Heartbeat-to-heartbeat cardiac tissue characterization

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Chapter 6

Heartbeat-to-heartbeat quantitative cardiac BOLD-MRI in hypertensive patients

Abstract

In this chapter the cardiac applicable gradient-echo spin-echo echo-planar-imaging (GESE-EPI) technique that has been described in the previous Chapter 5 is applied to a hypertensive populations to uncover the presence of microvascular dysfunction. Since the GESE-EPI sequence has shown to be reproducible and sensitive to the small blood oxygenation level dependent (BOLD) changes due to a breath-hold in healthy volunteers, the evaluation in hypertensive patients focusses on determining its sensitivity to the potentially small cardiovascular alterations. In healthy volunteers it has been shown that a breath-hold intervention triggers a cardiac BOLD-response caused by an increase in vascular CO_2 levels and myocardial vasodilation which results in an increase of T_2- and T_2^*-relaxation rates. For hypertensive patients it has been hypothesized that this process could be altered, since the reactivity of the vasculature could be slower or even non-existent. The work in this chapter confirms this hypothesis by showing reversed T_2 and T_2^* changes over the time of a breath-hold in hypertensive patients compared to healthy volunteers. Many other cardiovascular risk populations might have a similar difference in BOLD response and now this GESE-EPI based technique has shown to be sensitive enough, further evaluation in these populations seems promising.

6.1 Introduction

Cardiovascular diseases are often associated with a disruption of the oxygen demand and supply equilibrium, which can lead to functional impairments and heart failure (Cecchi et al. 2009). Numerous methods exist to diagnose myocardial ischemia using surrogate markers (Friedrich 2010), but these techniques often need contrast agents, vasodilators or radiation, and do not directly reflect the ischemic response (Friedrich and Karamitsos 2013).

Cardiac magnetic resonance imaging (MRI) can be used to assess myocardial oxygenation by using the blood oxygenation level dependent (BOLD) effect (Ogawa et al. 1990). Both T_2- and T_2^*-imaging and mapping approaches (Manka et al. 2010, Friedrich et al. 2003, Wacker et al. 1999) have been used as cardiac BOLD-MRI techniques to identify coronary artery disease (CAD) without the use of exogenous contrast (Fischer et al. 2018, Tsaftaris et al. 2013, Yang et al. 2019, Fischer et al. 2016). Breath-hold interventions are recognized to trigger a cardiac BOLD-response (Fischer et al. 2018, Fischer et al. 2016, Fischer et al. 2015, Guensch et al. 2013) by causing an increase in vascular CO_2 levels resulting in myocardial vasodilation within fifteen seconds (Sasse et al. 1996). Such BOLD response can result in an increase of the myocardial T_2- and T_2^*-relaxation rates.

In addition to detecting CAD, it has been hypothesized that cardiac BOLD-MRI may be able to detect microvascular dysfunction in conditions such as hypertension (Cecchi et al. 2009, McCommis et al. 2010) due to expected change in vascular responsiveness (Petersen and Pepine 2015). Detection of these relatively subtle differences using current BOLD-MRI techniques is challenging, but several exciting approaches have been developed to increase this feasibility. For example, signal-to-noise ratio (SNR) can be improved by averaging over multiple heartbeats or breath-holds (Friedrich et al. 2003, Tsaftaris et al. 2013, Yang et al. 2019), or can further be preserved while increasing the spatial resolution by introducing compressed sensing and subspace modeling (Feng et al. 2011). Furthermore, to improve BOLD sensitivity, mapping and increasing the field strength have been introduced (Wacker et al. 1999, Feng et al. 2011, Dharmakumar et al. 2006).

In this work, a multi-gradient-echo spin-echo (GESE) sequence was investigated to evaluate the feasibility of quantitative T_2- and T_2^*-mapping per heartbeat for detecting microvascular dysfunction with sufficient SNR, resolution, and sensitivity to BOLD changes due to breath-hold interventions. Quantitative and temporal improvements have been accomplished for BOLD-MRI in the heart using

this GESE sequence with echo-planar-imaging (EPI) readouts (Chapter 5) (Emblem et al. 2013, Manhard et al. 2019). Combining these readouts into T_2- and T_2^*-maps helps to correct for large vessel contributions (Prinster et al. 1997), mitigates the influence of heartrate changes (Chapter 5) during an breath-hold intervention and offers quantitative myocardial BOLD-readouts (Manhard et al. 2019). All together this allows for the detection of dynamic BOLD-response changes.

The present work explores the clinical applicability of the GESE-EPI sequence for quantitative heartbeat-to-heartbeat BOLD response imaging in hypertensive patients while executing an breath-hold to induce a CO_2 triggered intervention (Fischer et al. 2015, Sprinkart et al. 2015). The results are compared with the same GESE-EPI based BOLD acquisitions in healthy volunteers.

6.2 Methods

This study was IRB approved at two sites and written informed consent was obtained from all participants, the USA site was HIPAA compliant.

Study Participants

MRI was performed in eighteen healthy and nine prospectively recruited hypertension participants. Aside from the inclusion criteria of age 18-45 years and no prior cardiac events or smoking, the healthy participants also had the criteria of a BMI$\leqslant$25, while the hypertension population required clinically diagnosed hypertension, currently under treatment, a BMI$\geqslant$30 and an increased blood pressure of $\geqslant$120/80 measured right after the MRI examination (Table 6.1).

MRI Acquisition and Post-Processing

All scans were done on a 3-Tesla MRI Skyra with a Body-18 and Spine-32 coil or a 3-Tesla MRI Prisma with a Body-30 and Spine-30 coil (Siemens Healthcare, VE11C, Erlangen, Germany). A single GESE-EPI acquisition (Figure 5.4) was performed in the diastolic phase during an end-expiration breath-hold of a maximum of 30 data repetitions for all subjects, in addition to a parallel imaging calibration acquisition and four dummy repetitions (Manhard et al. 2019). In the same mid-ventricular

slice as the GESE-EPI acquisition, clinical standard T_2- and T_2^*-mapping protocols were performed in part of both populations for direct comparison of the T_2- and T_2^*-values (Chapter 5). Conventional 2D steady state free precession (SSFP) cine and late gadolinium enhancement (LGE) acquisitions were performed to rule out the presence of focal ischemia or change in ejection fraction in the hypertension participants. A single mid-ventricle axial slice (SAX) cine was acquired to define the appropriate delay time for the GESE-EPI acquisition.

A standard clinical cardiac MRI protocol was performed in the hypertensive participants to rule out any presence of ischemia or left ventricular remodeling. The sequences included in conventional SSFP based cines in a stack of the short-axis slices from the base to the apex as well as a single slice in the long-axis orientation capturing a 4 chamber (4CH) and 2 chamber (2CH) view (TR=44ms TE=1.3ms, slice thickness=6mm, matrix=256x232, slice gap=10mm, FA=44, BW=930Hz, FOV=271x300mm cardiac frames=25, prospective cardiac triggering) and conventional LGE imaging after 10 minutes after injection of 0.2mmol/kg Gd-DTPA with an inversion recovery gradient-echo sequence in the same slices as the cines (TR=753ms, TE=1.6ms, TI=based on TI-scout, BW=465Hz, FA=20, matrix=256x200, FOV=273x350mm, slice thickness=8mm, slice gap=10mm). The LV-EF were based on manually segmenting short axes cines by G.J.H. Snel using Circle cvi42 *(Circle Cardiovascular Imaging, version 5.10.1, Calgary, Canada)* in consensus with N.H.J. Prakken. Furthermore, the LGE images in each direction and slice were visually evaluated by both G.J.H. Snel and N.H.J. Prakken for focal enhancements and the indication of ischemia.

The gradient-echo spin-echo echo-planar-imaging (GESE-EPI) acquisition included multiple echo acquisitions (Schmiedeskamp et al. 2012a, Manhard et al. 2018, Manhard et al. 2019), before and after the 180-degree refocusing pulse, resulting in multiple gradient-echo (GE) and mixed gradient- and spin-echoes (mixed-SE) images which were used for parametric T_2- and T_2^*-mapping. Details of the GESE-EPI protocol can be found in the methods of Chapter 5 . In short the sequence in Figure 5.4 was applied in an short axis (SAX) within a readout time of 120ms and TR=RR-interval and the spatial resolution between 2.8x2.8mm and 3.0x3.0mm, depending on the chosen FOV_{Slice} (350-480mm) based on subject size for a fixed matrix size of 126x48. The total repeated measures during the breath-hold depended on the participants breath-hold capability but the maximum number of readouts was set to 30 after the dummies and parallel imaging training data acquisitions. T_2- and T_2^*-maps were calculated from the GESE-EPI images per heartbeat by using a multi-parametric voxel-by-voxel fitting approach that has been developed for the brain

(Schmiedeskamp et al. 2012a, Manhard et al. 2018, Manhard et al. 2019) and recently appleid to the heart (Chapter 5). In short, an initial voxel-based 4-parameter fit was used based on a simple matrix inversion that fits the R_2, R_2^* S_{0I} and S_{0II} as explained in detail in Chapter 5, equation 5.1.

GESE-EPI BOLD Analysis

Semi-automatic segmentation with Segment (*v2.0 RX6246, Lund, Sweden*) (Heiberg et al. 2010) of the endo- and epicardium was performed prior to mapping. The mean T_2- and T_2^*-values in a septal region of interest (ROI) acquired per heartbeat were used for further comparison. The changes of the septal T_2- and T_2^*-values in ms/heartbeat (ms/hb), over the course of a breath-hold were determined by linear regression over the acquired heartbeats and interpreted as the BOLD response to the breath-hold. Furthermore, the percentage change of T_2- and T_2^*-values over twenty heartbeats was calculated by using the y-axis intercept and slope of the linear fit.

Statistical Analysis

The mean T_2- and T_2^*-values from the first ten heartbeats of a septal ROI in the GESE-EPI based maps were compared with the standard T_2- and T_2^*-maps, using a paired student's t-test. Subject demographics and static T_2- and T_2^*-values between populations were compared using an unpaired student's t-test. Linear regression of the T_2- and T_2^*-values over a breath-hold were evaluated by testing the null hypothesis that the slopes are zero by an F-test and reported the R^2 and 95% confidence interval of the fit. The T_2- and T_2^*-slopes, or BOLD response, were compared between the healthy and hypertension subjects by a nonparametric Mann-Whitney test. All statistical analyses were performed using GraphPad Prism *(version 8.00; GraphPad, San Diego, CA, USA)* with a significance of $P<.05$.

6.3 Results

Study Participants

Participants demographics can be found in Table 6.1 which only showed difference in BMI (P=.001) between the healthy and hypertension populations. One hypertensive participant was excluded after the CMR examination, because no increased blood pressure was recorded, resulting eight hypertensive participants used in the present study. Furthermore, one participant was unable to finish the whole protocol and therefore no standard clinical readouts for this participant could be determined. Two participants (one healthy and one hypertensive) were able to hold their breath over the whole acquisition time and in contrast, the shortest breath-hold was 21 heartbeats long (including the dummies and parallel imaging data acquisitions) (Table 6.1). The ejection fractions of the hypertensive participants were within normal range and no scar tissue was present (Table 6.1) (Petersen et al. 2017).

MRI Acquisition

The voxel-by-voxel fitted T_2- and T_2^*-maps show low spatial variation across the myocardium (Figure 6.1), though dephasing artifacts can be seen in large B_0 variation voxels along the epi- and endocardium. The mean T_2- and T_2^*-values from the GESE-EPI acquisitions in the septal ROI across healthy participants were 43$\pm$5ms and 28$\pm$5ms, respectively, and 46$\pm$9ms and 22$\pm$5ms in the hypertensive participants (Table 6.1). These GESE-EPI based T_2- and T_2^*-values were comparable with the standard T_2-mapping values of 42$\pm$6ms (P=0.66) and T_2^*-mapping values of 24$\pm$3ms (P=0.17). The standard T_2-values of 40$\pm$3ms for the hypertensive population were slightly lower than the GESE-EPI based T_2-values (P=0.11) (Table 6.1).

BOLD effect in healthy and hypertensive participants

Across all healthy participants, the septal ROI showed increasing T_2- and T_2^*-values during the breath-hold, with a mean slope of 0.2$\pm$0.1ms/hb for T_2 and 0.2$\pm$0.1ms/hb for T_2^* (Table 6.1). Example T_2- and T_2^*-maps of a single heartbeat of a representative participant are shown in Figure 6.1A along with corresponding heartbeat-to-heartbeat measurements, showing a positive slope over the time of a breath-hold for both T_2- (P=.01) and T_2^*-values (P$<$.001).

	Healthy participants	Hypertensive participants	P
N	18	8	
Gender (M/F)	(14/4)	(4/4)	P=.20
Age (years)	31±6 [21-43]	37±8 [24-45]	P=.07
BMI (kg/m^2)	23.9±2.1 [20-29]	38.0±5.8 [30-76]	P=.001*
Smoking (n)	0	0	
Blood Pressure (mmHg)		SBP: 136±21 DBP: 90±10	
Time diagnosed (years)		5±2 [1-20]	
Medicine (time treatment in years)		Metformin (3) Metoprolol, Candesartan (1) Lisinopril (4) Labetalol, Lisinopril (1) Hydrochlorothiazide (20 and 1) Labetalol (5) Clonidine (2)	
LV EF (%)		61.7±3.9 [52.9-69.4] (n=7)	
LGE hyper-enhancement yes/no		0/7 (n=7)	
Standard T_2 (ms)	41.7±6.3 (n=15)	39.5±2.7	P=.38
Standard T_2^* (ms)	24.3±2.6 (n=8)		
GESE T_2 septum (ms)	43.4±5.1	45.5±8.9	P=.97
GESE T_2^* septum (ms)	27.5±4.8	22.2±5.0	P=.04*
Breath-hold (hb) (sec)	 28±5 [22-37] 29.1±3.6 [23.1-35.3]	 28±6 [21-37] 21.9±8.0 [14.1-38.1]	P=.62 P=.01*
RR-peak interval (ms)	1049±114	819±64	P<.001*

Table 6.1: Description and MRI parameters of the study groups
The P-values from an unpaired t-test between healthy and hypertension for the standard T_2, standard T_2^*, length breath-hold, RR-interval, GESE T_2 septum, GESE T_2^* septum, All others P-values result from a nonparametric Mann-Whitney test. M=male, F=female, hb=heartbeat, GESE=gradient-echo spin-echo, SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, LV-EF=left ventricle ejection fraction, LGE=late gadolium enhancement. (mean±SD [full range])

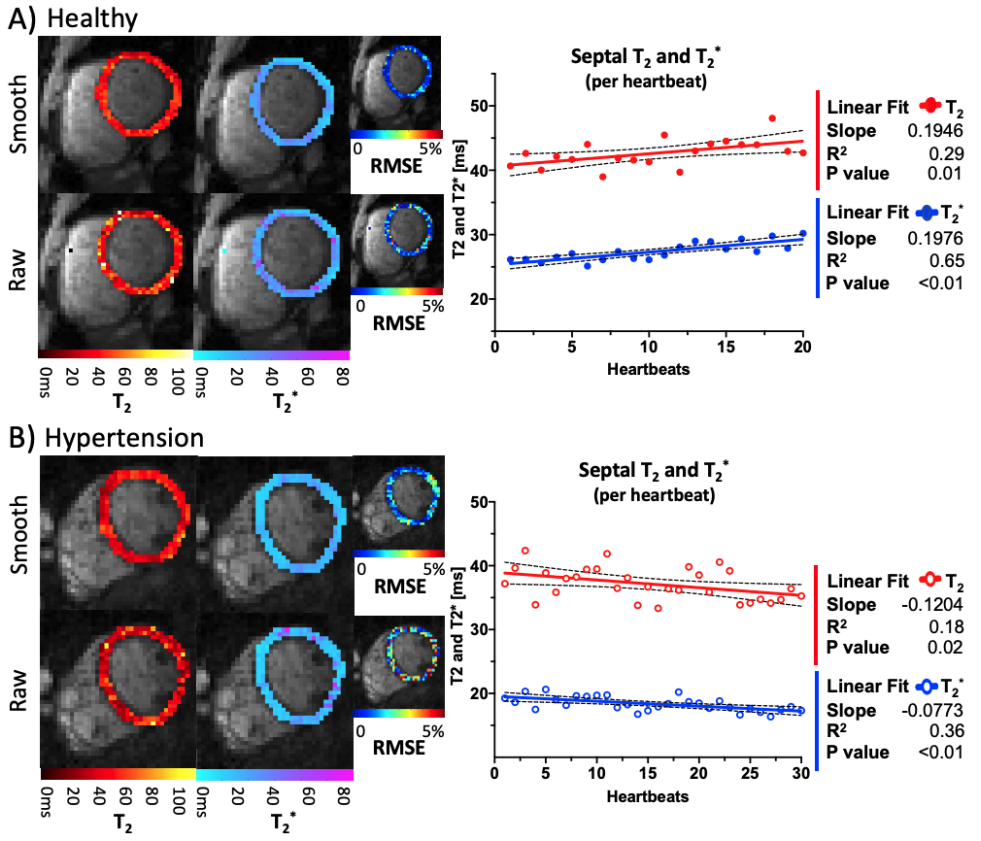

Figure 6.1: An example of the T_2- and T_2^*-maps of A) a healthy female of 25 years old and B) a hypertension male of 38 years old acquired from a single heartbeat. The smoothed maps are found using a local 3x3 Gaussian filter, and are only used for visualization, raw maps are used for all analysis. RMSE maps of the T_2- and T_2^*-fits per voxel are shown, voxels with a RMSE>5% are excluded from analysis. An ROI in the septum was used for BOLD analysis. The mean septal T_2- and T_2^*-values are plotted per heartbeat over the time of a breath hold, with a linear regression fit through these measures. *RMSE=root mean square error, BOLD=blood oxygen level dependent, ROI=region of interest, SI=signal intensity, Smooth=data with 3x3 local Gaussian filter, Raw=data with no filter.*

In hypertensive participants, decreasing T_2- and T_2^*-values were observed over the breath hold, with a mean slope of -0.2$\pm$0.2ms/hb for T_2 and -0.1$\pm$0.2ms/hb for T_2^* (Table1). Figure 6.1 B shows the T_2- and T_2^*-maps and linear fit of a rep-

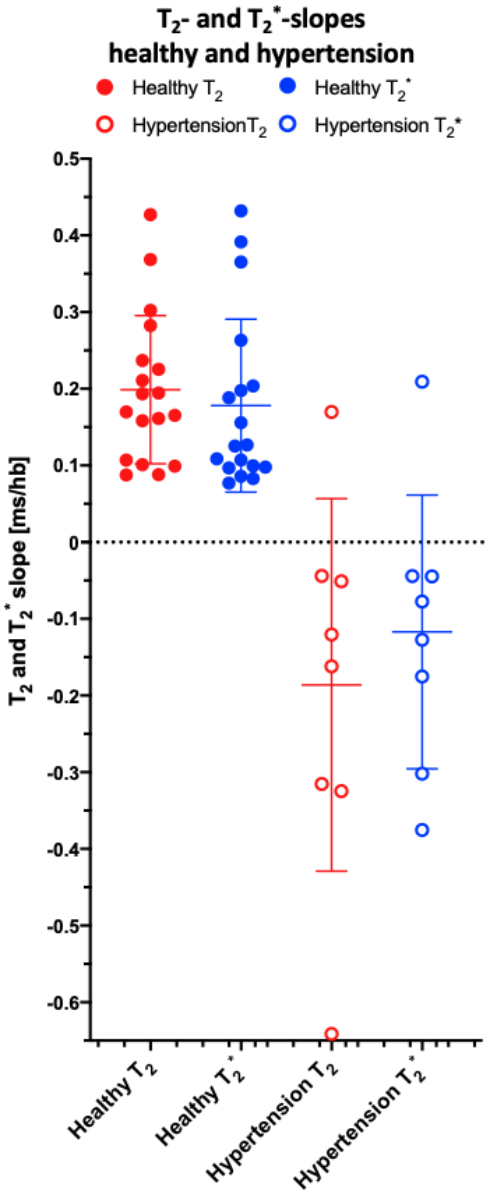

Figure 6.2: The T_2- and T_2^*-slopes are plotted for the n=18 healthy participants shown in red, with a mean slope of 0.2±0.1ms/hb for T_2 and 0.2±0.1ms/hb for T_2^*. The T_2- and T_2^*-slopes are plotted in blue for the n=8 hypertensive participants and have a mean slope of -0.2±0.2ms/hb for T_2 (P<.001) and -0.1±0.2ms/hb for T_2^* (P<.001), which are both different healthy participants despite the one hypertension participant that shows positive healthy T_2- and T_2^*-slopes. *hb=heartbeat*

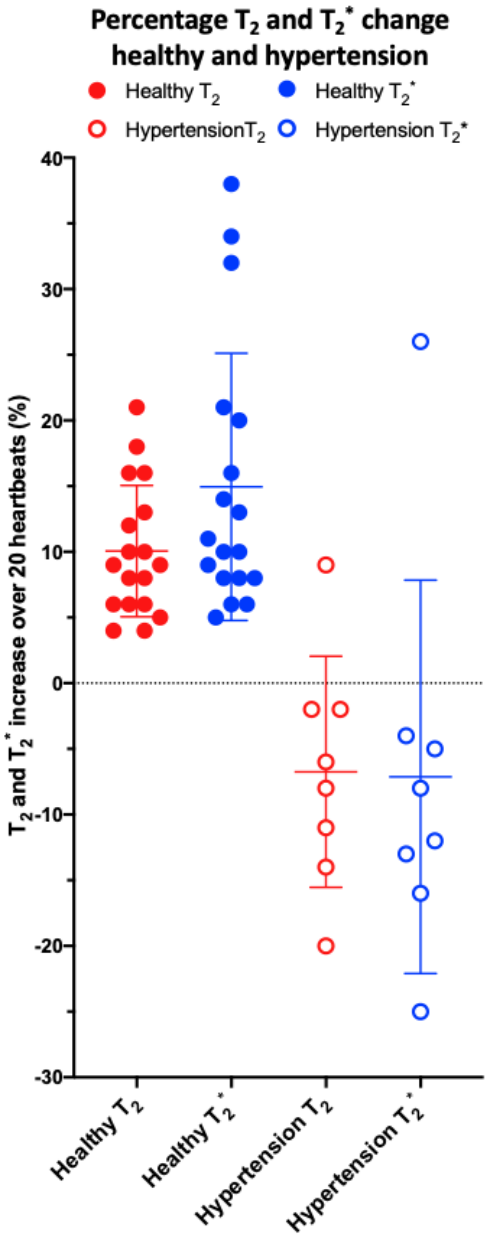

Figure 6.3: The T_2- and T_2^*-percentage changes over 20 heartbeats are plotted for the healthy participants shown in red, with a mean increase of 10.1±5.0% and 14.9±10.2% of T_2 and T_2^*, respectively. T_2- and T_2^*-percentage changes over 20 heartbeats are plotted in blue for the hypertensive participants and have a mean decrease of -6.8±8.8% (P<.001) and -7.1±15.0% (P<.001) of T_2 and T_2^*, respectively, compared to the healthy participants.

resentative hypertension participant with a negative slope for both T_2- (P=.02) and T_2^*-values (P<.001).

The fitted T_2- and T_2^*-slopes for all subjects are shown in Figure 6.2, which shows difference between mean T_2-slopes (P<.001) and mean T_2^*-slopes (P<.001) of healthy and hypertensive participants, indicating a different BOLD response to the breath-hold. The percentages change in T_2 and T_2^* over the first twenty heartbeats are shown in Figure Figure 6.3. All healthy participants exhibited positive T_2- and T_2^*-changes, while all but one hypertension subject showed negative T_2- and T_2^*-changes, suggesting that in this particular subject, despite having hypertension, the BOLD response to the breath-hold was in line with healthy subjects.

Time-series data from subjects with the lowest, mean and highest T_2- and T_2^*-slopes of both groups are shown in Figure 6.4. All healthy participants have positive slopes for T_2 and T_2^* that are significantly different from zero (Figure 6.4A), while for the hypertension participants these slopes are equal to zero, or negative and significantly different from zero (Figure 6.4 B and Appendix 6.A).

6.4 Discussion

Quantitative myocardial BOLD-readouts may allow the detection of subtle dynamic BOLD-response changes in populations with increased cardiovascular risk, such as hypertension. The mean increasing T_2- and T_2^*-slopes of 0.2 ± 0.1ms/hb in healthy participants is concordant with previously published results on breath-hold intervention but now without the need of additional breathing maneuvers, averaging over multiple heartbeats or sensitivity to heart-rate changes (Fischer et al. 2018, Fischer et al. 2015, Guensch et al. 2013).

Hypertensive patients are known to suffer from alterations in microvascular resistance (Cecchi et al. 2009, Camici et al. 2015) compared to healthy participants indicating that the BOLD-response due to the breath-hold is compromised, possibly due to a slower or non-existing vascular response to the increase in CO_2 (Sasse et al. 1996, Camici et al. 2015). The sensitivity of this dynamic cardiac BOLD-MRI approach using only a breath-hold could be achieved by allowing analysis of the rate of T_2- and T_2^*-changes instead of static comparisons between rest and stress states (Manka et al. 2010, Friedrich et al. 2003, Wacker et al. 1999, Yang et al. 2019, Fischer et al. 2016, McCommis et al. 2010). Interestingly, another cardiac BOLD-MRI technique evaluated in CAD-participants of which 54% were hypertensive also showed

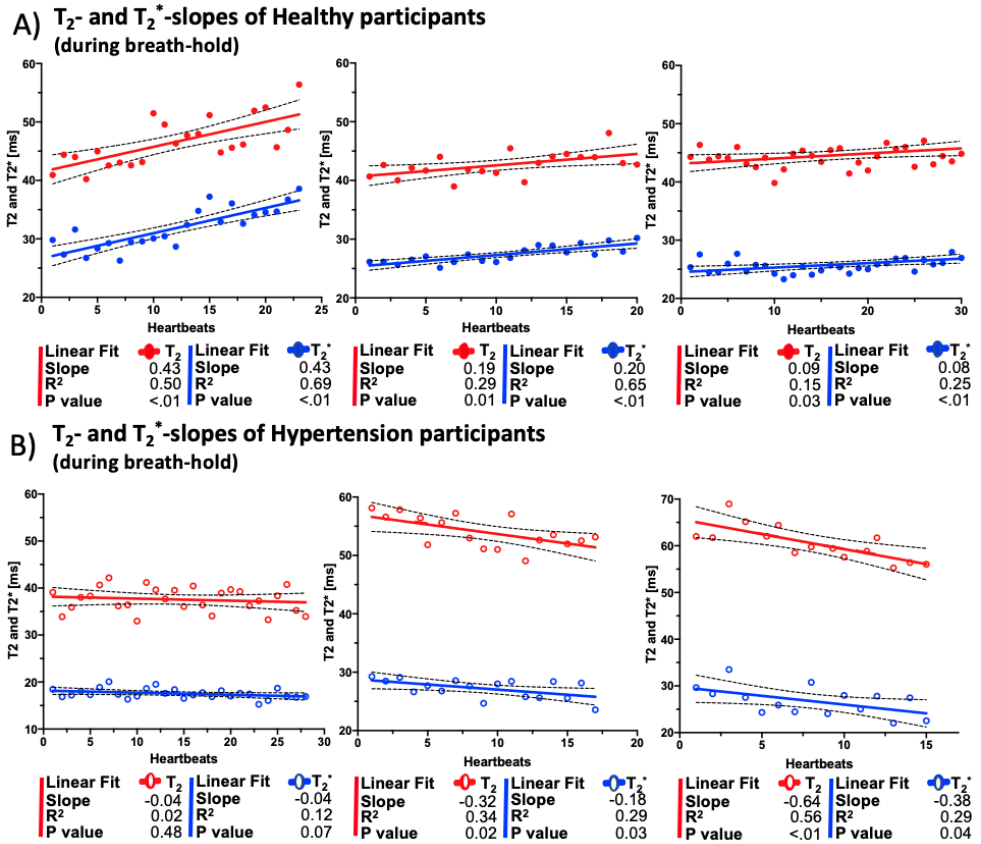

Figure 6.4: A) The T_2- and T_2^*-values over time of three representative healthy participants are shown, which all have a significant positive slope due to BOLD change during a breath-hold. B) The T_2- and T_2^*-slopes of three representative hypertensive participants displaying a compromised BOLD change during breath-hold. *BOLD=Blood Oxygenation Level Dependent, hb=heartbeat.*

a weaker BOLD-response in the remote areas compared to healthy controls (Fischer et al. 2018), which is similar to the GESE-EPI results presented here.

Although the differences in slopes between healthy and hypertensive participants are small, this quantitative and dynamic GESE-EPI approach shows to be able to detect these subtle changes due to its combination of dynamic and quantitative abilities. This creates opportunities in the context of population and longitudinal studies to investigate subtle BOLD response changes caused by cardiovascular diseases

but a broader populational study is needed to determine diagnostic abilities of this technique. Furthermore, other populations such as patients with diabetes or hypercholesterolemia are expected to have a similarly compromised vascular response and warrant further study (Camici et al. 2015).

Despite the promising differences of T_2- and T_2^*-slopes between healthy and hypertensive participants, the GESE-EPI BOLD-CMR technique has some limitations that constrain its wide clinical applicability. While the T_2^*-maps from GESE-EPI are sensitive to BOLD changes, the maps can suffer from dephasing artifacts on the lateral wall (Friedrich et al. 2003) and can be affected by lung volume changes due to B_0 inhomogeneity. To mitigate these T_2^* based limitations, this study restricted the acquisitions to end-expiration to reduce B_0 fluctuation throughout the breath-hold. Also, it constrained the BOLD analysis to a septal ROI, which is a representative of the whole myocardium in diffuse microvascular diseases such as hypertension (Camici et al. 2015). However, this approach would be less applicable in spatially varying CAD, such as circumflex occlusion. Possible solutions to this limitation include incorporating spiral or radial readouts or moving the acquisitions to a lower field strength, though this might result in lower sensitivity to BOLD changes (Dharmakumar et al. 2006). Furthermore, T_2-maps are more specific to macrovascular contribution and are less sensitive to the dephasing artifacts, but have a lower SNR (Prinster et al. 1997) that could compromise the interpretation of the subtle BOLD changes. Consequently, the combination of both T_2- and T_2^*-maps offers complementary information for the assessment BOLD in microvascular diseases.

The protocol was somewhat limited in the image encoding that could fit in the diastolic phase. A relatively large voxel size helps to maintain reasonable encoding times and SNR but increases the risk of obtaining compromised T_2- and T_2^*-maps due to partial volume averaging effects. The number of echoes was limited to five which may compromise the accuracy of the T_2- and T_2^*-maps. However, the number of TEs for this sequence were optimized by following the recommendations from the simulations in Chapter 5.

In addition to the presented evaluation study, it would be of interest to compare GESE-EPI BOLD-MRI with other existing cardiac BOLD-MRI techniques. Previous approaches have used hyperventilation followed by an extended breath-hold (Fischer et al. 2018, Fischer et al. 2016), which enhances the detectable BOLD effect by increasing the coronary vasomotion range. The GESE-EPI BOLD-MRI technique could also be applied in combination with these breathing maneuvers for a direct comparison to existing techniques.

In conclusion, the GESE-EPI sequence provides quantitative T_2- and T_2^*-maps per heartbeat and enables dynamic heartbeat-to-heartbeat BOLD imaging during a breath-hold intervention. This approach has the potential to contribute to the understanding of microvascular diseases. Further research in hypertensive and other increased cardiovascular risk populations (Camici et al. 2015, Petersen and Pepine 2015) should be performed to explore the actual diagnostic value of this BOLD-MRI approach.

Conclusion

The gradient-echo spin-echo echo-planar-imaging (GESE-EPI) sequence has shown to provide dynamic T_2- and T_2^*-maps per heartbeat that enable the detection of a difference in blood oxygenation level dependent (BOLD) response during a breath-hold perturbation between healthy volunteers and hypertensive participants. This change in BOLD responsiveness may be attributed to compromised vascular responses to the increasing CO_2 levels in the bloodstream during a breath-hold. However, further research is needed to determine the mechanistic details behind such breath-hold perturbation and the translatability of this GESE-EPI based BOLD approach to other cardiovascular risk population.

6.A T_2- and T_2^*-slopes of remaining hypertensive participants

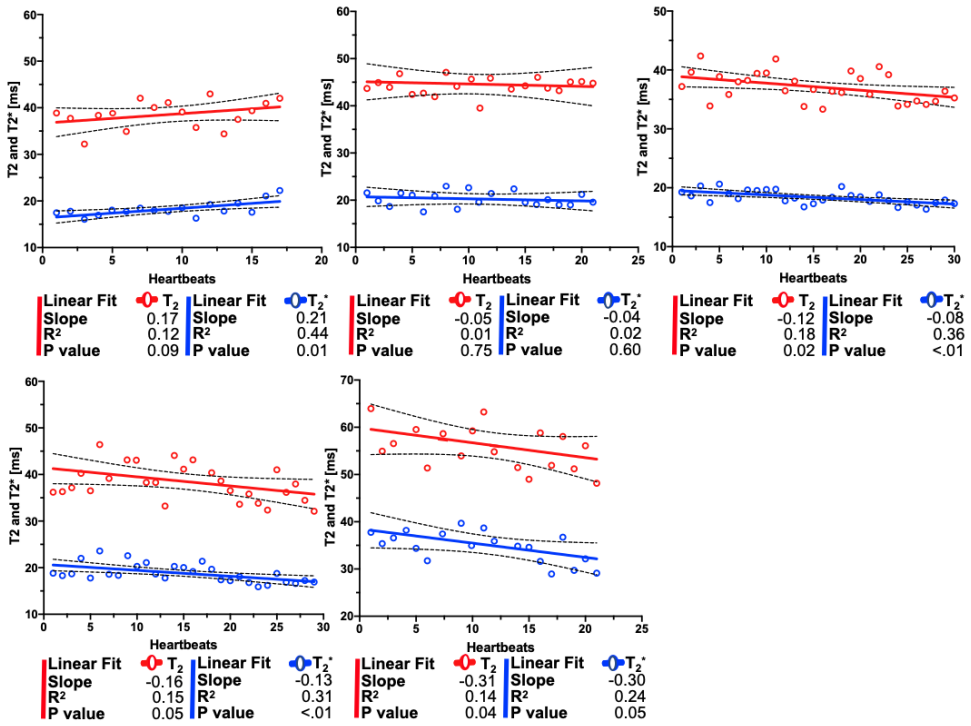

Figure 6.5: The T_2- and T_2^*-slopes of the remaining hypertensive participants displaying a normal increasing BOLD change for the participant depicted in the left top and a compromised or decreasing BOLD change for the other four participants over the time of a breath-hold. *BOLD=Blood Oxygenation Level Dependent*