Myocardial Effective Transverse Relaxation Time \(T_2^*\) is Elevated in Hypertrophic Cardiomyopathy: A 7.0 T Magnetic Resonance Imaging Study

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Hypertrophic cardiomyopathy (HCM) is the most common genetic disease of the myocardium and bares the risk of progression to heart failure or sudden cardiac death. Identifying patients at risk remains an unmet need. Recognizing the dependence of microscopic susceptibility on tissue microstructure and on cardiac macromorphology we hypothesized that myocardial \(T_2^*\) might be altered in HCM patients compared to healthy controls. To test this hypothesis, myocardial \(T_2^*\)-mapping was conducted at 7.0 Tesla to enhance \(T_2^*\)-contrast. 2D CINE \(T_2^*\)-mapping was performed in healthy controls and HCM patients. To ensure that \(T_2^*\) is not dominated by macroscopic magnetic field inhomogeneities, volume selective \(B_0\) shimming was applied. \(T_2^*\) changes in the interventricular septum across the cardiac cycle were analyzed together with left ventricular radius and ventricular septal wall thickness. The results show that myocardial \(T_2^*\) is elevated throughout the cardiac cycle in HCM patients compared to healthy controls. A mean septal \(T_2^* = 13.7 \pm 1.1\) ms (end-systole: \(T_2^*\),systole = 15.0 \pm 2.1\), end-diastole: \(T_2^*\),diastole = 14.3 \pm 1.3\) ms, \(T_2^*\),systole/\(T_2^*\),diastole ratio = 1.12) was observed in healthy controls. For HCM patients a mean septal \(T_2^* = 17.4 \pm 1.4\) ms (end-systole: \(T_2^*\),systole = 17.7 \pm 1.2\) ms, end-diastole: \(T_2^*\),diastole = 16.2 \pm 2.5\) ms, \(T_2^*\),systole/\(T_2^*\),diastole ratio = 1.09) was found. Our preliminary results provide encouragement that assessment of \(T_2^*\) and its changes across the cardiac cycle may benefit myocardial tissue characterization in HCM.

Hypertrophic cardiomyopathy (HCM) is the most common genetic disease of the myocardium. Epidemiological studies estimated the prevalence of HCM to be about 0.2–0.5% in the general population. The disease is characterized by myocardial hypertrophy in absence of an obvious extrinsic cause such as pressure or volume overload. Patients often remain asymptomatic, but the disease can have a severe outcome in a subgroup of patients where it may cause heart failure and unexpected sudden cardiac death (SCD) in any age group. Major basic research efforts and clinical science activities are underway to better characterize HCM patient populations.

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Cardiovascular magnetic resonance (CMR) imaging has emerged as an indispensable tool in the diagnosis and risk stratification of HCM. Vigorous research has resulted in an enormous body of literature that documents the merits of CMR and showed that the degree of hypertrophy or presence of myocardial fibrosis are associated with a poor outcome in HCM. Notwithstanding this success, understanding the pathophysiologic mechanisms of the imaging findings and identifying patients at risk of SCD or progression to heart failure remains an unmet clinical need. So far it has been extremely challenging to connect the molecular and cellular defects that characterize HCM to the level of major organ systems at which they play themselves out.

Quantitative mapping of the effective transversal relaxation time $T_2^*$ provides valuable means for myocardial tissue characterization without the need for exogenous contrast. A growing number of reports refers to mapping $T_2^*$ in basic research and emerging clinical CMR applications. Myocardial $T_2^*$ is commonly assumed to provide a surrogate for myocardial tissue oxygenation. Yet, the factors influencing $T_2^*$ are of multiple nature. Further to blood oxygenation, blood volume fraction per tissue volume, hematocrit, the oxyhemoglobin dissociation curve, main magnetic field inhomogeneities, tissue pH, tissue susceptibility, tissue iron content and tissue microstructure or morphomorphology were reported to govern $T_2^*$. Cardiac macromorphology including ventricular radius and ventricular wall thickness constitutes another category of physiological parameters that orchestrate $T_2^*$.

The linear relationship between magnetic field strength and microscopic susceptibility effects renders ultra-high field ($B_0 > 7.0$ T) CMR conceptually appealing for myocardial $T_2^*$ mapping. The enhanced susceptibility effects at 7.0 Tesla ($T_e$) may be used to lower the detection level and to extend the dynamic range of the sensitivity for monitoring $T_2^*$ changes. Moving to ultrahigh magnetic fields also enables cinematic $T_2^*$ mapping in scan times feasible for breath held acquisitions. Taking advantage of this gain, temporally resolved $T_2^*$ mapping at 7.0 T showed cyclic changes of myocardial $T_2^*$, demonstrated a close correlation with myocardial wall thickness and myocardial wall stress and suggested an association with alterations in myocardial blood volume fraction across the cardiac cycle. These findings hold the potential to exploit $T_2^*$ mapping for non-invasive probing of myocardial (patho)physiology in vivo.

It is established in the literature that HCM can cause alterations in the microstructure of myocardial tissue and can induce changes in cardiac macromorphometry including myocardial wall thickening and reduction in left ventricular inner radius. Based on the dependence of microscopic magnetic field perturbations on such changes, we hypothesize, that myocardial $T_2^*$ and its time course across the cardiac cycle might be altered in HCM patients compared to healthy controls and hence might provide an imaging based marker for HCM. To test this hypothesis myocardial $T_2^*$ of the intraventricular septum was examined at 7.0 Tesla using high spatio-temporally resolved, susceptibility weighted 2D CINE techniques in healthy controls and in HCM patients. This approach was paralleled by an assessment of the patterns and degree of myocardial hypertrophy.

Methods

Study population. Six healthy volunteers without any known history of cardiac disease (4 male, age = 50.0 ± 12.4 years (mean ± sd), BMI = 23.9 ± 2.9 kg/m²) and six patients with confirmed HCM (4 male, age = 52.7 ± 17.5 years (mean ± sd), BMI = 25.2 ± 1.9 kg/m²) were included in the study (Table 1) after due approval by the local ethical committee. The diagnosis of HCM was based on clinical parameters including echocardiography. Informed written consent was obtained from each volunteer prior to the study in compliance with the local institutional review board guidelines. All experiments were performed in accordance with the Declaration of Helsinki and the local institutional review board guidelines.

Late Gadolinium enhancement imaging. All HCM patients included in the study had previously undergone a clinical MRI exam including LGE imaging for detection of myocardial fibrosis. For this purpose a 3.0 T MR system (Magnetom Verio, Siemens, Erlangen, Germany) was employed using a 32-channel RF receive array. LGE images were acquired 10–15 minutes after application of gadobutrol (0.2 mmol/kg body weight) using a FLASH inversion recovery echo planar technique to detect fibrosis. Imaging parameters were: TE = 5.4 ms, TR = 10.5 ms, flip angle 30°, spatial resolution (1.5 × 1.5 × 6.0) mm³. LGE imaging at 3.0 T was performed for five of the six patients. For the sixth patient LGE imaging data were available from a 1.5 T system (Magnetom Avanto, Siemens, Erlangen, Germany). The slice planning during the current study was based on the previous clinical exams and carefully adjusted to achieve the same slice positioning.

$B_0$ shimming. To minimize the influence of macroscopic magnetic field inhomogeneities on $T_2^*$ and to ensure that $T_2^*$ is not dominated by macroscopic magnetic field inhomogeneities but rather governed by microscopic susceptibility effects, volume selective $B_0$ shimming was carefully carried out prior to $T_2^*$ mapping. A $B_0$ field map was acquired in a single breath hold in end-diastole using an axial stack of slices covering the entire heart. A cardiac triggered multi-echo gradient-echo technique (TEs = 2.04 ms and 4.08 ms, TR = 5.4 ms, spatial resolution (4.2 × 4.2 × 8.0) mm³, 18 slices) was employed. Based on this field map second order shimming was applied for a shim volume accommodating a four chamber view and a mid-ventricular short axis view of the heart. This shimming approach yielded magnetic field homogeneity in the heart comparable to what has been reported at 3.0 T.

CINE imaging and $T_2^*$ weighted image acquisition at 7.0 T. Experiments were performed in a 7.0 T whole body MR system (Magnetom, Siemens, Erlangen, Germany). A 16 channel transceiver RF coil array
Surface area; $P* (1.1\ MA, USA)$ routines. Prior to $T_2$ observed in the fitted maps$^{23,31}$. After de-noising, the $T_2$ volunteers and 46% in patients in comparison to fits from unfiltered images. No artifacts due to filtering were employed for cardiac triggering and gating.

High spatial resolution CINE $T_2^*$ mapping was performed with a segmented multi-shot multi breath hold gradient echo technique$^{22}$ using: $TE = 2.04–10.20$ ms, $\Delta TE = 1.02$ ms, $TR = 12.16$ ms, spatial resolution $(1.1 \times 1.1 \times 4.0)$ mm$^3$, flip angle 20°, GRAPPA acceleration factor 4. $T_2^*$ weighted CINE acquisitions were split in three sub-acquisitions, each acquired in one breath-hold$^{22}$ (Fig. 1I). High blood-myocardium contrast 2D CINE FLASH acquisitions (spatial resolution $(1.4 \times 1.4 \times 4.0)$ mm$^3$, flip angle 32°, $TE = 2.67$ ms, $TR = 5.66$ ms, GRAPPA acceleration factor 2) were used as anatomic reference. Mid-ventricular short axis views were acquired.

### Data processing.

Data processing (Fig. 1) was performed offline using MATLAB (The Mathworks, Natick, MA, USA) routines. Prior to $T_2^*$ fitting, all $T_2^*$ sensitized images were de-noised using a spatially adaptive non-local means (SANLM) filter$^{30,31}$ (VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8/)). SANLM filtering decreased the estimated fit standard deviation of $T_2^*$ in the myocardium by approximately 32% in healthy volunteers and 46% in patients in comparison to fits from unfiltered images. No artifacts due to filtering were observed in the fitted maps$^{23,31}$. After de-noising, the $T_2^*$ weighted CINE images from the three breath holds were co-registered employing a non-rigid registration provided by the MIRT MATLAB toolbox (https://sites.google.com/site/myronenko/research/mirt). Images of the three registered scans were combined to form multi-echo series covering nine echoes with increasing $T_2$ weighting (Fig. 1II). Subsequently, non-linear $T_2^*$ fitting was performed using the MATLAB trust region algorithm in combination with a mono-exponential signal decay model (Fig. 1III). Goodness-of-fit was evaluated by $R^2$. Additionally the fit standard deviation ($T_2^*$-STD) was estimated$^{25}$. Voxels with decreased fit quality ($R^2 < 0.7$ or $T_2^*$-STD > 3 ms) or unnaturally high/low $T_2^*$ were considered unreliable and excluded from further analysis.

### Data analysis.

For each subject the left ventricular (LV) myocardium was manually segmented for all cardiac phases. LV wall thickness and inner radius were calculated for 2.5° wide radial sections covering the whole myocardium. This procedure was executed for all cardiac phases resulting in a total sample size of 18720 sections for the healthy controls and in 17712 sections for the HCM patients. Median $T_2^*$ and mean wall thickness were calculated for each cardiac phase to allow assessment of temporal changes. For this purpose only the anteroseptal and inferoseptal segments$^{33}$ (6326 septal sections in controls and 5904 sections in HCM patients) were considered, because $T_2^*$ measurements have been shown to be most reliable in the ventricular septum$^{10}$ (Fig. 1IV). Mean inner LV radius was calculated per phase by averaging over all sections. The averaged values of $T_2^*$, wall thickness and LV radius per cardiac phase were determined for all subjects. For calculation of group averages cardiac cycle duration was normalized and the number of phases was unified using linear interpolation. The overall distribution of septal $T_2^*$ was analyzed using the histogram of the relative frequencies of $T_2^*$ for all septal voxels in all subjects within the respective group. Evaluation of LV-morphology was described recently$^{37}$.

### Statistical analysis.

Statistical analysis was performed using R$^{34}$ and MATLAB. Continuous data are expressed as mean ± SD. Group differences were analyzed for significance using a student’s t-test for normally

| Parameter                                      | HCM Patients | Healthy Controls | $P$ Value |
|------------------------------------------------|--------------|------------------|-----------|
| $n$                                            | 6            | 6                |           |
| Sex (male/female)                              | 4/2          | 4/2              |           |
| Age, y                                         | 52.7 ± 17.5  | 50 ± 12.4        | 0.77      |
| Height, cm                                     | 170 ± 10     | 172 ± 8          | 0.71      |
| Weight, kg                                     | 73.12 ± 9.6  | 71.5 ± 14.1      | 0.82      |
| BMI, kg/m$^2$                                   | 25.19 ± 1.9  | 23.9 ± 2.9       | 0.39      |
| BSA, m$^2$                                     | 1.84 ± 0.18  | 1.84 ± 0.21      | 0.97      |
| Systolic blood pressure, mmHG                   | 142.3 ± 22.8 | 135.5 ± 14.9     | 0.56      |
| Diastolic blood pressure, mmHG                  | 85.8 ± 17.5  | 86.3 ± 13.6      | 0.96      |
| Heart rate, min$^{-1}$                          | 65.17 ± 10.83| 71.7 ± 9.8       | 0.30      |
| Mean end-systolic septal wall thickness, mm     | 16.6 ± 1.8   | 9.8 ± 1.4        | 0.001*    |
| Mean end-diastolic septal wall thickness, mm    | 13.0 ± 3.1   | 6.2 ± 1.2        | 0.002*    |
| Mean $T_2^*$ averaged across all phases, ms     | 17.4 ± 1.4   | 13.7 ± 1.1       | 0.001*    |
| Mean end-systolic $T_2^*$, ms                   | 17.7 ± 1.2   | 15.0 ± 2.1       | 0.025*    |
| Mean end-diastolic $T_2^*$, ms                  | 16.2 ± 2.5   | 13.4 ± 1.3       | 0.039*    |
| LVEDV, ml                                      | 128.8 ± 33.3 | 121.02 ± 21.88   | 0.64      |
| LVESV, ml                                      | 51.3 ± 20.0  | 49.35 ± 12.96    | 0.85      |
| LVEF                                           | 60.9 ± 8.5   | 59.3 ± 6.3       | 0.47      |
| LV mass, g                                     | 168.9 ± 68.0 | 93.1 ± 17.0      | 0.041*    |
| Presence of late gadolinium enhancement         | 6/6          | —                |           |

Table 1. Subject characteristics. Values are given as mean ± standard deviation. The $P$ value stems from a student’s t-test except for LVEF where it stems from a Mann-Whitney u-test. BMI, body mass index; BSA, body surface area; *$P < 0.05$.
determined distributed data and a Mann-Whitney u-test otherwise. Normal distribution was verified using a Shapiro-Wilk test. P values of $P < 0.05$ were considered significant.

**Availability of data.** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Results

Assessment of cardiac morphology. All scans could be performed without any complication. Mean examination time for the assessment of cardiac morphology was 22 ± 7 minutes in healthy volunteers and 21 ± 2 minutes in patients. Ample blood myocardium contrast with a contrast-to-noise-ratio of about 55, image sharpness and signal uniformity across the heart were achieved for all subjects. Mean septal wall thickness (SWT) averaged over all subjects for all cardiac phases was found to be 7.3 ± 1.2 mm in healthy controls and 14.1 ± 2.5 mm in HCM patients. For end-systole mean SWT was 9.8 ± 1.4 mm in healthy controls compared to 16.6 ± 1.8 mm in HCM patients (Table 1). LV analysis confirmed the substantial difference in LV-mass between healthy volunteers (93 ± 17 g) and HCM patients (169 ± 68 g) (P = 0.04). No significant differences in left ventricular end-diastolic volume (LVEDV) (P = 0.64), left ventricular end-systolic volume (LVESV) (P = 0.85) and left ventricular ejection fraction (LVEF) (P = 0.47) were found.

CINE T2* mapping. All volunteers and patients tolerated the breath-hold 2D CINE T2* mapping acquisitions (mean examination: 1:28 ± 0:19 minutes in healthy volunteers and 1:26 ± 0:13 minutes in patients). B0 shimming resulted in macroscopic field dispersions of ΔB0 < 3 Hz per mm (in-plane) and ΔB0 < 1 Hz per mm (through-plane) in the ventricular septum which is similar to what has been previously reported for cardiac MRI at 7.0 T and 3.0 T indicating, that T2* was not dominated by macroscopic magnetic field variations22,23. Averaging T2* over all healthy controls for all cardiac phases (6323 septal sections) revealed a mean T2* = 13.7 ± 1.1 ms (Table 1). Figure 2 surveys LV T2* maps obtained for all healthy volunteers during systole and diastole. For this cohort a mean septal T2* = 15.0 ± 2.1 ms was observed for end-systole. For end-diastole mean septal T2* = 13.4 ± 1.3 ms was determined. The T2*,systole/T2*,diastole ratio was 1.12 for healthy subjects. The mean range (max – min) of T2* over the cardiac cycle was 4.0 ± 1.2 ms which is significantly higher (P < 0.01) than the 0.7 ± 0.4 ms T2* change attributed to the periodic macroscopic B0 variation23.

In comparison, averaging T2* over all HCM patients and for all cardiac phases (5904 septal sections) revealed mean septal T2* = 17.4 ± 1.4 ms (Table 1, Fig. 3) which was significantly higher (P < 0.001) than in healthy controls. For patients mean septal T2* was 17.7 ± 1.2 ms at end-systole and 16.2 ± 2.5 ms at end-diastole (Fig. 2). The T2*,systole/T2*,diastole ratio was 1.09. No significant difference was found for the mean range (max – min) of T2* over the cardiac cycle compared to controls (T2*(max-min) = 3.8 ± 1.2 ms).

Figure 2. Mid ventricular short axis view of systolic and diastolic myocardial T2* maps of healthy controls (top) and HCM patients (bottom) derived from CINE T2* mapping superimposed to FLASH CINE images. Spatial resolution = (1.0 × 1.0 × 4.0)mm3. T2* differences between systole and diastole can be observed. Distinct regions of increased T2* can be identified in the patients.
Figure 3 highlights the time course of mean septal wall thickness, median septal T2\* and mean inner ventricular radius over the cardiac cycle for HCM patients and healthy controls. Cyclic T2\* changes across the cardiac cycle were found. A T2\* increase during systole which is paralleled by an increase in the SWT and a decrease in the left-ventricular radius was observed for healthy controls and HCM patients. Also a decrease of T2\* during diastole was noted for healthy controls and for HCM patients. The overall shape of the curves was similar for patients and controls, with the diastolic T2\* decrease being less pronounced in patients. Plotting mean septal T2\* against mean septal wall thickness revealed two clearly separable clusters for HCM patients and normal controls (Fig. 4a). Analysis of the overall distribution of T2\* across all septal sections and all cardiac phases showed a significant increase of T2\* in patients compared to healthy controls (Fig. 4b).

Discussion

This study sought to test the hypothesis, that myocardial T2\* and its time course across the cardiac cycle are altered in HCM patients compared to healthy controls. The main finding of this study is that septal T2\* is significantly elevated in HCM patients versus healthy controls. Cyclic variations of T2\* across the cardiac with T2\* increasing in systole and decreasing in diastole were observed in both, healthy controls and HCM patients. The overall shape of the curves was similar for patients and controls, with the the diastolic T2\* decrease being less pronounced in patients. Plotting mean septal T2\* against mean septal wall thickness revealed two clearly separable clusters for HCM patients and normal controls (Fig. 4a). Analysis of the overall distribution of T2\* across all septal sections and all cardiac phases showed a significant increase of T2\* in patients compared to healthy controls (Fig. 4b).
of scar tissue, which is also found in HCM patients, has been shown by histologic studies. These conditions result in a reduced myocardial blood volume fraction in HCM and consequently decrease the impact of the deoxygenated hemoglobin on T2*. which could explain the observed T2* prolongation in hypertrophic regions versus normal or remote myocardium.

An association between microvascular dysfunction and late gadolinium enhancement (LGE) has been described in HCM in the literature. Chiribiri et al. reported a coincidence of mid-myocardial LGE with reduced resting state perfusion and greater degrees of hypertrophy. LGE was also present in all HCM patients in the current study. This finding supports the hypothesis that the observed T2* increase might be related to microvascular dysfunction. Reduced myocardial blood flow as observed in microvascular dysfunction and subsequent ischemia has been associated with an unfavorable outcome in HCM and suggested as a strong predictor of clinical deterioration and death. This hints that myocardial T2* mapping might provide an element of risk stratification in HCM. Arguably, increased myocardial T2* often coinciding with LGE has been described in HCM and was associated with inflammation and edema as well as ischemia and fibrosis. A T2* increase would also result in elevated T2*, providing a further explanation for the observed results. Admittedly these interpretations cannot be ultimately proven at this point. Further investigations including animal models of HCM are required to better understand the relationship of MR parameter changes and underlying microstructural and pathophysiologic mechanisms which cannot be definitely verified in vivo. Yet, this study provides new insights and directions for further investigations which will help to link pathological processes to MR findings also in humans.

It is no secret that the increase of magnetic susceptibility effects at higher fields not only affects microscopic susceptibility changes of (patho)physiological origin but can also result in stronger macroscopic field distortions e.g. at air-tissue interfaces. This is often a concern about T2* mapping at high and ultrahigh fields. While careful B0 shimming is certainly of high importance for this, in fact, dedicated shimming techniques have been shown to provide B0 field uniformities in the heart at 7.0 T similar to what has been described at 3.0 T. Combined data from six healthy volunteers and six HCM patients for all cardiac phases. A clear shift toward higher T2* can be observed in the HCM patients.

![Figure 4](https://www.nature.com/scientificreports/) (a) Scatter plot of septal wall thickness and T2* in HCM patients and healthy controls at 7.0 T. Each marker corresponds to one cardiac phase. Errorbars indicate SEM. Two clusters for patients and for volunteers can clearly be separated using mean septal T2* and wall thickness. (b) Histogram (top) and cumulative frequency plot (bottom) of T2* in the mid ventricular septum. Combined data from six healthy volunteers and six HCM patients for all cardiac phases. A clear shift toward higher T2* can be observed in the HCM patients.
Conclusions
Myocardial T₂* is elevated throughout the cardiac cycle in HCM patients compared to healthy controls at 7.0 T. A reduction in tissue blood volume fraction in the hypertrophied myocardium and a T₁ increase related to inflammatory processes were suggested as potential causes for this finding. These factors have been associated with a higher risk for a poor outcome of HCM patients. Our preliminary results provide encouragement, that assessment of T₂* and its changes across the cardiac cycle may benefit myocardial tissue characterization in hypertrophic cardiomyopathy.

References
1. Mozaffarian, D. et al. Heart disease and stroke statistics—2016 update a report from the american heart association. Circulation, CIR. 0000000000000000350, https://doi.org/10.1161/CIR.0000000000000350 (2015).
2. Semsarian, C., Ingles, J., Maron, M. S. & Maron, B. J. New perspectives on the prevalence of hypertrophic cardiomyopathy. Journal of the American College of Cardiology 65, 1249–1254, https://doi.org/10.1016/j.jacc.2015.01.019 (2015).
3. Elliott, P. M. et al. 2014 esc guidelines on diagnosis and management of hypertrophic cardiomyopathy. European Heart Journal, ehu284 (2014).
4. Kramer, C. M. et al. Hypertrophic cardiomyopathy registry: The rationale and design of an international, observational study of hypertrophic cardiomyopathy. Am Heart J 170, 223–230, https://doi.org/10.1016/j.ahj.2015.05.013 (2015).
5. Bogaert, J. & Olivotto, I. Mr imaging in hypertrophic cardiomyopathy: From magnet to bedside. Radiology 273, 329–348, https://doi.org/10.1148/radiol.14131626 (2014).
6. Nelles-Vallespin, S. et al. Assessment of myocardial microstructural dynamics by in vivo diffusion tensor cardiac magnetic resonance. J Am Coll Cardiol 69, 661–676, https://doi.org/10.1016/j.jacc.2016.11.051 (2017).
7. Nourdelin, R. A. et al. The diagnosis of hypertrophic cardiomyopathy by cardiovascular magnetic resonance. Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance 14, 17, https://doi.org/10.1186/s12968-013-0298-x (2012).
8. Elliott, P. M. et al. Sudden death in hypertrophic cardiomyopathy: Identification of high risk patients. Journal of the American College of Cardiology 36, 2212–2218 (2000).
9. Olivotto, I. et al. Maximum left ventricular thickness and risk of sudden death in patients with hypertrophic cardiomyopathy. Journal of the American College of Cardiology 41, 315–321 (2003).
10. Green, J. I., Berger, J. S., Kramer, C. M. & Salerno, M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC. Cardiovascular imaging 5, 370–377, https://doi.org/10.1016/j.jcmg.2011.11.021 (2012).
11. Chan, R. H. et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 130, 484–495, https://doi.org/10.1161/ CirculationAHA.113.007094 (2014).
12. Kühler, S. et al. Visualization of myocardial microstructure using high-resolution T₂* imaging at high magnetic field. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine 49, 371–375, https://doi.org/10.1002/mrm.10346 (2003).
13. Zinner, C. H. et al. Signal evolution in the local magnetic field of a capillary - analogy to the dumped driven harmonic oscillator. Magnetic resonance imaging 30, 540–553, https://doi.org/10.1016/j.mri.2011.12.006 (2012).
14. Friedrich, M. G. & Karamitsos, T. D. Oxygenation-sensitive cardiovascular mri: T₂* relaxometry. Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance 15, 43, https://doi.org/10.1186/s12968-015-0143-4 (2013).
15. Wahidiyat, P. A. et al. Evaluation of cardiac and hepatic iron overload in thalassemia major patients with T2* magnetic resonance imaging. Hematology, 1–7 (2017).
16. Niendorf, T. et al. How bold is blood oxygenation level-dependent (bold) magnetic resonance imaging of the kidney? Opportunities, challenges and future directions. Acta Physiol (Oxf) 213, 19–38, https://doi.org/10.1111/apha.12393 (2015).
17. Christen, T. et al. Quantitative mr estimates of blood oxygenation based on T2*: A numerical study of the impact of model assumptions. Magnetic Resonance in Medicine 67, 1458–1468, https://doi.org/10.1002/mrm.23094 (2012).
18. Lee, J. et al. T2*-based fiber orientation mapping. Neuroimage 57, 225–234, https://doi.org/10.1016/j.neuroimage.2011.04.026 (2011).
19. Niendorf, T. et al. W(h)ether human cardiac and body magnetic resonance at ultrahigh fields? Technical advances, practical considerations, applications, and clinical opportunities. NMR in biomedicine 29, 1173–1197, https://doi.org/10.1002/nbm.2268 (2016).
20. Meloni, A. et al. Detailing magnetic field strength dependence and segmental artifact distribution of myocardial effective transverse relaxation rate at 1.5, 3.0, and 7.0 T. Magn Reson Med 71, 2224–2230, https://doi.org/10.1002/mrm.24856 (2014).
21. Niendorf, T. et al. High field cardiac magnetic resonance imaging: A case for ultrahigh field cardiac magnetic resonance. Circulation. Cardiovascular imaging 10, e005460, https://doi.org/10.1161/CIRCIMAGING.116.005460 (2017).
22. Hezel, F., Thalhammer, C., Waiczies, S., Schultz-Menger, J. & Niendorf, T. High spatial resolution and temporally resolved T2* mapping of normal human myocardium at 7.0 tesla: An ultrahigh field magnetic resonance feasibility study. PloS one 7, e53234, https://doi.org/10.1371/journal.pone.0053234 (2012).
23. Huelnhaen, T. et al. Myocardial effective transverse relaxation time T2* correlates with left ventricular wall thickness: A 7.0 t mri study. Magnetic Resonance in Medicine 77, 2381–2389, https://doi.org/10.1002/mrm.26312 (2017).
24. Huelnhaen, T., Paul, K., Ku, M.-C., Serradas Duarte, T. & Niendorf, T. Myocardial T2* mapping with ultrahigh field magnetic resonance: Physics and frontier applications. Frontiers in Physics 5, https://doi.org/10.3389/fphy.2017.00022 (2017).
25. Christen, T. et al. Evaluation of a quantitative blood oxygenation level-dependent (qbold) approach to map local blood oxygen saturation. NMR in biomedicine 24, 393–403 (2011).
26. van Nierop, B. J. et al. Assessment of myocardial fibrosis in mice using a T2*-weighted 3d radial magnetic resonance imaging sequence. PloS one 10, e0129899 (2015).
27. Prothmann, M. et al. High spatial resolution cardiovascular magnetic resonance at 7.0 tesla in patients with hypertrophic cardiomyopathy - first experiences: Lesson learned from 7.0 tesla. PloS one 11, e0148066, https://doi.org/10.1371/journal.pone.0148066 (2016).
28. Thalhammer, C. et al. Two-dimensional sixteen channel transmit/receive coil array for cardiac mri at 7.0 t: Design, evaluation, and application. Journal of magnetic resonance imaging: JMRI 36, 847–857, https://doi.org/10.1002/jmri.23724 (2012).
29. Frauenrath, T. et al. Acoustic cardiac triggering: A practical solution for synchronization and gating of cardiovascular magnetic resonance at 7 tesla. Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance 12, 67, https://doi.org/10.1186/1532-429X-12-67 (2010).
30. Manjon, J. V., Coupe, P., Marti-Bonmati, L., Collins, D. L. & Robles, M. Adaptive non-local means denoising of mr images with spatially varying noise levels. Journal of Magnetic Resonance Imaging 31, 192–203, https://doi.org/10.1002/jmri.22083 (2010).
31. Feng, Y. et al. Improved pixel-by-pixel MRI R2* relaxometry by nonlocal means. Magnetic Resonance in Medicine 72, 260–268, https://doi.org/10.1002/mrm.24914 (2014).
32. Sandino, C. M., Kellman, P., Arai, A. E., Hansen, M. S. & Xue, H. Myocardial T2* mapping: Influence of noise on accuracy and precision. Journal of cardiovascular magnetic resonance: official journal of the Society for Cardiovascular Magnetic Resonance 17, 7, https://doi.org/10.1186/s12968-015-0115-3 (2015).

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Author Contributions
T.H., J.S.M. and T.N. conceived and designed the study. T.H. carried out the experiments with help of M.P., T.H. performed data processing and analysis with help of A.P., T.S., E.S. and B.F. H.R. helped with data presentation. T.H., J.S.M. and T.N. performed statistical analysis with help of C.E. V.F., E.S. and B.F. T.H. read and approved the final manuscript.

Additional Information
Competing Interests: Thoralf Niendorf is founder and CEO of MRI.TOOLS GmbH, Berlin, Germany. Thoralf Niendorf received travel funds from Siemens Healthcare, Erlangen, Germany and Siemens Healthcare, SAS, Saint-Denis cedex, France. Thoralf Niendorf is chair of the Highfield and Applications study group of the International Society of Magnetic Resonance in Medicine. Victor A. Ferrari is member of the executive committee of the Society for Cardiovascular Magnetic Resonance (Past President); the editorial board of the Journal of Cardiovascular Magnetic Resonance; the editorial board of ACCEL, American College of Cardiology; Chair of the Imaging Council of the American College of Cardiology and immediate past chair of the Cardiac MR Study Group of the International Society for Magnetic Resonance in Medicine. Jeanette Schulz-Menger is member of the executive committee of the Society for Cardiovascular Magnetic Resonance (Immediate Past President); member of the board of trustees of the International Society of Magnetic Resonance in Medicine and runs research collaboration with Siemens Healthineers, Erlangen, Germany and with CIRCLE CVI, Calgary, Canada. The remaining authors declare that they have no competing interests.

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