Till Huelnhagen*, Bert Flemming, Erdmann Seeliger, Jeanette Schulz-Menger and Thoralf Niendorf

Myocardial T_2^* mapping at ultrahigh magnetic fields: in vivo myocardial tissue characterization and assessment of cardiac physiology with magnetic resonance imaging

Abstract: Mapping the effective transverse relaxation time T_2^* represents an emerging MRI tool for non-invasive myocardial tissue characterization and holds the promise to provide means for assessing myocardial (patho)physiology in vivo. This work takes advantage of the linear increase of susceptibility effects with magnetic field strength which renders it appealing to perform T_2^* mapping at ultrahigh magnetic fields and enables temporally resolved T_2^* mapping. Recognizing this potential this study examines the applicability of myocardial CINE T_2^* mapping in healthy volunteers and hypertrophic cardiomyopathy (HCM) patients at 7.0 Tesla and investigates its capability to distinguish between healthy myocardium and myocardium affected by HCM.

Keywords: magnetic resonance imaging, myocardial tissue characterization, physiology, ultrahigh field MR.

https://doi.org/10.1515/cdbme-2017-0092

***Corresponding author: Till Huelnhagen:** Berlin Ultrahigh Field Facility (B.U.F.F.), Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Robert-Rössle-Strasse 10, 13125 Berlin, Germany, e-mail: till.huelnhagen@mdc-berlin.de
Bert Flemming, Erdmann Seeliger: Institute for Physiology, Charité University Medicine, Berlin, Germany
Jeanette Schulz-Menger: Working Group on Cardiovascular Magnetic Resonance, Experimental and Clinical Research Center, a joint cooperation between the Charité Medical Faculty and the Max Delbrück Center for Molecular Medicine, Berlin, Germany; HELIOS Clinics Berlin Buch, Department of Cardiology and Nephrology, Berlin, Germany
Thoralf Niendorf: Berlin Ultrahigh Field Facility (B.U.F.F.), Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany; Experimental and Clinical Research Center, a joint cooperation between the Charité Medical Faculty and the Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany

1 Introduction

Myocardial tissue characterization with parametric MR (T_1, T_2 and T_2^*) is in the spotlight for the study of cardiac diseases such as hypertrophic cardiomyopathy (HCM) which is the most common genetic cardiac disease. T_2^* mapping is of particular relevance since it is a surrogate of a number of physiological parameters including blood oxygenation, blood volume fraction, hematocrit and myocardial wall stress. T_2^* mapping at ultrahigh magnetic field strengths ($B_0 \geq 7.0$ T) permits the temporal assessment of myocardial T_2^* changes across the cardiac cycle [1, 2] which allows probing of different (patho)physiological states of the myocardium and holds the promise to facilitate distinction of healthy and pathologic tissue. Additionally, the increase of susceptibility effects at higher magnetic fields may be useful to lower the detection level and to extend the dynamic range of the sensitivity for monitoring T_2^* changes [3] which renders it conceptually appealing to perform T_2^* mapping at ultrahigh fields. Myocardial BOLD contrast or T_2^* are commonly regarded as surrogates for myocardial tissue oxygenation [4], but the factors influencing T_2^* are manifold [5]. Meaningful interpretation of myocardial T_2^* requires careful identification of influential factors and their contributions to T_2^*. To this end, this study examines the temporal evolution of T_2^* across the cardiac cycle in relation to cardiac macromorphology including myocardial wall thickness and left ventricular inner radius. It is established in the literature that HCM can cause structural and physiologic changes in the myocardium. Based on the dependence of microscopic susceptibility on structural and physiologic changes [5, 6] 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 validate this hypothesis myocardial T_2^* of the left ventricle was examined at 7.0 T using high spatio-temporally resolved susceptibility weighted 2D CINE techniques in healthy controls and HCM patients.

2 Material and methods

For this proof-of-principle study six healthy volunteers (4 male, age=50.0±12.4, BMI=23.9±2.9 kg/m^2) and six age and body mass index matched patients with confirmed HCM (4 male, age=52.7±17.5, BMI=25.2±1.9 kg/m^2) were examined using a 7.0 T whole body MR system (Siemens, Erlangen, Germany) equipped with a 16 channel RF-transceiver array enabling cardiac MRI at 7.0 Tesla [7]. High spatial resolution CINE T_2^* mapping was implemented employing a cardiac triggered interleaved multi-echo gradient-echo technique [1] (TE=(2.04-10.20)ms, ΔTE=1.02ms, TR=12.16ms, flip angle 20° spatial resolution = (1.1x1.1x4.0)mm^3). For data analysis a post-processing pipeline was developed in MATLAB (The Mathworks, Natick, MA, USA). T_2^* mapping was conducted using a mono-exponential signal decay model. Prior to T_2^* fitting, images were de-noised [8] and co-registered. The left ventricular myocardium was manually segmented for each cardiac phase and septal wall thickness, left ventricular inner radius and septal T_2^* were analyzed. Figure 1 illustrates exemplary end-diastolic and end-systolic T_2^* maps of a healthy subject and an HCM patient. For T_2^* analysis only anteroseptal and inferoseptal segments [9] were considered, because T_2^* measurements have been shown to be most reliable in the septum [10]. To characterize local variations of myocardial T_2^* across the cardiac cycle, non-linear iterative image registration of the T_2^* weighted images was performed using the Advanced Normalization Tools [11] to eliminate cardiac motion. After image registration, mono exponential T_2^* fitting was applied to the multi-echo data. Voxel wise relative T_2^* changes (max-min) with respect to the mean over all phases was calculated from the motion compensated T_2^* maps as a potential (patho)physiological marker. The resulting ΔT_2^* maps were compared with late Gadolinium enhancement (LGE) imaging, which is the clinical standard for visualizing microstructural changes in the myocardium such as (diffuse) fibrosis. For this purpose LGE-MRI was performed 10 to 15 minutes after application of gadobutrol (0.2mmol/kg body weight) using an inversion recovery gradient echo technique (TR=10.5ms, TE=5.4ms, FA=30°, spatial resolution = (1.4x1.6x6.0) mm^3) at 3.0 T (Verio, Siemens, Erlangen, Germany).

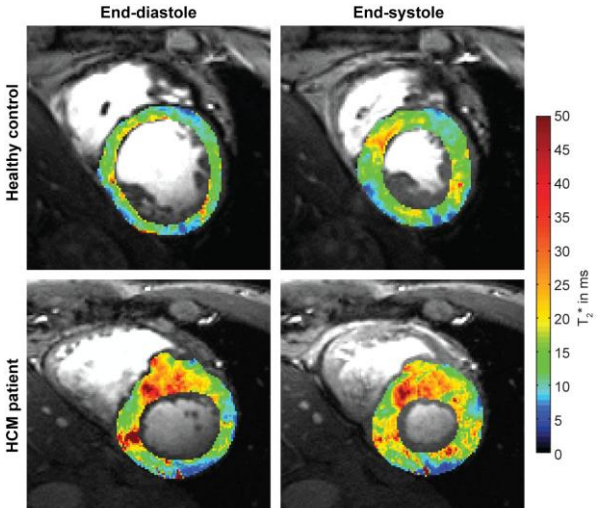

Figure 1: Temporally resolved myocardial CINE T_2* maps in a healthy subject (**top**) and an HCM patient (**bottom**) overlaid onto FLASH CINE images depicting end-diastole (**left**) and end-systole (**right**). An overall increase of T_2* pronounced in septal segments can be observed in the patient. Also an overall T_2* increase in systole cycle can be recognized.

3 Results

All volunteers and patients involved in the clinical proof-of-principal study tolerated the breath-hold 2D CINE T_2^* mapping acquisitions (mean examination time: 13±1 minutes in healthy volunteers and 12±1 minutes in patients). Myocardial T_2^* was found to change periodically across the cardiac cycle in healthy controls and HCM patients. A systolic increase and diastolic decrease of T_2^* were observed in both groups. The diastolic T_2^* decrease was less steep in patients. The periodic T_2^* variation was paralleled by changes in septal wall thickness (SWT) and inner LV radius. Figure 3 shows average time courses of septal T_2^*, wall thickness and inner LV radius across the cardiac cycle for healthy controls and patients. Both, SWT and T_2^* were significantly higher in patients compared to healthy controls. Mean SWT averaged for all cardiac phases was found to be 7.3±1.2mm in healthy controls compared to 14.1±2.5mm in patients. Mean septal T_2^* was T_2^*=13.7±1.1ms in controls and T_2^*=17.45±1.4ms in patients. Mean end-systolic SWT=9.8±1.4 mm and mean T_2^*=15.0±2.1ms were observed in healthy controls compared to end-systolic SWT=16.6±1.8 mm and T_2^*=17.7±1.2ms in patients. Mean end-diastolic SWT=6.2±1.2mm and

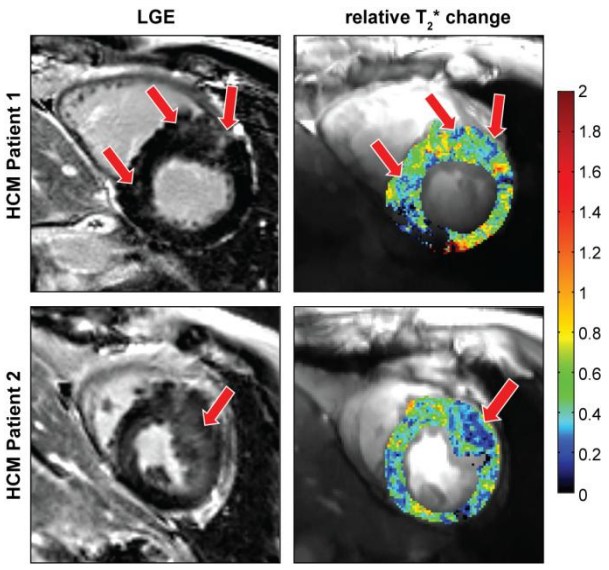

Figure 2: Comparison of voxel wise analysis of relative temporal T_2^* change (max-min) with respect to the mean over all cardiac phases in two HCM patients compared to late Gadolinium enhancement imaging (LGE). Areas showing high LGE signal, which is associated with presence of fibrosis, show lower relative T_2^* changes (arrows).

T_2^*=13.4±1.3ms were determined in controls opposed to end-diastolic SWT=13.0±3.1mm and T_2^*=16.2±2.5ms for patients. Areas presenting hyperintense in LGE images coincided with areas of increased T_2^*. Analysis of localized relative T_2^* changes across the cardiac cycle (ΔT_2^*) by means of motion compensated T_2^* maps revealed areas of reduced ΔT_2^* in HCM patients coinciding with hyperintense areas indicating fibrotic tissue identified by LGE-MR (Figure 2). Unlike HCM patients healthy controls presented global but no focal T_2^* changes across the cardiac cycle.

4 Discussion and conclusion

This study investigated the relation of myocardial T_2^* and morphology and sought to validate the hypothesis, that myocardial T_2^* and its time course across the cardiac cycle might be altered in HCM patients compared to healthy controls. The main finding of this study is that ventricular septal T_2^* changes periodically across the cardiac cycle in healthy controls and patients suffering from HCM and that it is significantly increased in HCM patients. While temporal variations of myocardial T_2^* have been attributed previously to changing myocardial blood volume fraction related to left ventricular blood pressure and resulting wall stress rather than changes in tissue oxygenation [2], two main factors are assumed to cause the observed overall T_2^* increase in HCM. Improved tissue oxygenation in the presence HCM is very unlikely and was hence excluded as a potential cause for the observed T_2^* increase. Instead, first, T_2 has been reported to be elevated in HCM [12, 13] related to inflammation and resulting edema associated with the formation of fibrosis. A T_2 increase would also increase T_2^* and is supported by hyperintense areas in LGE images associated with fibrosis coinciding with areas of increased T_2^*. Second, reduced myocardial perfusion and ischemia are common in HCM [14]. This condition reduces tissue blood volume fraction thereby decreasing the impact of deoxygenated hemoglobin on T_2^* and could hence explain the T_2^* increase. Presence of LGE and perfusion deficits were associated with a higher risk for a poor outcome in HCM patients [15, 16]. Hence our results suggest that myocardial T_2^* mapping might support risk stratification in HCM. The coincidence of regions showing reduced T_2^* changes across the cardiac cycle as

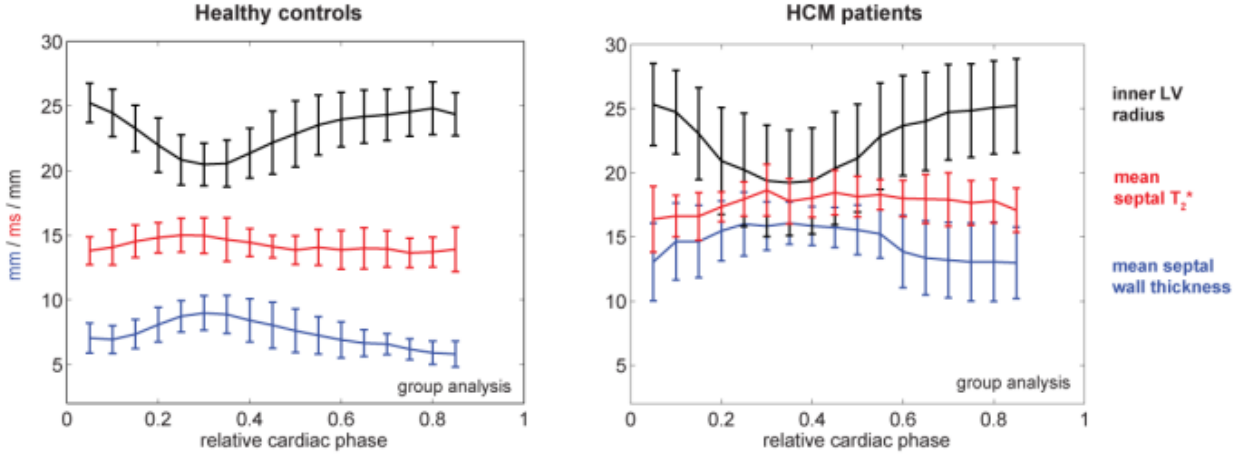

Figure 3: Course of mean septal wall thickness, inner LV radius and mean septal T_2^* plotted over the cardiac cycle averaged for all healthy controls **(left)** and all patients **(right)**. Relative cardiac phase 0 indicates the beginning of the cardiac cycle. T_2^* changes periodically over the cardiac cycle increasing in systole and decreasing in diastole in both, healthy controls and HCM patients, but is significantly higher in HCM patients.

revealed by relative ΔT_2^* maps may be explained by reduced blood volume fraction changes due to the presence of fibrotic tissue which is stiffer and hence likely shows lower changes in tissue blood volume fraction across the cardiac cycle.

To conclude, myocardial T_2^* mapping at ultrahigh fields provides means for assessing myocardial (patho) physiology. Myocardial T_2^* and its time course across the cardiac cycle are elevated in HCM patients compared to healthy controls. Our feasibility study suggests that myocardial areas exhibiting reduced ΔT_2^* across the cardiac cycle accord with hyperintense areas indicating fibrotic tissue identified by LGE-MR. Temporally resolved T_2^* mapping could provide new means for non-invasive myocardial tissue characterization.

Acknowledgment: The authors wish to thank Peter Kellman, PhD (National Institutes of Health, NHLBI, Laboratory of Cardiac Energetics, Bethesda, USA) for his support with the multi-echo gradient-echo pulse sequence. We acknowledge Antje Els and Denise Kleindienst for acquiring CMR data and Elke Nickel-Szczech and Antje Els for assisting in the organization of the CMR scans.

Author's Statement

Research funding: This work was supported (in part, T.H. and T.N.) by the DZHK (German Centre for Cardiovascular Research, BER 601). Conflict of interest: Thoralf Niendorf is founder and CEO of MRI.Tools GmbH. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

[1] Hezel F, Thalhammer C, Waiczies S, et al., 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, 2012. 7(12):e52324.

[2] Huelnhagen T, Hezel F, Serradas Duarte 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, 2016. (Epub ahead of print).

[3] Niendorf T, Paul K, Oezerdem C, et al., W(h)ither human cardiac and body magnetic resonance at ultrahigh fields? technical advances, practical considerations, applications, and clinical opportunities. NMR Biomed, 2016. 29(9):1173-1197.

[4] Friedrich MG and Karamitsos TD, Oxygenation-sensitive cardiovascular magnetic resonance. J Cardiovasc Magn Reson, 2013. 15:43.

[5] Christen T, Lemasson B, Pannetier N, et al., Evaluation of a quantitative blood oxygenation level-dependent (qBOLD) approach to map local blood oxygen saturation. NMR Biomed, 2011. 24(4):393-403.

[6] van Nierop BJ, Bax NA, Nelissen JL, et al., Assessment of myocardial fibrosis in mice using a T2*-weighted 3D radial magnetic resonance imaging sequence. PLoS One, 2015. 10(6):e0129899.

[7] Thalhammer C, Renz W, Winter L, et al., Two-dimensional sixteen channel transmit/receive coil array for cardiac MRI at 7.0 T: design, evaluation, and application. J Magn Reson Imaging, 2012. 36(4):847-57.

[8] Manjon JV, Coupe P, Marti-Bonmati L, et al., Adaptive non-local means denoising of MR images with spatially varying noise levels. Journal of Magnetic Resonance Imaging, 2010. 31(1):192-203.

[9] Cerqueira MD, Weissman NJ, Dilsizian V, et al., Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation, 2002. 105(4):539-42.

[10] Meloni A, Hezel F, Positano V, 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. Magnetic Resonance in Medicine, 2014. 71(6):2224-2230.

[11] Avants BB, Tustison NJ, Song G, et al., A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage, 2011. 54(3):2033-2044.

[12] Abdel-Aty H, Cocker M, Strohm O, et al., Abnormalities in T2-weighted cardiovascular magnetic resonance images of hypertrophic cardiomyopathy: regional distribution and relation to late gadolinium enhancement and severity of hypertrophy. J Magn Reson Imaging, 2008. 28(1):242-5.

[13] Hueper K, Zapf A, Skrok J, et al., In hypertrophic cardiomyopathy reduction of relative resting myocardial blood flow is related to late enhancement, T2-signal and LV wall thickness. PLoS One, 2012. 7(7):e41974.

[14] Johansson B, Mörner S, Waldenström A, et al., Myocardial capillary supply is limited in hypertrophic cardiomyopathy: a morphological analysis. Int J Cardiol, 2008. 126(2):252-257.

[15] Cecchi F, Olivotto I, Gistri R, et al., Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. New England Journal of Medicine, 2003. 349(11):1027-1035.

[16] Ismail TF, Hsu L-Y, Greve AM, et al., Coronary microvascular ischemia in hypertrophic cardiomyopathy-a pixel-wise quantitative cardiovascular magnetic resonance perfusion study. J Cardiovasc Magn Reson, 2014. 16:49.