# Clinical evaluation of the Multimapping technique for simultaneous myocardial $T_1$ and $T_2$ mapping

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## Abstract

The Multimapping technique was recently proposed for simultaneous myocardial $T_1$ and $T_2$ mapping. In this study we evaluate its correlation with clinical reference mapping techniques in patients with a range of cardiovascular diseases (CVD), compare image quality and inter- and intra-observer repeatability. Multimapping consists of a ECG-triggered, 2D single-shot bSSFP readout with inversion recovery and $T_2$ preparation modules, acquired across 10 cardiac cycles. The sequence was implemented at 1.5T and compared to clinical reference mapping techniques, Modified Look-Locker inversion recovery (MOLLI) and $T_2$ prepared bSSFP with four echo times ($T_2$bSSFP), and compared in 47 patients with CVD (of which 44 were analyzed). In diseased myocardial segments (defined as presence of late gadolinium enhancement) there was a high correlation between Multimapping and MOLLI for native myocardium $T_1$ ($r^2$=0.73), ECV ($r^2$=0.91) and blood $T_1$ ($r^2$=0.88), and Multimapping and $T_2$bSSFP for native myocardial $T_2$ ($r^2$=0.80). In healthy myocardial segments a bias for native $T_1$ (Multimapping=1116±21 ms, MOLLI=1002±21, $P$<0.001), post-contrast $T_1$ (Multimapping=479±31 ms, MOLLI=426±27 ms, 0.001), ECV (Multimapping=21.5±1.9%, MOLLI=23.7±2.3%, $P$=0.001) and native $T_2$ (Multimapping=48.0±3.0 ms, $T_2$bSSFP=53.9±3.5 ms, $P$<0.001) was observed. The image quality for Multimapping was scored as higher for all mapping techniques (native $T_1$, post-contrast $T_1$, ECV and $T_2$bSSFP) compared to the clinical reference techniques. The inter- and intra-observer agreement was excellent (intraclass correlation coefficient, ICC>0.9) for most measurements, except for inter-observer repeatability of Multimapping native $T_1$ (ICC=0.87), post-contrast $T_1$ (ICC=0.73) and $T_2$bSSFP native $T_2$ (ICC=0.88). Multimapping show high correlations with clinical reference mapping techniques for $T_1$, $T_2$ and ECV in a diverse cohort of patients with different cardiovascular diseases. Multimapping enables simultaneous $T_1$ and $T_2$ mapping and can be performed in a short breath-hold, with image quality superior to that of the clinical reference techniques.

## 1 Introduction

Myocardial $T_1$ and/or $T_2$ values are altered in many cardiovascular diseases (1). $T_1$ and $T_2$ quantification, along with disease-specific patterns of regional and global distribution, can be captured with myocardial mapping techniques (2). In the last 15-20 years a number of $T_1$ and $T_2$ mapping techniques have been published, with different strengths and weaknesses in terms of quantification accuracy, precision, scan time, spatial resolution and coverage (3). Despite being one of the first $T_1$ mapping techniques, the modified Look-Locker inversion recovery (MOLLI) remains the most clinically used method due to its high precision and availability on all major scanner platforms (4,5). However, MOLLI $T_1$ accuracy is relatively low and the quantification is susceptible to confounding effects from heart-rate or $T_2$-dependent variability, magnetization transfer effects, motion artifacts and system imperfections (5,6). Different $T_1$ mapping methods have been proposed to address these shortcomings, yet have failed to make significant inroads in the market share of clinical use (7–11). Myocardial $T_2$ mapping can be performed with multi-echo spin-echo or $T_2$-prepared balanced steady-state free precession ($T_2$bSSFP) techniques (12–14). The latter approach is likely the most widely used clinically due to its relative robustness to physiological motion.

In recent years, there has been a growing interest in techniques to simultaneously map $T_1$ and $T_2$ in a single scan (15–21). Advantages of this approach compared to conventional mapping, which is performed separately for $T_1$ and $T_2$, is that the images are intrinsically spatially aligned, scan time is typically shorter and the confounding effects of $T_1$ or $T_2$ on the quantification of the opposite parameter is minimized. Despite the many theoretical advantages of simultaneous $T_1$ and $T_2$ mapping, there is a paucity of translational studies using these techniques in patients with cardiovascular disease (22,23). This may be due to the more sophisticated acquisition, reconstruction and mapping strategies necessary for such techniques, which pose challenges for clinical translation. Recently, a new technique for simultaneous $T_1$ and $T_2$ mapping, termed Multimapping, was proposed using a standard Cartesian trajectory and evaluated (primarily) in healthy subjects (24). Due to its simplicity Multimapping may be readily applied in a clinical setting to enable evaluation of simultaneous $T_1$ and $T_2$ mapping in patients with cardiovascular disease.

The primary aim of this study is to validate Multimapping $T_1$ and $T_2$ values against clinical reference techniques in patients with different cardiovascular diseases in terms of parameter quantification and image quality. A secondary study aim is to evaluate Multimapping intra- and inter-observer variability.

## 2 Materials and Methods

### 2.1 Study population

All patients provided written informed consent prior to participation and the study was approved by the local ethics committee (Linköping Regional Ethics Committee, 2015/396–31) and conducted according to the Declaration of Helsinki. Patients referred for CMR at Linköping University Hospital between June and November 2021 were considered for inclusion in this study. In total, 47 patients were recruited. Datasets from three patients were excluded, two because no late gadolinium enhancement (LGE) images were acquired and one due to excessive fold-over artifacts. Clinical characteristics of the remaining patients can be seen in Table 1. Of the included patients, normal cardiac MRI scan was found in 15 (34.1%) patients, myocarditis in 11 (25%) patients, dilated cardiomyopathy (DCM) in 6 (13.6%) patients, ventricular hypertrophy (hypertrophic cardiomyopathy or hypertrophy of unknown origin) in 5 (11.4%) patients, ischemic myocardial injury (acute/recent or old) in 3 (6.8%) patients,

arrhythmogenic right ventricular cardiomyopathy in 2 (4.5%) patients, pericarditis in 1 (2.3%) patient
and congenital heart disease in 1 (2.3%) patient.

**2.2     Data acquisition and reconstruction**

All scans were performed on a 1.5T Philips clinical CMR scanner (Philips Healthcare, Best, The
Netherlands) using a 28-channel torso coil. The Multimapping pulse sequence and post-processing
steps are illustrated in Figure 1. Ten single-shot images are acquired across consecutive cardiac cycles
using balanced-steady state free precession (bSSFP) readouts, triggered to the mid-diastolic rest period.
Adiabatic inversion radiofrequency (RF) pulses with delay times of 300 ms are performed in the 1$^{st}$
and 5$^{th}$ cardiac cycle to improve $T_1$ sensitization. The inversion pulse used a hyperbolic secant shape,
had a duration of 8.4 ms and a $B_1$ amplitude of 13.5 µT. A previous study has shown that similar
settings yield an inversion efficiency of approximately 0.89 (25), which was assumed for this study.
$T_2$ preparation modules with hard 90º RF pulses and four adiabatic refocusing RF pulses are performed
in the 8$^{th}$, 9$^{th}$, and 10$^{th}$ cardiac cycles to improve $T_2$ sensitization using echo times of 30, 50 and 70 ms,
respectively. The Multimapping imaging parameters for all experiments are: field-of-view = 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. The Multimapping scan was acquired in a mid-ventricular
short axis slice (except in one patient which was mistakenly acquired in a four-chamber view) during
a breath-hold. Native Multimapping was acquired in all 47 patients, and post-contrast Multimapping
was performed in 31 patients approximately 15 to 20 minutes after contrast agent administration (0.2
mmol/kg gadobutrol). Due to clinical prioritization, the post-contrast Multimapping was performed
after the acquisition of post-contrast MOLLI and LGE.

All Multimapping source images were reconstructed on the scanner and transferred to an offline
workstation (Intel Core i7-8565U 1.80 GHz processor with 16Gb RAM) to generate $T_1$ and $T_2$ maps
using MATLAB R2021b (The MathWorks, Natick, MA). The MATLAB code used to generate the
maps, including example Multimapping source images from one subject, is available at
https://github.com/Multimapping/Matlab_files. Since blood samples were not available for all patients,
Multimapping synthetic ECV maps were generated using synthetic hematocrit values, based on the
native MOLLI left ventricular blood pool measurements, as previously outlined (26). Image
registration using a rigid body transformation was applied to spatially align the native and post-contrast
$T_1$ maps prior to ECV calculation.

MOLLI was acquired in all 47 patients and T₂bSSFP was acquired in 45 patients, in the same slice as
Multimapping and used as clinical reference techniques for $T_1$ and $T_2$ mapping, respectively. All
imaging parameters for the reference techniques (field-of-view, spatial resolution etc.) were the same
as for Multimapping, except for the flip angle which was 35º. MOLLI was acquired with the 5(3s)3
scheme and used the same adiabatic inversion pulse as Multimapping. T₂bSSFP was acquired with four
images at different $T_2$ preparation echo times (0, 23, 46 and 70 ms) and used 3 pause cardiac cycles
between each image. Furthermore, T₂bSSFP used the same RF pulse types for the $T_2$ preparation
module as Multimapping. The reference maps were reconstructed on the scanner using vendor-
provided inline mapping algorithms, except for the ECV maps which were generated offline using
MATLAB. Similar to Multimapping, synthetic ECV maps were generated using a synthetic hematocrit
value derived from the left ventricular blood pool $T_1$ measured in the native MOLLI image. As for
Multimapping, image registration was applied to native and post-contrast MOLLI $T_1$ maps before ECV
was calculated. LGE imaging parameters were TR/TE = 5.6/2.0 ms, flip angle = 25º, FOV = 350×350
mm$^2$, spatial resolution = 1.8×1.8 mm$^2$.

### 2.3 Image Analysis

$T_1$ (native and post-contrast), $T_2$ (native) and ECV measurements were made by drawing manual regions-of-interest (ROI) in all datasets. To compare Multimapping to the clinical reference techniques, two sets of myocardial measurements were performed, one targeting any diseased myocardium and one targeting healthy myocardium. For the measurements of diseased myocardium in all maps, ROIs were drawn in the area corresponding with the most prominent positive LGE findings of each patient. Since only a subset of patients had positive LGE findings in the imaged slice, this resulted in 21 measurements for native $T_1$ and $T_2$, and 12 measurements for post-contrast $T_1$ and ECV. For the measurements of healthy myocardium in all maps, ROIs were drawn in the area remote of any LGE abnormality and preferentially in the interventricular septum if it was free of abnormal LGE. Patients were excluded from this analysis if there were indications suggestive of global or diffuse myocardial disease. The measurements in the healthy myocardium were performed in a total of 19 patients for native $T_1$, 12 patients for $T_1$ post-contrast and ECV, and 18 patients for $T_2$.

Measurements were performed in all patients by one observer (CJ, 1 year of CMR experience). To allow intra-observer variability analysis, measurements were repeated in 23 patients by the same observer two weeks later. For inter-observer variability analysis, the same 23 patients were measured by two additional observers (MH and CJC with 14 and 21 years of CMR experience, respectively). Furthermore, to compare blood $T_1$ (native and post-contrast), ROIs were drawn in the left ventricular blood pool (avoiding any papillary muscles) in the Multimapping $T_1$ and MOLLI images.

The image quality of the acquired maps were qualitatively compared using a Likert scale as devised by Jaubert et al. (22) with the following categories: 1 = uninterpretable, 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 = negligible blurring or residual artifacts. Visual scoring was performed for $T_1$ (native and post-contrast), $T_2$ (native) and ECV separately using the different mapping techniques and this analysis was performed in 20 patients. The visual scoring was performed by consensus of two blinded observers (CJ and CJC).

### 2.4    Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD. Categorical variables are expressed as counts and percentages. For the remote measurements, two-tailed Student paired t-tests were performed to compare Multimapping to MOLLI for native $T_1$, post-contrast $T_1$ and ECV, and Multimapping and $T_2$bSSFP for native $T_2$. For the remote measurements, all parameters tested positive for normality using a Shapiro-Wilk test. Bland-Altman and correlation plots were used to evaluate the agreement and correlation, respectively, between Multimapping and the reference techniques of the measurements in diseased myocardium for native $T_1$, post-contrast $T_1$, ECV and native $T_2$. To investigate any heart-rate dependency for the mapping techniques, the measurements of the remote myocardium was correlated with the heart-rate at the time of the scan. Similarly, dependency on $T_2$ for $T_1$ (and vice-versa) was evaluated by correlating remote $T_1$ with $T_2$ for both Multimapping and the reference techniques, and testing for statistical significance. To account for multiple comparisons, Bonferroni correction was performed on the threshold for all significance tests. Since four comparisons were performed (native and post-contrast $T_1$, native $T_2$ and ECV), a threshold of $0.05/4 = 0.0125$ was used. Intra-observer repeatability and inter-observer repeatability was assessed with intraclass correlation coefficient (ICC) analysis. ICC was calculated using absolute agreement two-way mixed model. Statistical analysis was performed using IBM SPSS Statistics, version 27.0.

**3    Results**

Representative parameter maps acquired with Multimapping, reference techniques and LGE in a
patient with no cardiovascular disease findings are shown in Figure 2. Parameter maps from a patient
with myocarditis are shown in Figure 3, with prominently altered quantitative values seen in both
Multimapping and reference techniques. The final example, in Figure 4, shows parameter maps from
a patient with myocardial infarction with a clearly delineated area of infarction in the Multimaps,
correlating     with     LGE.     Multimaps     for     all     patients     can     be     downloaded     from
https://github.com/Multimapping/Patient_study/raw/main/MapReconstructions.pdf.

**3.1    Comparison of Multimapping and reference techniques in remote myocardium**

The Multimapping native T$_1$ was 1116±21 ms and for MOLLI 1002±21 ms, resulting in a statistically
significant bias of 114 ms ($P < 0.001$). Multimapping post-contrast T1 was 479±31 ms and for MOLLI
426±27 ms, yielding a bias of 53 ms which was statistically significant ($P < 0.001$). Multimapping
ECV was 21.5±1.9%, MOLLI ECV was 23.7±2.3%, resulting in a bias of -2.2% which was statistically
significant ($P = 0.001$). Multimapping native T$_2$ was 48.0±3.0 ms while T$_2$bSSFP was 53.9±3.5 ms, a
statistically significant bias of -5.9 ms ($P < 0.001$) (Figure 5).

There was no correlation between native T$_1$ and T$_2$ for neither Multimapping nor MOLLI and T$_2$bSSFP.
Multimapping T$_1$ (native and post-contrast), T$_2$ or ECV and MOLLI T$_1$ (native and post-contrast) or
ECV did not correlate with heart-rate either. However, T$_2$bSSFP showed a correlation with heart rate
($P < 0.001$) (Figure 5).

**3.2    Comparison of Multimapping and reference techniques for diseased myocardium**

In general, the correlation between Multimapping and the clinical reference techniques was very strong
(r$^2$ > 0.7) for most variables (Figure 6). A strong correlation coefficient (r$^2$ > 0.5) was found between
Multimapping and MOLLI for myocardial T$_1$ post-contrast (r$^2$ = 0.66) and blood T$_1$ post-contrast (r$^2$ =
0.53).

**3.3    Inter- and intra-observer variability**

The myocardial measurements and measurements of the left ventricular blood pool for intra-
repeatability assessment showed excellent repeatability (myocardial ICC > 0.97, LV blood pool ICC
= 1.00) (Table 2). The myocardial measurements for inter-repeatability showed moderate to excellent
repeatability (ICC > 0.73) for all mapping techniques. The native and post-contrast T$_1$ measurements
of the blood pool for inter-repeatability showed good to excellent repeatability (ICC > 0.92).

**3.4    Image quality assessment**

The image quality was scored significantly higher for Multimapping compared to T$_2$bSSFP ($P <$
0.001), MOLLI native T$_1$ ($P = 0.007$), MOLLI post-contrast T$_1$ ($P < 0.001$), and MOLLI ECV ($P <$
0.001) (Figure 7).

**4    Discussion**

In this study, a new method for simultaneous T$_1$ and T$_2$ mapping was compared to clinical reference
mapping technique in a cohort of patients with cardiovascular disease. We found a strong to very strong
correlation between the methods for all measured parameters (native T$_1$, post-contrast T$_1$, ECV and

native $T_2$), while the image quality was considered better using the proposed Multimapping technique
compared to the reference methods. Furthermore, intra- and inter-observer variability of Multimapping
parameter measurements were in general low and similar to those obtained with the clinical reference
techniques.

In segments of healthy/remote myocardium we measured a mean native $T_1$ of 1116 ms using
Multimapping, more than 100 ms higher than for MOLLI. However, MOLLI is known to significantly
underestimate $T_1$ when compared to more accurate methods such as SASHA (5), which typically yields
native $T_1$ of around 1200 ms at 1.5T (7,27). The native $T_1$ Multimapping values are also in line with
the previous study using this technique in healthy volunteers which measured 1114 ms (24). For post-
contrast $T_1$ mapping there was also a significantly longer $T_1$ using Multimapping (479 ms) compared
to MOLLI (427 ms). Although post-contrast $T_1$ values are more difficult to compare between studies
due to differences in contrast agents and the timing of acquisition after injection, previous studies have
shown underestimation of post-contrast $T_1$ for MOLLI compared to more accurate techniques such as
SASHA (28,29). The study by Nordlund et al. (29) also demonstrated that MOLLI overestimates ECV
by approximately 4% in healthy volunteers compared to SASHA, the latter technique correlating more
closely with radioisotopes in pigs. This suggests that the significantly lower ECV measured in this
study with Multimapping (22%) may be more accurate compared to MOLLI (24%). However, the
conversion from $T_1$ to hematocrit was based on the relationship established for MOLLI in a previous
study, which may bias measurements if applied to Multimapping synthetic ECV. For Multimapping
synthetic ECV to be used independently of MOLLI then the relationship between Multimapping blood
$T_1$ and hematocrit should be established. Alternatively, the hematocrit could be directly measured to
calculate Multimapping ECV without the need for a MOLLI acquisition. Correlation of $T_1$ and $T_2$
values with potential confounding variables such as heart-rate or the opposite ($T_2$ or $T_1$) parameter did
not show any particular dependency for Multimapping in this regard. However, $T_2$bSSFP appeared to
be inversely correlated with heart-rate. This suggest additional delay cardiac cycles may be required to
yield less biased $T_2$ values for high heart-rates. Conversely, Multimapping may be a more robust
approach for $T_1$ and $T_2$ mapping at higher heart rates as no additional modification of the pulse
sequence is required.

In the measurements of myocardial segments with disease, we found a high correlation between
Multimapping and the clinical reference techniques for native $T_1$ (blood and myocardium), $T_2$, and
ECV. While correlations for post-contrast $T_1$ (blood and myocardium) was more moderate, this may
be explained by the confounding factor of time after injection, which affect the $T_1$ measurements.
Furthermore, measured post-contrast $T_1$ in this study had a narrower range for both Multimapping and
MOLLI compared to native $T_1$ which can contribute to a weaker correlation between techniques.
Nevertheless, a very strong correlation between Multimapping and reference techniques for native $T_1$,
$T_2$ and ECV indicates that Multimapping is a useful technique that can be used to detect disease.

Dictionary-based mapping techniques such as Multimapping typically assumes that there is no
through-plane motion, which is not the case for flowing blood. Such through-plane motion leads to $T_1$
over-estimation as inflowing spins has seen fewer RF pulses and is therefore less saturated. This can
explain the observed over-estimation of blood (particularly native) $T_1$ relative to MOLLI. However, it
should also be noted that, due to the strong correlation for native blood $T_1$ blood between Multimapping
and MOLLI, the Multimapping technique can likely still capture variability in blood $T_1$ (due to e.g.
different hematocrit levels) with a similar sensitivity as MOLLI.

The image quality was superior using Multimapping compared to all clinical reference techniques. This
could be due to the higher flip angle of 50º using Multimapping, compared to MOLLI and $T_2$bSSFP

which both use a flip angle 35º, with otherwise identical imaging parameters to Multimapping. A higher
flip angle for bSSFP-based mapping techniques leads to a higher signal-to-noise ratio which typically
contributes to improved image quality. The shorter duration of Multimapping (10 beats) compared to
both MOLLI (11 beats) and T$_2$bSSFP (16 beats) means that Multimapping is less prone to respiratory
motion-induced misalignment, which may also contribute to a better image quality. While the
Multimapping and MOLLI pulse sequences are very similar (both inversion recovery with bSSFP
readouts), Multimapping benefits from phase sensitive inversion recovery post-processing step which
has been shown to improve T$_1$ map image quality compared to fitting with magnitude images (30),
used in the vendor provided fitting algorithm for MOLLI. Compared to Multimapping, T$_2$bSSFP uses
significantly fewer source images for T$_2$ mapping, and while only three T$_2$ preparation modules are
included in the Multimapping pulse sequence, the bSSFP readout is intrinsically T$_2$/T$_1$ weighted which
contributes to the T$_2$ sensitivity and may explain the improved image quality.

The intra- and inter-observer repeatability analysis showed an excellent repeatability for most
measurements using both Multimapping and reference techniques. While Multimapping post-contrast
myocardial T$_1$ inter-observer ICC of 0.73 was relatively low compared to that of MOLLI (ICC = 0.95),
post-contrast T$_1$ mapping is primarily used to generate ECV maps, and here Multimapping and MOLLI
yielded near identical ICC values of 0.94 and 0.93, respectively.

**4.1    Comparison with other simultaneous T$_1$ and T$_2$ mapping techniques**

Several simultaneous T$_1$ and T$_2$ mapping techniques have been proposed over the last years,
comparable to Multimapping. Published studies using similar methods in healthy volunteers are
summarized in Table 3, including Multimapping (24). Multimapping has a shorter scan duration than
nearly all other simultaneous T$_1$ and T$_2$ mapping techniques, requiring 10 beats, which is also shorter
than both MOLLI and T$_2$bSSFP. As many patients with cardiovascular diseases struggle to hold their
breath for an extended period, reducing the scan time of mapping techniques is important and has been
the focus of several studies (11,31). This is also in line with the endeavor of utilizing less time-
consuming CMR protocols in order to improve adoption of CMR in routine cardiovascular practice.
Inversion recovery magnetization preparation pulses are often used for myocardial T$_1$ mapping as they
increase quantification precision compared to saturation recovery (5), using the full dynamic range of
the longitudinal magnetization, at the expense of accuracy as inversion pulses are more sensitive to
confounding elements such as magnetization transfer and transverse relaxation during the pulses,
which reduce their efficiency (6,25,32). Therefore, saturation recovery technique measurements are
generally considered to be closer to the "true" in-vivo T$_1$ times, typically several 100 ms higher than
MOLLI on either 1.5T and 3T scanners. In this regard, Multimapping which uses inversion recovery,
generates T$_1$ values in healthy/remote myocardium of 1116 ms, which is closer to the saturation
recovery based techniques (of approximately 1200 ms) than MOLLI (approximately 1000 ms) or the
most comparable simultaneous T$_1$ and T$_2$ mapping studies, Blume et al. (15) and Jaubert et al. (33),
which report a myocardial T$_1$ of 1017 ms and 1045 ms, respectively. This may be due to the assumed
lower inversion efficiency of 0.89 for the inversion pulses, incorporated into the Multimapping signal
model, which is likely closer to the true inversion efficiency than assuming perfect efficiency.
However, the inversion efficiency potentially varies between field strengths and vendors, or even
spatially across an image due to B$_0$ and B$_1$ inhomogeneity. Furthermore, the current Multimapping
technique does not consider magnetization transfer. To yield more accurate T$_1$ values, reproducible
across scanner platforms, these confounding effects should be included in the Multimapping signal
model, preferably on a pixel-wise basis, although this will likely negatively impact the precision.

It can be difficult to precisely pinpoint the sources of differences in $T_1$ and $T_2$ values for the different
techniques outlined in Table 3, particularly as many techniques rely on unconventional acquisition,
reconstruction and mapping strategies. These include, for example, non-Cartesian (radial or spiral)
trajectories with iterative reconstruction algorithm, coupled with sophisticated and advanced mapping
techniques which may be difficult to reproduce. In contrast, the Multimapping pulse sequence consists
of a MOLLI-like acquisition scheme (inversion recovery with Cartesian single-shot 2D bSSFP readout)
which are available on all major vendor platforms, with the addition of $T_2$prep modules which have
also been implemented on all vendor platforms. For transparency, the Multimapping parameter
mapping method using dictionary matching has been provided open source to enable reproduction of
this technique by other investigators which may also enable direct comparison of Multimapping with
other simultaneous $T_1$ and $T_2$ mapping techniques.

### 4.2    Limitations

This study has several limitations: no respiratory motion correction was performed. Correcting for
respiratory-induced image misalignment is important even for breath-held scans and can be achieved
using image registration (34). Although image registration could be readily applied to Multimapping
source image to this end, this was not performed in order to have a fair comparison with MOLLI and
$T_2$bSSFP maps which were generated using inline vendor algorithm without motion correction. A
second technical limitation of Multimapping is that manual interaction is required to define a ROI in
the myocardial septum for the $B_1$ estimation. However, this is a relatively simple step, comparable to
the input required to define ROIs for ECV maps. Further work is required to automatize this step or to
incorporate $B_1$ in the high resolution $T_1$ and $T_2$ dictionary matching, which would obviate the need for
any manual interaction but with a potential penalty to the precision. A study limitation is that the patient
cohort consisted of a small, heterogeneous population of patients with various cardiovascular diseases,
and performed on a single 1.5T Philips scanner. Further studies are required to evaluate the
performance of Multimapping at 3T and using other vendors. The evaluation of heart-rate dependence
of the mapping techniques was limited by the relatively narrow heart rates of nearly all patients (only
one with heart-rate over 100 bpm).

### 5    Conclusions

325  Multimapping $T_1$ and $T_2$ values show high correlations with clinical reference mapping techniques in
326  a diverse cohort of patients with different cardiovascular diseases. Multimapping enables simultaneous
327  $T_1$ and $T_2$ mapping and can be performed in a short (10 cardiac beats) breath-hold, with image quality
328  superior to that of the clinical reference techniques.

### 6    Conflict of Interest

330  The authors declare that the research was conducted in the absence of any commercial or financial
331  relationships that could be construed as a potential conflict of interest.

### 7    Author Contributions

333  MH and CJC conceived of the study. MH developed the methods, acquired the data, performed image
334  reconstruction and processing. MH, CJ, and CJC analyzed the data. All authors participated in revising
335  the manuscript, read and approved the final manuscript.

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**9      Acknowledgments**

Not applicable.

**10     Data Availability Statement**

The Multimapping post-processing pipeline (Matlab code) can be downloaded from:
https://github.com/Multimapping/Matlab_files. Images for all patients included in this study can be
downloaded from:
https://github.com/Multimapping/Patient_study/raw/main/MapReconstructions.pdf.

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**12    Figures**

Figure 1. Multimapping pulse sequence (A) and post-processing (B). The pulse sequence consists of
ECG-triggered 2D single-shot acquisitions in 10 consecutive cardiac cycles, preceded by inversion
pulses in cycles 1 and 5, and $T_2$prep with different echo times (TE) in cycles 8, 9 and 10. The post-
processing involves first performing a phase sensitive inversion recovery (PSIR) operation to restore
the polarity of the signal, followed by an initial dictionary matching (Dict match 1) to estimate a global
$B_1$ correction factor based on a ROI in the myocardial septum. The dictionary matching finds the pixel-
wise closest match between acquired data and the simulated acquisition (with scan-specific delays) for
different $T_1$, $T_2$ and RF scaling factor ($B_1$) combinations. A second dictionary matching step (Dict
match 2) is then performed for only $T_1$ and $T_2$ with high temporal granularity (1 ms resolution) to
generate the final $T_1$ and $T_2$ maps.

Figure 2. LGE and parameter maps (native $T_2$, native $T_1$, post-contrast $T_1$ and ECV) are shown for a
patient with no cardiovascular disease findings. The parameter maps were acquired using either
Multimapping (top row) or reference techniques (bottom row). Septal $T_2$ was 49.6 ms and 56.7 ms for
Multimapping and $T_2$bSSFP, respectively. Septal (native/post-contrast) $T_1$ was 1144/422 ms and
1003/381 ms for Multimapping and MOLLI, respectively. Septal ECV was 24.9% and 23.8% for
Multimapping and MOLLI, respectively.

Figure 3. LGE and parameter maps in a patient with myocarditis, as indicated by the increased signal
in the lateral wall in the LGE and also apparent as altered values in the parameter maps
(Multimapping top row, reference techniques bottom row). Measurements in the area of enhancement
(lateral wall) yielded $T_2$ of 65.7 ms and 62.4.6 ms for Multimapping and $T_2$bSSFP, respectively. $T_1$
values (native/post-contrast) in the same area were 1286/446 ms and 1111/423 ms for Multimapping
and MOLLI, respectively. ECV was 26.6% and 28.3% in the enhanced area for Multimapping and
MOLLI, respectively.

Figure 4. LGE and parameter maps in a patient with myocardial infarction, clearly visualized using
all techniques, both native and post-contrast. Measurements in the area of enhancement (anterolateral
segment) yielded $T_2$ of 90.5 ms and 88.6 ms for Multimapping and $T_2$bSSFP, respectively. $T_1$ values
(native/post-contrast) in the same area were 1516/355 ms and 1440/338 ms for Multimapping and
MOLLI, respectively. ECV was 33.3% and 33% in the enhanced area for Multimapping and MOLLI,
respectively.

Figure 5. The two top rows show the correlation analysis of heart-rate dependency to $T_1$ (native and
post-contrast), ECV and $T_2$. The bottom row shows the correlation analysis between native $T_1$ and $T_2$.

Figure 6. Correlation and Bland-Altman plots comparing Multimapping (MM) to MOLLI and
$T_2$bSSFP. For the correlation plots, black and grey lines indicate line of best fit, and the dottet lines
show the identity lines. The black lines indicate bias in the Bland-Altman plots. Correlation coefficient
($r^2$) is reported in the correlation plots and mean difference, lower and upper limits of agreement (1.96
SD) in the Bland-Altman plots.

Figure 7. Distribution of image quality scores for Multimapping (MM) and in-vivo reference
techniques.

**13   Tables**

Table 1. Clinical Characteristics

| | |
|---|---|
| Patients (n) | 44 |
| Age (years) | 49±20 |
| Male sex, n (%) | 28 (64) |

| | |
|---|---|
| BMI (kg/m2) | 25±4 |
| Height (cm) | 176±10 |
| Weight (kg) | 78±12 |
| Heart rate (bpm) | 67±14 |
| LVEF (%) | 53±11 |
| LVSV (ml) | 94±18 |
| LVEDV (ml) | 186±54 |

513    BMI, body mass index; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke
514    volume; LVEF, left ventricular end-diastolic volume.

516    Table 2. Inter and intra-observer ICC (95% confidence interval).

| | Myocardium | | Blood pool | |
|---|---|---|---|---|
| | **Intra-repeatability** | **Inter-repeatability** | **Intra-repeatability** | **Inter-repeatability** |
| MM T$_1$ Native | 0.99 (0.97-1.00) | 0.87 (0.76-0.94) | 1.00 (1.00-1.00) | 0.92 (0.85-0.96) |
| MOLLI T$_1$ Native | 0.99 (0.97-0.99) | 0.93 (0.88-0.97) | 1.00 (1.00-1.00) | 0.97 (1.00-1.00) |
| MM T$_1$ PC | 0.99 (0.98-1.00) | 0.73 (0.54-0.86) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| MOLLI T$_1$ PC | 0.97 (0.93-0.99) | 0.95 (0.90-0.98) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| MM ECV | 0.99 (0.98-1.00) | 0.94 (0.89-0.97) | | |
| MOLLI ECV | 0.99 (0.97-0.99) | 0.93 (0.87-0.97) | | |
| MM T$_2$ | 0.99 (0.96-0.99) | 0.91 (0.82-0.95) | | |
| T$_2$bSSFP | 0.98 (0.94-0.99) | 0.88 (0.78-0.95) | | |

517 MM, Multimapping; ECV, extracellular volume fraction; MOLLI, modified Look-Locker inversion
518 recovery; T$_2$bSSFP, T$_2$ prepared balanced steady-state free precession.

520    Table 3. Comparable published simultaneous T$_1$ and T$_2$ mapping techniques.

| Study | Scan time | FB/ BH | IR/SR | Readout | Subjects | Additional mapping | Field strength | Native T1 (ms) | Native T2 (ms) |
|---|---|---|---|---|---|---|---|---|---|
| Blume et al. (15) | Around 3 minutes | FB | IR | 2D Cartesian bSSFP | 19 HV | - | 1.5T | 1017±91 | 50±4 |
| Kvernby et al. (17) | 15 beats | BH | IR | 3D Cartesian GRE | 10 HV | - | 3T | 1083±43 | 50.4±3.6 |
| Akçakaya et al. (18) | 13 beats | BH | SR | 2D Cartesian bSSFP | 10 HV | - | 1.5T | 1210±24 | 48.2±2.8 |
| Santini et al. (35) | 8 beats | BH | IR | 2D Cartesian bSSFP | 5 HV | - | 3T | 1227±68 | 37.9±2.4 |
| Hamilton et al. (36) | 15 beats | BH | IR | 2D spiral GRE | 11 HV | - | 3T | 1235, range 1199 - 1316 | 38, range 32 – 43 |
| Jaubert et al. (33) | 15 beats | BH | IR | 2D radial ME-GRE | 10 HV | PDFF | 1.5T | 1045±32 | 42.8±2.6 |
| Christodoulou et al. (19) | 88 seconds | FB | IR | 2D radial GRE | 10 HV | Cardiac motion | 3T | 1216±67 | 47.8±4.9 |
| Shao et al. (37) | 11 beats | BH | IR | 2D radial GRE | 10 HV | - | 3T | 1366±31 | 37.4±0.9 |
| Guo et al. (38) | 1.4±0.3 minutes (WH) | FB | SR | M2D Cartesian bSSFP | 13 HV | - | 3T | 1373±50 | 48.7±2.5 |
| Hermann et al. (39) | 18.5 seconds (+resp gating) | FB | SR | 2D Cartesian ME-GRE | 10 HV | T2* | 3T | 1573±86 | 33.2±3.6 |
| Chow et al. (40) | 11 beats | BH | SR | 2D Cartesian bSSFP | 10 HV | - | 3T | 1523±18 | 36.7±1.1 |
| Jarkman et al. | 10 beats | BH | IR | 2D Cartesian bSSFP | Remote myocardium 19 patients | - | 1.5T | 1116±21 | 48.0±3.0 |

521    WH, whole-heart; FB, free-breathing; BH, breath-hold; IR, inversion recovery; SR, saturation
522    recovery; bSSFP, balanced steady-state free precession; GRE, spoiled gradient echo; ME-GRE,
523    multi-echo spoiled gradient echo; M2D, multi-slice 2D; HV, healthy volunteer; PDFF, proton density
524    fat fraction.

**LGE**

**Multimapping T$_2$**　**Multimapping Native T$_1$**　**Multimapping PC T$_1$**　**Multimapping ECV$_{Syn}$**

**T$_2$bSSFP**　**MOLLI Native**　**MOLLI PC**　**MOLLI ECV$_{Syn}$**

| 0 | 50 | 100 | 150 |
|---|---|---|---|

**T$_2$ (ms)**

| 0 | 500 | 1000 | 1500 | 2000 |
|---|---|---|---|---|

**T$_1$ (ms)**

| 0 | 200 | 400 | 600 | 800 | 1000 |
|---|---|---|---|---|---|

**T$_1$ (ms)**

| 0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
|---|---|---|---|---|---|

**ECV (%)**

| LGE | Multimapping T$_2$ | Multimapping Native T$_1$ | Multimapping PC T$_1$ | Multimapping ECV$_{Syn}$ |
| --- | --- | --- | --- | --- |
| | T$_2$bSSFP | MOLLI Native | MOLLI PC | MOLLI ECV$_{Syn}$ |

T$_2$ (ms): 0  50  100  150

T$_1$ (ms): 0  500  1000  1500  2000

T$_1$ (ms): 0  200  400  600  800  1000

ECV (%): 0  0.1  0.2  0.3  0.4  0.5

| | **Multimapping T$_2$** | **Multimapping Native T$_1$** | **Multimapping PC T$_1$** | **Multimapping ECV$_{Syn}$** |
|---|---|---|---|---|

**LGE**

| | **T$_2$bSSFP** | **MOLLI Native** | **MOLLI PC** | **MOLLI ECV$_{Syn}$** |
|---|---|---|---|---|

T$_2$ (ms): 0 50 100 150

T$_1$ (ms): 0 500 1000 1500 2000

T$_1$ (ms): 0 200 400 600 800 1000

ECV (%): 0 0.1 0.2 0.3 0.4 0.5