High Spatial Resolution and Temporally Resolved $T_2^*$ Mapping of Normal Human Myocardium at 7.0 Tesla: An Ultrahigh Field Magnetic Resonance Feasibility Study

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Abstract

Myocardial tissue characterization using $T_2^*$ relaxation mapping techniques is an emerging application of (pre)clinical cardiovascular magnetic resonance imaging. The increase in microscopic susceptibility at higher magnetic field strengths renders myocardial $T_2^*$ mapping at ultrahigh magnetic fields conceptually appealing. This work demonstrates the feasibility of myocardial $T_2^*$ imaging at 7.0 T and examines the applicability of temporally-resolved and high spatial resolution myocardial $T_2^*$ mapping. In phantom experiments single cardiac phase and dynamic (CINE) gradient echo imaging techniques provided similar $T_2^*$ maps. In vivo studies showed that the peak-to-peak $B_0$ difference following volume selective shimming was reduced to approximately 80 Hz for the four chamber view and mid-ventricular short axis view of the heart and to 65 Hz for the left ventricle. No severe susceptibility artifacts were detected in the septum and in the lateral wall for $T_2^*$-weighting ranging from $TE = 2.04$ ms to $TE = 10.2$ ms. For $TE > 7$ ms, a susceptibility weighting induced signal void was observed within the anterior and inferior myocardial segments. The longest $T_2^*$ values were found for anterior ($T_2^* = 14.0$ ms), anteroseptal ($T_2^* = 17.2$ ms) and inferoseptal ($T_2^* = 16.5$ ms) myocardial segments. Shorter $T_2^*$ values were observed for inferior ($T_2^* = 10.6$ ms) and inferolateral ($T_2^* = 11.4$ ms) segments. A significant difference ($p = 0.002$) in $T_2^*$ values was observed between end-diastole and end-systole with $T_2^*$ changes of up to approximately 27% over the cardiac cycle which were pronounced in the septum. To conclude, these results underscore the challenges of myocardial $T_2^*$ mapping at 7.0 T but demonstrate that these issues can be offset by using tailored shimming techniques and dedicated acquisition schemes.

Introduction

Emerging cardiovascular magnetic resonance (CMR) imaging applications include $T_2^*$ relaxation sensitized techniques, which are increasingly used in basic research and (pre)clinical imaging. Methodological developments in $T_2^*$ sensitized imaging \cite{1-4} and simulations of myocardial vasculature \cite{5,6} have been indispensable. Applications include investigation of the microstructure of the isolated rat heart \cite{7}, detection of myocardial ischemia \cite{8-14}, probing of vasodilator or dipyridamole-induced changes in myocardial perfusion \cite{15-18}, visualization of scarred myocardium \cite{19}, imaging of capillary recruitment \cite{20} and assessment of tissue oxygenation related to endothelium-dependent blood flow changes \cite{21}. $T_2^*$ mapping has also been shown to be of substantial clinical value for the ascertainment of myocardial iron levels \cite{22-29}.

The most widely used methods for $T_2^*$ mapping are echo planar imaging (EPI) and gradient echo based techniques. Unlike conventional CINE gradient echo imaging, the relatively strong $T_2^*$-weighting required to make gradient echo sequences sensitive to changes in magnetic susceptibility asks for a long evolution time (TE) between RF excitation and data acquisition. Consequently, gradient echo based myocardial $T_2^*$ mapping is commonly restricted to a single slice and single cardiac phase that can be accommodated in a single breath-hold at 1.5 T and 3.0 T \cite{30-32}.

The linear relationship between magnetic field strength and microscopic susceptibility \cite{33-35} renders it conceptually appealing. This work demonstrates the feasibility of ultrahigh field susceptibility-weighted myocardial imaging and examines its applicability for temporally-resolved and high spatial resolution myocardial $T_2^*$ mapping at 7.0 T. To meet this goal, the applicability of 2D spoiled gradient-echo multi-echo based techniques for fast CINE $T_2^*$ mapping at 7.0 T is closely investigated in phantom experiments. The feasibility of gradient-echo multi-echo based techniques for fast CINE $T_2^*$ mapping of the human heart is
demonstrated at 7.0 T. We also present the suitability of this technique for high spatial resolution myocardial $T_2^*$ mapping by using thin slices (slice thickness = 2.5 mm) and in-plane spatial resolution of (1.1 x 1.1) mm$^2$. Our initial volunteer studies serve as a mandatory precursor to a broader clinical study. The merits and limitations of $T_2^*$ mapping using 2D spoiled gradient-echo multi-echo imaging at 7.0 T are discussed and implications for cardiac MR at 7.0 T are considered.

**Methods**

**MR-Hardware**

Imaging was conducted using a 7.0 T whole body MR scanner (Magnetom, Siemens Healthcare, Erlangen, Germany) equipped with a gradient system (Avanto, Siemens Healthcare, Erlangen, Germany) capable of supporting a slew rate of 200 mT/m/ms and a maximum gradient strength of 40 mT/m. A 16 channel transmit/receive coil array was used for excitation and signal reception. The coil was designed for cardiac imaging and comprises an anterior and posterior former, each laid out on a two-dimensional 2 by 4 grid of loop elements. For further details about the coil please see [36,37]. An MR stethoscope (EasyACT, MRI TOOLS GmbH, Berlin, Germany) was used for cardiac triggering [38,39].

**T$_2^*$ Mapping Techniques**

Myocardial $T_2^*$ mapping is commonly conducted with cardiac triggered, segmented multi-echo spoiled gradient echo (ME) techniques that use breath-held acquisitions for respiratory motion compensation [8,9,15,18,40]. In this work, various ME configurations have been used for (i) time resolved CINE and for (ii) single cardiac phase acquisitions (Figure 1).

For single cardiac phase imaging, the acquisition period is commonly placed into end-diastole, which limits the viable window of data acquisition to 100 ms to 200 ms. Data acquisition is segmented over a series of cardiac cycles with each segment acquiring a set of echoes during the quiescent interval (Figure 1a). The number of segments and echoes per segment are dictated by the longest TE used for $T_2^*$ weighting as outlined in Figure 1a. To avoid $T_2^*$ errors due to signal modulations induced by fat-water phase shift, it is essential to choose echo times where fat and water are in-phase [4]. At 1.5 T and 3.0 T TE increments equivalent to the fat-water shift are 4.4 ms and 2.2 ms, respectively. At 7.0 T this inter echo time is 1.02 ms, which is beneficial for rapid multi-echo acquisitions. However, if a larger data matrix size is needed for high spatial resolution $T_2^*$ mapping, the readout/acquisition window can easily exceed 1.02 ms even when short dwell times are used. Consequently, it is elusive to accomplish inter-echo time increments of 1.02 ms for high spatial resolution $T_2^*$ mapping at 7.0 T using sequential multi echo gradient echo imaging.

CINE $T_2^*$ mapping might be feasible at 7.0 T assuming a $T_2^*$ reduction at 7.0 T versus 1.5 T and 3.0 T and considering the relationship between proper $T_2^*$ weighting and range of echo times to be covered. To this end, a maximum TE = 10 ms would be compatible with the needs of CINE imaging but would also provide sufficient coverage of the $T_2^*$ decay at 7.0 T.

For all these reasons, two imaging strategies were employed at 7.0 T:

i. Interleaved multi-shot multi-echo (MS) gradient echo technique for single cardiac phase myocardial $T_2^*$ mapping (Figure 1b). This approach addresses the competing constraints of inter echo time and spatial resolution of the ME approach by adding more excitations and by interleaving the echoes.

ii. Multi-breath-hold multi-echo (MB CINE) gradient echo technique for CINE myocardial $T_2^*$ mapping (Figure 1c). This approach runs the trait that all k-space lines required to form the final image for a given echo time are acquired in a single breathhold.

**Phantom Studies**

For the evaluation of MS and MB CINE $T_2^*$ mapping strategies, phantom experiments were conducted using a long $T_2^*$ and medium $T_2^*$ phantom. For long $T_2^*$, a cylindrical water phantom (diameter = 15 cm) containing an agarose copper sulfate solution (4 g CuSO$_4$ +2 g NaCl +2 g agarose dissolved in 1.0 l H$_2$O) was used. A glass capillary (inner diameter = 0.5 mm) filled with air and a tube (inner diameter = 5 mm) filled with water were placed inside the phantom to create strong susceptibility gradients of limited spatial extension within the uniform phantom. For the medium $T_2^*$ phantom, a cylindrical water phantom (diameter = 8 cm) containing agarose (5 mg agarose dissolved in 250 ml H$_2$O) was used. $T_2^*$ was reduced by ultrasmall superparamagnetic iron oxide particles (500 µl Modylak ION (10 mg Fe/ml), BioPal, Worchester, USA), which afforded a $T_2^*$ of approximately 20 ms.

In the phantom experiments, MS (Figure 1b) and MB CINE (Figure 1c) $T_2^*$ mapping strategies were benchmarked against other $T_2^*$ mapping techniques, which are already established at 1.5 T and 3.0 T but are unsuitable for myocardial $T_2^*$ mapping at 7.0 T due to echo time and acquisition time constraints. These reference methods include:

i. conventional multi-echo (ME) gradient echo for single cardiac phase $T_2^*$ mapping (Figure 1a).

ii. multi-echo CINE (ME CINE) gradient echo (Figure 1d).

iii. multi-shot multi-echo CINE (MS CINE) gradient echo (Figure 1c).

For phantom $T_2^*$ mapping, an image matrix of 320 x 240, a field of view of (360 x 270) mm$^2$, an in-plane resolution of (1.1 x 1.1) mm$^2$, and a slice thickness ranging from 2.5 mm to 8 mm were used. A unipolar readout using gradient flyback was applied together with echo times ranging from 2.04 ms to 10.29 ms. This approach results in nine equidistant echoes with an inter echo time of 1.02 ms with the exception of ME and ME CINE due to gradient switching induced peripheral nerve stimulation constraints. For ME and ME CINE 6 echoes with an inter echo time of 3.06 ms and a TEmax = 2.04 ms were used. For the MS, MS CINE and MB CINE techniques three excitations together with 5 echoes were used to ensure an inter-echo time of 1.02 ms. With the first excitation echo 1, 4 and 7 were acquired. The second excitation covered echo 2, 5 and 8 while echo 3, 6, and 9 were recorded after the third excitation. A simulated heart rate of 60 bpm was used for prospective triggering of the phantom experiments.

**Ethics Statement**

For the in vivo feasibility study, 8 healthy subjects (mean age: 27±3 years, 5 females, mean BMI: 24 kg/m$^2$, mean heart rate: 78 bpm) without any known history of cardiac disease were included after due approval by the local ethical committee (registration number DE/CA73/5350/09, Landesamt für Arbeitsschutz, Gesundheitsschutz und technische Sicherheit, Berlin, Germany).
Informed written consent was obtained from each volunteer prior to the study.

For each volunteer, slice positioning was carried out following international consensus by the same technician to omit inter-operator variability. Myocardial T2* mapping was conducted using the MS and the MB CINE imaging strategies for all volunteer studies.

Volunteer Studies
For each volunteer, slice positioning was carried out following international consensus by the same technician to omit inter-operator variability. Myocardial T2* mapping was conducted using the MS and the MB CINE imaging strategies for all volunteer studies.

Figure 1. Synopsis of multi-echo gradient echo strategies used for T2* mapping at 7.0 T. A). Conventional multi-echo (ME) gradient echo for single cardiac phase myocardial T2* mapping. Multiple echoes are acquired after excitation to obtain a set of T2* weighted images. The competing constraints of inter echo time and spatial resolution inherent to the ME approach are addressed by the B) interleaved multi-shot multi-echo (MS) gradient echo technique. In MS a set of excitations is employed together with echo interleaving echoes to acquire a set of T2* weighted images. C) The multi-breath-hold multi-echo (MB CINE) gradient echo technique allows myocardial CINE T2* mapping by interleaving the echoes over several breath-holds. For benchmarking D) multi-echo CINE (ME CINE) gradient echo and E) multi-shot multi-echo CINE (MS CINE) were applied for T2* mapping in phantom studies. To guide the eye vertical dashed lines refer to k-space lines. Vertical solid lines refer to cardiac phases. A unipolar readout using gradient flyback was applied for all strategies.

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shaping to enhance B1 voxel model “Duke” were conducted for transmission field and electromagnetic field (EMF) simulations using the human otherwise stated. A nominal flip angle of Echo times ranging from 2.04 ms to 10.20 ms were applied. Three acquisition data matrix = 256 a four chamber view were used. Imaging parameters were set to: subjects. For this purpose, a mid-ventricular short axis view and in vivo study phantom were conducted for T2 mapping protocols. For in vivo T2 mapping MS and MB CINE were applied. CINE protocols provided an acquisition window length of about 36 ms, which renders the impact of cardiac motion effects rather low. The acquisition window length is given by the number of k-spaces lines acquired per cardiac cycle times the repetition time. doi:10.1371/journal.pone.0052324.t002

The scan duration of MS protocols is doubled versus ME protocols. For in vivo T2 mapping, volume selective B0 shimming was applied. CINE protocols provided an acquisition window length of about 36 ms, which renders the impact of cardiac motion effects rather low. The acquisition window length is given by the number of k-spaces lines acquired per cardiac cycle times the repetition time. doi:10.1371/journal.pone.0052324.t001

Table 1. Synopsis of scan time duration and temporal resolution used for the single cardiac phase and CINE T2* mapping protocols.

<table>
<thead>
<tr>
<th>ME</th>
<th>MS</th>
<th>MB CINE</th>
<th>ME CINE</th>
<th>MS CINE</th>
</tr>
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<tbody>
<tr>
<td>scan duration</td>
<td>25s</td>
<td>49s</td>
<td>3×81s</td>
<td>121s</td>
</tr>
<tr>
<td>phantom study</td>
<td>-</td>
<td>-</td>
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</table>

The scan duration of MS protocols is doubled versus ME protocols. For in vivo T2* mapping MS and MB CINE were applied. CINE protocols provided an acquisition window length of about 36 ms, which renders the impact of cardiac motion effects rather low. The acquisition window length is given by the number of k-spaces lines acquired per cardiac cycle times the repetition time. For in vivo study, echo 1, 4 and 7, were acquired. The second excitation covered echo 2, 5 and 8. Echo 3, 6, and 9 were recorded after the third excitation. Moderate acceleration (R = 2 for MS and R = 3 for MB CINE) in conjunction with GRAPPA reconstruction [42] was applied to reduce the breath-hold time. For single cardiac phase acquisitions, the MS protocol was prospectively triggered to place data acquisition at end-diastole or end-systole. For prospectively triggered CINE T2* mapping, 25 cardiac phases were acquired for a heart rate of 60 bpm. Phase images of the first two echoes (TE1 = 2.04 ms, TE2 = 3.06 ms) of MS were used to determine B0 field maps offline.

Prior to T2* mapping, volume selective B0 shimming was conducted to reduce static magnetic field inhomogeneities [43,44]. In doing so, the susceptibility weighting will be dictated by microscopic B0 susceptibility gradients, rather than by macroscopic B0 field inhomogeneities. For this purpose, a 2D multi-slice, cardiac gated, breath-hold double echo (DE) gradient echo sequence (TE1 = 3.06 ms, TE2 = 3.10 ms) was used for B0 field mapping. Cardiac gating and breath-holding were applied to reduce and possibly eliminate phase contributions induced by cardiac and respiratory motion. The shim volume was adjusted to cover the left and right ventricle in the four chamber view and in the short axis view of the heart. Data acquisition for B0 shimming was adjusted to diastole. This choice is based on previous reports which demonstrated that field maps showed a negligible temporal variation across the cardiac cycle [43]. For the shim volumes, linear and second order room temperature shims were calculated to reduce the frequency shift across the phantom or across the slice.

Table 2. Survey of T2* derived from phantom studies for single cardiac phase and for CINE T2* mapping techniques.

<table>
<thead>
<tr>
<th>Slice thickness</th>
<th>ME mean ± std</th>
<th>MS mean ± std</th>
<th>MB CINE mean ± std</th>
<th>ME CINE mean ± std</th>
<th>MS CINE mean ± std</th>
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<tr>
<td>[mm]</td>
<td>[ms]</td>
<td>[ms]</td>
<td>(temporal std)</td>
<td>(temporal std)</td>
<td>(temporal std)</td>
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<tr>
<td>8</td>
<td>26.1 ± 3.7</td>
<td>26.7 ± 3.0</td>
<td>28.3 ± 2.8</td>
<td>26.9 ± 3.2</td>
<td>27.2 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>(0.4)</td>
<td>(0.4)</td>
<td>(0.3)</td>
<td>(0.3)</td>
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<tr>
<td></td>
<td>18.3 ± 0.8</td>
<td>18.6 ± 0.8</td>
<td>19.5 ± 0.9</td>
<td>18.6 ± 0.7</td>
<td>19.3 ± 0.7</td>
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<tr>
<td></td>
<td>(0.3)</td>
<td>(0.1)</td>
<td>(0.3)</td>
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<tr>
<td>6</td>
<td>27.5 ± 2.5</td>
<td>27.2 ± 1.8</td>
<td>28.5 ± 1.9</td>
<td>27.9 ± 2.3</td>
<td>27.6 ± 1.7</td>
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<tr>
<td></td>
<td>(0.4)</td>
<td>(0.5)</td>
<td>(0.4)</td>
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<tr>
<td></td>
<td>19.0 ± 0.6</td>
<td>19.2 ± 0.7</td>
<td>19.7 ± 0.7</td>
<td>19.2 ± 0.6</td>
<td>19.5 ± 0.9</td>
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<tr>
<td></td>
<td>(0.4)</td>
<td>(0.2)</td>
<td>(0.4)</td>
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<tr>
<td>4</td>
<td>28.6 ± 1.6</td>
<td>27.7 ± 1.3</td>
<td>30.2 ± 1.5</td>
<td>29.0 ± 1.5</td>
<td>28.7 ± 1.2</td>
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<tr>
<td></td>
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<td></td>
<td>19.4 ± 0.7</td>
<td>19.3 ± 0.6</td>
<td>19.8 ± 1.0</td>
<td>19.5 ± 0.8</td>
<td>19.7 ± 1.3</td>
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<tr>
<td></td>
<td>(0.7)</td>
<td>(0.4)</td>
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<tr>
<td>2.5</td>
<td>30.0 ± 1.3</td>
<td>28.7 ± 1.1</td>
<td>30.7 ± 1.3</td>
<td>30.2 ± 1.3</td>
<td>29.8 ± 1.3</td>
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<tr>
<td></td>
<td>(0.7)</td>
<td>(0.6)</td>
<td>(0.8)</td>
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<tr>
<td></td>
<td>19.6 ± 0.9</td>
<td>19.5 ± 2.2</td>
<td>20.1 ± 1.7</td>
<td>19.9 ± 1.3</td>
<td>20.1 ± 2.1</td>
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<tr>
<td></td>
<td>(1.2)</td>
<td>(0.6)</td>
<td>(1.2)</td>
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</table>

Table 2. Survey of T2* derived from phantom studies for single cardiac phase and for CINE T2* mapping techniques.

Mean T2* and standard deviation of T2* derived from ME, MS, ME CINE, MS CINE and MB CINE acquisitions using a slice thickness ranging from 8 mm to 2.5 mm. For all slice thicknesses the top rows show T2* for the long T2* phantom while the bottom rows show T2* for the medium T2* phantom. For the long T2* phantom T2* was observed for a ROI (diameter 2 cm) placed in the iso-center of an axial slice of the phantom. For the medium T2* phantom T2* was observed for a ROI (diameter 6 cm). Please note, for CINE protocols temporal T2* variation is given in parentheses as standard deviation of mean T2* over the CINE cycle.

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heart with the goal to render $B_0$ uniform. The overall protocol time, including localizer, slice angulation, volume selective $B_0$ mapping routine, 2D FLASH CINE imaging (4 chamber view and short axis view) and $T_2^*$ mapping using MS and MB CINE, was approximately 30 minutes. Table 1 outlines the breath hold times used for MS and MB CINE $T_2^*$ mapping in healthy volunteers.

Figure 2. Survey of $T_2^*$ maps derived from phantom studies. $T_2^*$ maps obtained for all imaging strategies using a long $T_2^*$ (A) and a medium $T_2^*$ phantom (B). Slice thicknesses ranging from 8 mm to 2.5 mm (top to bottom) were applied. $T_2^*$ analysis revealed similar results for all $T_2^*$ mapping strategies. For a slice thickness of 8 mm $T_2^*$ varied substantially across both phantoms. The uniformity in $T_2^*$ was improved for a slice thickness of 6 mm and even further enhanced for a slice thickness of 4 mm or 2.5 mm.

doi:10.1371/journal.pone.0052324.g002
Figure 3. $B_0$ distribution for global and volume selective $B_0$ shimming of a four chamber view of the heart. A) Four chamber view of the heart illustrating the positioning of the volume (marked in red) used for global (left) and volume selective (right) shimming. B) $B_0$ field variation derived from global and volume selective shimming. For this subject the global shim provided a peak-to-peak field variation of about 400 Hz across the entire heart. After volume selective shimming peak-to-peak $B_0$ variation across the heart was reduced to approximately 80 Hz. The direction of the maximal $B_0$ gradient is illustrated by the dashed black line in B) and the corresponding profile of $B_0$ field distribution is plotted in C). To guide the eye the epicardial borders are marked in B) and C) by two triangles. The histogram of the field distribution over the left ventricle is shown in D). The full width at half maximum is approximately 200 Hz for the globally shimmed $B_0$ field map and was reduced to about 80 Hz after volume selective shimming.

doi:10.1371/journal.pone.0052324.g003
Image datasets were transferred to a MATLAB (The Mathworks, Natick, USA) workstation and processed offline. For all datasets, $T_2^*$ was estimated based on a linear equation set obtained from the logarithm of Equation 1, where $S(0)$ was estimated through $S(TE_{\text{min}})$. The $T_2^*$ and $S_0$ estimation was used as initialization values to fit the data points to a mono exponential

**Figure 4.** $B_0$ distribution for global and volume selective shimming of a mid-ventricular short axis view of the heart. A) Mid-ventricular short axis view of the heart illustrating the positioning of the volume (marked in red) used for volume selective shimming. B) $B_0$ field maps. C) $B_0$ profile along the direction of the strongest $B_0$ gradient which is highlighted by the dashed black line in B). To guide the eye the epicardial borders are marked in B) and C) by two triangles. D) Frequency histogram across the left ventricle. After volume selective shimming a strong susceptibility gradient at the inferior region of the heart could be reduced. The full width at half maximum is approximately 300 Hz for the globally shimmed field map and was reduced to about 80 Hz after volume selective shimming.

doi:10.1371/journal.pone.0052324.g004

**Post-Processing and Image Analysis**

Image datasets were transferred to a MATLAB (The Mathworks, Natick, USA) workstation and processed offline. For all
decay (Equation 1) based on the MATLAB region trust algorithm.

$$S_{(TE)} = S_0 * e^{-\frac{TE}{T_2^*}}$$  (1)

For $T_2^*$ assessment of the phantom data, a ROI covering the entire central axial view of the phantom was used. Average and standard deviation of $T_2^*$ were determined.

For examination of the in vivo data, an affine registration of the MB CINE datasets was incorporated into the post-processing procedure to compensate for misalignments due to the use of multiple breath-hold periods. The affine registration is landmark based. It shifts and shears the datasets derived from multiple breath-held acquisitions. Landmarks were set manually. Mid-ventricular short axis $T_2^*$ maps were segmented according to the standardized myocardial segmentation and nomenclature for tomographic imaging of the heart [45]. For each segment of the

![Figure 5. Short axis views derived from single cardiac phase and dynamic CINE $T_2^*$ weighted imaging of the heart.](image)

Echo times ranging from 2.04 ms to 10.20 ms were used for MS and MB CINE acquisitions. A low nominal flip angle of 20° was used to preserve myocardial signal. Image quality observed for MS and MB CINE acquisitions is comparable. No severe susceptibility artifacts were detected in the septum and in the lateral wall for TEs ranging between 2.04 ms to 10.20 ms. For anterior and inferior myocardial areas encompassing major cardiac veins susceptibility weighting related signal void was observed for TE >7 ms as highlighted by white arrows.

doi:10.1371/journal.pone.0052324.g005

![Figure 6. $T_2^*$ maps derived from single cardiac phase and dynamic CINE mapping of a four chamber and short axis view of the heart at end-diastole and end-systole.](image)

For MS and MB CINE, systolic and diastolic phase was chosen to match the cardiac phase with the end-systolic and end-diastolic phase derived from MS. $T_2^*$ maps deduced from MS and MB CINE showed no significant differences between both methods in the segmental analysis of $T_2^*$ values. When comparing systolic and diastolic $T_2^*$ maps significant differences were found with $p = 0.002$ for MS and $p = 0.01$ for MB CINE.

doi:10.1371/journal.pone.0052324.g006
mid-ventricular slice (segment 7–12 according to [45]), T2* values were calculated during end-diastole and end-systole for the single cardiac phase approach. For assessment of temporal changes in T2* throughout the cardiac cycle ROIs encompassing segment 7 to 12 were defined and analysed for all cardiac phases derived from MB CINE. For this purpose, the position and shape of the ROI was carefully adjusted throughout the cardiac cycle to account for myocardial contraction and relaxation. Also, this approach was used to include only compact myocardium into the analysis so that blood or trabecular tissue contributions can be eliminated. For careful delineation of the myocardial borders 2D CINE FLASH (flip angle = 32°, acquisition data matrix = 256 × 224, FOV = (288 × 252) mm², in-plane resolution = (1.1 × 1.1) mm², slice thickness = 4 mm, TE = 2.8 ms, TR = 4.2 ms) was used. Mean values and standard deviation of T2* were calculated for all ROIs. Statistical analysis was performed to test for data distribution and group differences using R project for statistical computing (OpenSource: www.r-project.org). A p-value below 0.05 was considered as statistically significant.

Results

Phantom Studies

T2* maps derived with all imaging strategies for the phantom experiments are surveyed in Figure 2 and Table 2 and show that all imaging strategies provide similar T2* maps. For the long T2* phantom, T2* varied from 13.6 ms to 37.4 ms across the entire central axial slice when using a slice thickness of 8 mm. The non-uniformity in T2* was reduced for 6 mm slices with T2* ranging from 12.4 ms to 17.2 ms. Mean T2* (in ms) averaged over all subjects for each cardiac segment of a mid-ventricular short axis derived from single cardiac phase MS and from MB CINE acquisitions at end-diastole and at end-systole. T2* values obtained for both approaches show a fair agreement. The statistical analysis showed no significant difference between T2* derived from MS and T2* deduced from MB CINE acquisitions.

Table 3. Summary of mean and standard deviation of T2* (in ms) at end-diastole and at end-systole.

<table>
<thead>
<tr>
<th>cardiac segment</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB CINE end-systole</td>
<td>13.7±2.9</td>
<td>17.4±2.5</td>
<td>14.8±1.8</td>
<td>10.5±4.2</td>
<td>8.3±2.4</td>
<td>10.9±1.7</td>
</tr>
<tr>
<td>MB CINE end-diastole</td>
<td>16.8±2.2</td>
<td>17.3±1.4</td>
<td>16.3±2.2</td>
<td>12.0±3.6</td>
<td>11.4±2.8</td>
<td>12.5±1.9</td>
</tr>
<tr>
<td>MS end-systole</td>
<td>12.4±2.1</td>
<td>17.2±2.7</td>
<td>15.7±2.9</td>
<td>7.6±2.1</td>
<td>10.2±2.0</td>
<td>13.6±1.9</td>
</tr>
<tr>
<td>MS end-diastole</td>
<td>14.0±1.8</td>
<td>17.2±2.6</td>
<td>16.5±2.0</td>
<td>10.6±4.4</td>
<td>11.4±2.5</td>
<td>15.7±2.0</td>
</tr>
</tbody>
</table>

Mean T2* (in ms) averaged over all subjects for each cardiac segment of a mid-ventricular short axis derived from single cardiac phase MS and from MB CINE acquisitions at end-diastole and at end-systole. T2* values obtained for both approaches show a fair agreement. The statistical analysis showed no significant difference between T2* derived from MS and T2* deduced from MB CINE acquisitions.

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Figure 7. CINE T2* maps over the cardiac cycle. Short axis view T2* colour maps derived from MB CINE acquisitions across the cardiac cycle overlaid to conventional 2D CINE FLASH images. T2* values are increasing from diastole to systole, especially for endocardial layers. Macroscopic susceptibility induced T2* reduction effects were present at the epicardium at inferior regions.

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from 19.7 ms to 33.9 ms across the entire central axial slice. $T_2^*$ non-uniformity across the central axial slice was further reduced upon further reducing the slice thickness to 4 mm and 2.5 mm, which showed $T_2^*$ of $(29.1 \pm 1.5)$ ms and $(29.9 \pm 1.7)$ ms, respectively. $T_2^*$ values derived from a ROI (d = 2 cm) placed in the iso-center of the central axial slice of the phantom varied between 26.1 ms (ME) and 28.3 ms (MB CINE), for a slice thickness of 8 mm. In comparison, $T_2^*$ values ranging from 28.7 ms (MS) to 30.7 (MB CINE) were observed for the same small ROI when using a slice thickness of 2.5 mm. $T_2^*$ values derived from CINE imaging remained constant (std <1 ms) throughout the cycle given by the gating paradigm.

For the medium $T_2^*$ phantom, mean $T_2^*$ varied between 18.3 ms and 19.5 ms for a ROI covering the entire central axial slice (slice thickness = 8 mm). For a slice thickness of 6 mm, mean $T_2^*$ values were ranging from 19.0 ms to 19.9 ms. $T_2^*$ mapping using a slice thickness of 4 mm yielded mean $T_2^*$ values ranging from 19.3 ms to 19.8 ms. For a 2.5 mm slice thickness the range of mean $T_2^*$ values encompassed 19.5 ms to 20.1 ms. For this slice thickness the standard deviation of $T_2^*$ across the central slice of the phantom was approximately 2 ms for MS, MB and MS CINE due to SNR constraints. $T_2^*$ values derived from CINE imaging remained constant (std <1 ms) throughout the cycle given by the cardiac gating paradigm.

In all phantom experiments, the acquisition time of the MS approach was doubled versus the ME approach, as summarized in Table 1. In MS, only 5 views per segment were recorded while ME used 10 views per segment. This approach has been deliberately chosen already at this stage to ensure that the acquisition windows do not exceed the cardiac rest period in the in vivo studies. For ME CINE, only two views per segment were used to accomplish an acquisition window of 38 ms which increased the total scan duration to 121 s in the phantom studies. This scan duration was doubled for MS CINE since only one view per segment could be used for this approach.

Figure 8. Analysis of $T_2^*$ across the cardiac cycle. Synopsis of the evolution of mean $T_2^*$ averaged over all subjects for standard mid-ventricular segments of the heart. $T_2^*$ derived from each cardiac segment are plotted versus the cardiac cycle. $T_2^*$ changes over the cardiac cycle. Averaging $T_2^*$ over all mid-ventricular myocardial segments revealed that $T_2^*$ increases approximately 27% between systole and diastole. Myocardial $T_2^*$ was derived from MB CINE acquisitions. Prospective triggering was used which resulted in a gap at end-diastole of approximately 100 ms depending on the heart rate. For this reason the cardiac cycle is normalized for all subjects without including this gap. doi:10.1371/journal.pone.0052324.g008
Volunteer Studies

For the in vivo studies, MS and MB CINE were applied using a slice thickness of 4 mm to balance the competing constraints between SNR and B₀ background gradients. A reduction in slice thickness helps to reduce intra-voxel dephasing due to B₀ gradients along the slice direction. This slice thickness is afforded by the in-plane spatial resolution of (1.1 x 1.1) mm². Compared to the results obtained with MB CINE using a slice thickness of 4 mm, changes in T₂* from epicardial to endocardial septal myocardial layers are more pronounced, in particular during systole.

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A closer examination revealed a significant difference between myocardial T₂* obtained at end-diastole and those derived from end-systolic acquisitions and p = 0.01 for MB CINE acquisitions at end-diastole is given in Table 3.

A synopsis of T₂* values averaged over all subjects for MS and MB CINE acquisitions at end-diastole is given in Table 3.

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A closer examination revealed a significant difference between myocardial T₂* obtained at end-diastole and those derived from end-systolic acquisitions. Indeed, an increase in T₂* can be clearly observed, particularly at the septum, during systolic phases (Figure 6, Figure 7). Figure 7 shows exemplary CINE T₂* maps for all phases of the cardiac cycle and illustrates the changes of T₂* over the cardiac cycle. A paired t-test comparing end-diastolic and end-systolic phase T₂* values for all segments revealed p = 0.002 for single cardiac phase MS and MB CINE acquisitions and p = 0.01 for MB CINE acquisitions. When averaging the T₂* time course from all subjects an increase in T₂* of 27%±6% in all cardiac segments
could be observed over the cardiac cycle (Figure 8). The shortest $T_2^*$ values were noted for a cardiac phase placed in systole. For all cardiac segments, the longest $T_2^*$ values were found after the onset of diastole. The largest $T_2^*$ increase over the cardiac cycle was found for segment 7 ($\Delta T_2^* = +3.7 \text{ ms}$) and segment 10 ($\Delta T_2^* = +9.4 \text{ ms}$).

To demonstrate the baseline SNR advantage of 7.0 T and to further reduce intravoxel dephasing along the slice direction, the slice thickness was reduced to 2.5 mm while maintaining the in-plane spatial resolution of $(1.1 \times 1.1) \text{ mm}^2$ in the MB CINE protocol. Figure 9 shows short axis and four chamber view T2* maps, which demonstrate the high spatial resolution. This approach further manifests the observed changes in $T_2^*$ during systole and diastole and also indicates the high sensitivity of susceptibility mapping by visualizing differences in $T_2^*$ between endocardial and epicardial layers of the myocardium.

**Discussion**

This work shows the feasibility of high spatially and temporally resolved myocardial $T_2^*$ mapping at 7.0 T. For this purpose $T_2^*$-weighted, gradient echo based imaging techniques using single cardiac phase (MS) and CINE (MB CINE) acquisition regimes were benchmarked against $T_2^*$ mapping techniques commonly used in current clinical practice at 1.5 T and 3.0 T. These two imaging techniques were first examined in detail in phantom experiments.

It might be considered as a remaining limitation that our results might be affected by residual macroscopic $B_0$ gradients. However, our $B_0$ mapping results suggest that a reasonable $B_0$ uniformity across the heart and the left ventricle can be achieved at 7.0 T which is embodied by a mean through-plane gradient of 3 Hz/mm across the left ventricle. In this regard it should be also noted that our measurements of the $B_0$ field distribution after volume selective shimming of our uniform phantom provided a through slice peak-to-peak $B_0$ variation of 80 Hz along a distance of 4 cm which translates into 2 Hz/mm. This $B_0$ field gradient is similar to what has been observed for the left and right ventricle which showed a mean of 3 Hz/mm.

The frequency shift across the heart reported here compares well with previous 3.0 T studies which reported a peak-to-peak off-resonance variation of $(262 \pm 58) \text{ Hz}$ over the left ventricle and the right ventricle (basal short axis view) for a global shim [48]. This $B_0$ inhomogeneity was improved to $(176 \pm 30) \text{ Hz}$ and $(121 \pm 31) \text{ Hz}$ with the use of localized linear and second-order shimming [48]. The use of an enhanced locally optimized shim algorithm, which is tailored to the geometry of the heart, afforded a reduction of the peak-to-peak frequency variation over the heart from 235 Hz to 86 Hz at 3.0 T [49]. Another pioneering study showed a peak-to-peak off-resonance of $(71 \pm 14) \text{ Hz}$ for short axis views acquired at 1.5 T [40] using global shimming.

Previous reports on brain imaging/spectroscopy suggest that third-order and even higher order shims help to further enhance $B_0$ uniformity across the target anatomy [50, 51]. For this purpose extra shim drum inserts are retrofitted to the scanner. Notwithstanding its utility the current implementation limits the available space inside of the MR scanner bore which would be prohibitive for cardiac or body MRI at 7.0 T. Other attempts to integrate third order shim coils into high performance 7.0 T whole body gradient coil designs were found to show pronounced gradient non-linearity for spherical volumes with a diameter larger than (20–25) cm; a behavior which does not meet the requirements of cardiac or body MR. Obviously, another approach to further reduce the residual impact of through-plane gradients and intra-voxel dephasing $B_0$ gradients is the use of even thinner slices and the reduction in voxel size. To meet this goal we pushed the envelope by using a slice thickness as thin as 2.5 mm together with an in-plane resolution of $(1.1 \times 1.1) \text{ mm}^2$. This slice thickness and in-plane resolution is afforded by the SNR advantage inherent to 7.0 T. The corresponding voxel size is by a factor of five smaller than commonly used for $T_2^*$ mapping at 1.5 T and 3.0 T. However, it should be noted that the move to even thinner slices and smaller voxel sizes – ideally one might opt to use an infinitesimal small voxel – would disturb the balance dictated by the competing constraints of SNR and background gradients effects.

This study sheds further light to the current literature since it demonstrates the applicability of MS and MB CINE for $T_2^*$ mapping of normal myocardium at 7.0 T. While we recognize a limitation due to the limited number of healthy subjects studied, we believe this feasibility study to be an essential precursor to a larger 7.0 T study involving healthy and patient cohorts. Such a study would aid to establish the lower limits for normal myocardial $T_2^*$ values versus the clinically established normal values for $T_2^*$ and $T_2^*$ of healthy myocardium at 1.5 T and 3.0 T. To this end, $T_2^*$ mapping at 7.0 T may be useful to extend the capabilities and the dynamic range of the sensitivity of the established approach used for quantification of myocardial iron content. With this in mind, we anticipate to extend our efforts towards clinical studies at 7.0 T including thalassemia major patients, whose $T_2^*$ relaxation times will be benchmarked against the normal values of healthy subjects.

Our results show that $T_2^*$ obtained for human myocardial muscle tissue at 7.0 T ranges from 9 ms to 18 ms. This is in line with $T_2^* = (15.8 \pm 0.2) \text{ ms}$ recently observed for hind limb skeletal muscle in rats at 7 Tesla [52]. Admittedly, the absolute spatial resolution demonstrated for $T_2^*$ mapping of the human heart at 7.0 T is still by an order of magnitude below that previously reported for ex vivo MR microscopy based $T_2^*$ mapping of the isolated rat heart [7], which demonstrated that $T_2^*$ mapping provides an insight into the complex architecture of the heart musculature. However, the effective anatomical spatial resolution – voxel size per anatomy – is getting close to what has been demonstrated for animal models. This improvement might be beneficial to gain a better insight into the myocardial microstructure in vivo with the ultimate goal to visualize myocardial fibers or to examine helical angulation of myocardial fibers using $T_2^*$ mapping, since the susceptibility effects depend on the tilt angle between blood filled capillaries and the external magnetic field [53]. Myocardial fibre tracking using $T_2^*$ mapping holds the promise to be less sensitive to bulk motion than diffusion-weighted MR of the myocardium [54, 55]. Our results also suggest that the increased susceptibility contrast available at 7.0 T could be exploited to quantitatively study iron accumulations in organs other than the heart with high sensitivity and temporal and spatial resolution superior to what can be achieved at 1.5 T and 3.0 T.

For normal myocardium a $T_2^*$ value of approximately 37 ms was found at 1.5 T [23]. At 3.0 T a $T_2^*$ of approximately 27 ms was observed for normal myocardium [56]. These measurements are usually limited to the septum, which shows the lowest spatial variation in $T_2^*$ [57]. It is elusive to study temporal changes in $T_2^*$ at 1.5 and 3.0 T due to scan time constraints which are prohibitive for CINE $T_2^*$ mapping. Of course, single cardiac phase $T2^*$ mapping can be applied to diastole and systole as reported previously [58]. This 1.5 T study with thalassemia patients demonstrated mean $T_2^*$ values of $(26.4 \pm 14.2) \text{ ms}$ for early systole and $(25.2 \pm 13.2) \text{ ms}$ for late diastole, which were found to be not significantly different ($P = 0.27$). However, the limited $T_2^*$
sensitivity together with the temporal resolution used in the study presents a challenge for tracking temporal changes in T2* [17]. Please also note, that these data exhibit a rather large standard deviation of approximately ± 13.0 ms, which presents another challenge for assessment of temporal T2* changes.

A careful literature research revealed that no 1.5 T and 3.0 T T2* mapping study has been reported yet which uses a high spatial resolution accomplished here. We would also like to point out that our study is the first study which affords CINE T2* mapping due to inter echo time shortening at 7.0 T. To this end it is interesting to note that the myocardial BOLD effect has been investigated using SSFP imaging, which is sensitive to changes in the relaxation times T1 and T2. In this regard it has been shown recently that the signal intensity derived from SSFP imaging of the myocardium varies across the cardiac cycle [59]. This study showed a systole-to-diastole T2 ratio of approximately 1.1 for normal myocardium.

The ability to probe for changes in tissue oxygenation using T2* sensitized imaging/mapping offers the potential to address some of the spatial and temporal resolution constraints of conventional first pass perfusion imaging and holds the promise to obviate the need for exogenous contrast agents. Since microscopic susceptibility increases with field strength, thus making the BOLD effect due to (patho)physiology of interest more pronounced, T2* mapping at 7.0 T might be beneficial to address some of the BOLD sensitivity constraints reported for the assessment of regional myocardial oxygenation changes in the presence of coronary artery stenosis [60] or for the characterization of vasodilator-induced changes of myocardial oxygenation at 1.5 T and at 3.0 T [17].

Conclusion

Our results underscore the challenges of myocardial T2* mapping at 7.0 T due to the propensity to macroscopic susceptibility artefacts and T2* shortening, but demonstrate that these issues can be offset by using tailored shimming techniques together with dedicated acquisition schemes.

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Author Contributions

Conceived and designed the experiments: FH CT JSM TN. Performed the experiments: FH CT TN. Analyzed the data: FH JSM. Contributed reagents/materials/analysis tools: FH SW. Wrote the paper: FH CT SW JSM TN.

References


