeltlch N. Cardiac magnetic resonance fingerprinting: technical overview and initial results. JACC Cardiovasc Imaging. 2018;11:1837-1853.

26. Liu Y, Hamilton J, Eck B, Griswold M, Seibeltlch N. Myocardial T1 and T2 quantification and water-fat separation using cardiac MR fingerprinting with rosette trajectories at 3T and 1.5T. Magn Reson Med. 2021;85:103-119.

27. Hamilton JJ, Jiang Y, Chen Y, et al. MR fingerprinting for rapid quantification of myocardial T1, T2, and proton spin density. Magn Reson Med. 2017;77:1446-1458.

28. Jaubert O, Cruz G, Bustin A, et al. Water-fat Dixon cardiac magnetic resonance fingerprinting. Magn Reson Med. 2020;83:2107-2123.

29. Kvernby S, Warntjes MJB, Haraldsson H, Carlhäll C-J, Engvall J, Ebbers T. Simultaneous three-dimensional myocardial T1 and T2 mapping in one breath hold with 3D-QALAS. J Cardiovasc Magn Reson. 2014;16:102.

30. Hamilton JJ, Jiang Y, Ma D, et al. Investigating and reducing the effects of confounding factors for robust T1 and T2 mapping with cardiac MR fingerprinting. Magn Reson Imaging. 2018;53:40-51.

31. Vishnevskiy V, Gass T, Szekely G, Tanner C, Goksel O. Isotropic total variation regularization of displacements in parametric image registration. IEEE Trans Med Imaging. 2017;36:385-395.

32. Kellman P, Arai AE, McVeigh ER, Aletras AH. Phase-sensitive inversion recovery for detecting myocardial infarction using gadolinium-delayed hyperenhancement. Magn Reson Med. 2002;47:372-383.

33. Keenan KE, Boss M, Jackson EF, Kwon SI, Jennings DL, Russek SE. NIST/ISMRM MRI system phantom T1 measurements on multiple MRI systems. In Proceedings of the 21st Annual Meeting of ISMRM, Salt Lake City, Utah, USA, 2013. Abstract 4338.

34. Shridhar Konar A, Qian E, Geethanath S, et al. Quantitative imaging metrics derived from magnetic resonance fingerprinting using ISMRM/NIST MRI system phantom: an international multicenter repeatability and reproducibility study. Med Phys. 2021;48:2438-2447.
35. Rincón-Domínguez T, Menini A, Solana AB, et al. Accelerated multi-snapshot free-breathing B1+ mapping based on the dual refocusing echo acquisition mode technique (DREAM): an alternative to measure RF nonuniformity for cardiac MRI. *J Magn Reson Imaging*. 2019;49:499-507.

36. Nehrke K, Börnert P. DREAM—a novel approach for robust, ultrafast, multislice B1 mapping. *Magn Reson Med*. 2012;68:1517-1526.

37. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. *J Cardiovasc Magn Reson*. 2002;4:203-210.

38. Roujol S, Weingärtner S, Foppa M, et al. Accuracy, precision, and reproducibility of four T1 mapping sequences: a head-to-head comparison of MOLLI, ShMOLLI, SASHA, and SAPPHIRE. *Radiology*. 2014;272:683-689.

39. Milotta G, Bustin A, Jaubert O, Neji R, Prieto C, Botnar RM. 3D whole-heart isotropic-resolution motion-compensated joint T1/T2 mapping and water/fat imaging. *Magn Reson Med*. 2020;84:3009-3026.

40. Bernard O, Lalande A, Zotti C, et al. Deep learning techniques for automatic MRI cardiac multi-structures segmentation and diagnosis: is the problem solved? *IEEE Trans Med Imaging*. 2018;37:2514-2525.

41. Roy C, Slimani A, De Meester C, et al. Age and sex corrected normal reference values of T1, T2, T2* and ECV in healthy subjects at 3T CMR. *J Cardiovasc Magn Reson*. 2017;19.

42. Luetkens JA, Voigt M, Faron A, et al. Influence of hydration status on cardiovascular magnetic resonance myocardial T1 and T2 relaxation time assessment: an intraindividual study in healthy subjects. *J Cardiovasc Magn Reson*. 2020;22.

43. Ding H, Fernandes-De-Manuel L, Schär M, et al. Three-dimensional whole-heart T2 mapping at 3T. *Magn Reson Med*. 2015;74:803-816.

44. Chow K, Flewitt JA, Green JD, Pagano JJ, Friedrich MG, Thompson RB. Saturation recovery single-shot acquisition (SASHA) for myocardial T1 mapping. *Magn Reson Med*. 2014;71:2082-2095.

45. Weingärtner S, Akçakaya M, Basha T, et al. Combined saturation/inversion/recovery sequence for improved evaluation of scar and diffuse fibrosis in patients with arrhythmia or heart rate variability. *Magn Reson Med*. 2014;71:1024-1034.

46. Nordio G, Bustin A, Odille F, et al. Faster 3D saturation-recovery based myocardial T1 mapping using a reduced number of saturation points and denoising. *PLoS One*. 2020;15.

47. Bellman P, Arai AE, Xue H. T1 and extracellular volume mapping in the heart: estimation of error maps and the influence of noise on precision. *J Cardiovasc Magn Reson*. 2013;15.

48. Cavassila S, Deval S, Huegen C, Van Ormond D, Graveron-Demilly D. Cramer-Rao bounds: an evaluation tool for quantitation. *NMR Biomed*. 2001;14:278-283.

49. Baeßler B, Schaarsschmidt F, Stehning C, Schnackenburg B, Maintz D, Bunck AC. A systematic evaluation of three different cardiac T2-mapping sequences at 1.5 and 3T in healthy volunteers. *Eur J Radiol*. 2015;84:2161-2170.

50. Bönnner F, Janzari N, Jacoby C, et al. Myocardial T2 mapping reveals age- and sex-related differences in volunteers. *J Cardiovasc Magn Reson*. 2015;17.

51. Granitz M, Motloch LJ, Granitz C, et al. Comparison of native myocardial T1 and T2 mapping at 1.5T and 3T in healthy volunteers: reference values and clinical implications. *Wien Klin Wochenschr*. 2019;131:143-155.

52. Wieszmueller M, Wuest W, Heiss R, Treutlein C, Uder M, May MS. Cardiac T2 mapping: robustness and homogeneity of standardized in-line analysis. *J Cardiovasc Magn Reson*. 2020;22.

53. Cruz G, Jaubert O, Qi H, et al. 3D free-breathing cardiac magnetic resonance fingerprinting. *NMR Biomed*. 2020;33.

54. Jaubert O, Cruz G, Bustin A, et al. T1, T2, and fat fraction cardiac MR fingerprinting: preliminary clinical evaluation. *J Magn Reson Imaging*. 2021;53:1253-1265.

55. Hamilton JJ, Pahwa S, Adedigba J, et al. Simultaneous mapping of T1 and T2 using cardiac magnetic resonance fingerprinting in a cohort of healthy subjects at 1.5T. *J Magn Reson Imaging*. 2020;52:1044-1052.

56. Akçakaya M, Basha TA, Weingärtner S, Roujol S, Berg S, Nezafat R. Improved quantitative myocardial T2 mapping: impact of the fitting model. *Magn Reson Med*. 2015;74:93-105.

57. Scheffler K. On the transient phase of balanced SSFP sequences. *Magn Reson Med*. 2003;49:781-783.

58. Mordi I, Carrick D, Bezerra H, Tzemos N. T1 and T2 mapping for early diagnosis of dilated non-ischaemic cardiomyopathy in middle-aged patients and differentiation from normal physiological adaptation. *Eur Heart J Cardiovasc Imaging*. 2016;17:797-803.

59. von Knobelsdorff-Brenkenhoff F, Schüler J, Dogangüliz S, et al. Detection and monitoring of acute myocarditis applying quantitative cardiovascular magnetic resonance. *Circ Cardiovasc Imaging*. 2017;10.

60. Snel GJH, van den Boomen M, Hernandez LM, et al. Cardiovascular magnetic resonance native T2 and T2* quantitative values for cardiomyopathies and heart transplantations: a systematic review and meta-analysis. *J Cardiovasc Magn Reson*. 2020;22.

61. Roccia E, Vidya Shankar R, Neji R, et al. Accelerated 3D T2 mapping with dictionary-based matching for prostate imaging. *Magn Reson Med*. 2019;81:1795-1805.

62. Piechnik SK, Ferreira VM, Dall’Armellina E, et al. Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within a 9 heartbeat breathhold. *J Cardiovasc Magn Reson*. 2010;12.

63. Mehta BB, Chen X, Bilchick KC, Salerno M, Epstein FH. Accelerated and navigator-gated Look-Locker imaging for cardiac T1 estimation (ANGIE): development and application to T1 mapping of the right ventricle. *Magn Reson Med*. 2015;73:150-160.

64. Weingärtner S, Roujol S, Akçakaya M, Basha TA, Nezafat R. Free-breathing multislice native myocardial T1 mapping using the slice-interleaved T1 (STONE) sequence. *Magn Reson Med*. 2015;74:115-124.

65. Captur G, Gatehouse P, Keenan KE, et al. A medical device-grade T1 and ECV phantom for global T1 mapping quality assurance - the T1 mapping and ECV standardization in cardiovascular magnetic resonance (TIMES) program. *J Cardiovasc Magn Reson*. 2016;18:1-20.

66. Ma D, Coppo S, Chen Y, et al. Slice profile and B1 corrections in 2D magnetic resonance fingerprinting. *Magn Reson Med*. 2017;78:1781-1789.

67. Buonincontri G, Schulte RF, Cosottini M, Tosetti M. Spiral MR fingerprinting at 7T with simultaneous B1 estimation. *Magn Reson Imaging*. 2017;41:1-6.
SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

FIGURE S1 Pulse sequence diagrams of different versions of the Multimapping techniques with variations of the magnetization preparation pulses (pre-pulses) to manipulate $T_1$ and $T_2$ sensitization. MM NoPrep does not contain any pre-pulses which should yield poor $T_1$ and $T_2$ sensitivity. MM 3I-2T$_3$p is particularly sensitized to $T_1$ and contain three inversion pulses at different inversion times and two $T_2$ preparation modules with echo times of 30 and 70 ms. MM 1I-5T$_3$p is sensitized to $T_2$ and contains a single inversion pulse and five $T_2$ preparation modules, with echo times ranging from 30 to 110 ms with 20 ms increments. Finally, MM 2I-3T$_3$p aims to balance $T_1$ and $T_2$ sensitivity and consist of two inversion pulses and three $T_2$ preparation modules with echo times of 30, 50 and 70 ms

FIGURE S2 Simulations of the Multimapping pulse sequences illustrated in Figure S1 for a numerical phantom of the heart. Differences in configuration of inversion and $T_2$ preparation pulses lead to different root mean square errors (RMSE) for $T_1$ and $T_2$ of myocardium. A comparably low RMSE for both $T_1$ and $T_2$ is achieved using Multimapping MM 2I-3T$_3$p

FIGURE S3 $T_1$ and $T_2$ Multimaps generated using the 3I-2T$_3$p, 1I-5T$_3$p and 2I-3T$_3$p schemes in one healthy subject. 3I-2T$_3$p and 2I-3T$_3$p generate similar $T_1$ maps, although the latter scheme has a slightly higher spatial variability as indicated by the standard deviation. In comparison, 1I-5T$_3$p yields higher myocardial mean $T_1$ and spatial variability. Mean $T_2$ was approximately the same for all schemes, while $T_2$ spatial variability was highest for 3I-2T$_3$p and lowest for 1I-5T$_3$p

FIGURE S4 Normalized root mean square error (NRMSE) versus processing time for the $T_2$ partial dictionary (left) and NRMSE versus processing time for the $T_1$ partial dictionary (right)

FIGURE S5 Example Multimapping and dual refocusing echo mode (DREAM) $B_1$ maps from one healthy subject.

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