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Research article

Cardiac magnetic resonance including parametric mapping in acute Takotsubo syndrome: Preliminary findings

Darius Dabir*, Julian Luetkens, Daniel L.R. Kuetting, Andreas Feisst, Alexander Isaak, Hans H. Schild, Daniel Thomas

Department of Radiology, University of Bonn, Sigmund-Freud-Str. 25, 53127, Bonn, Germany

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ABSTRACT

Introduction: T1 and T2 mapping have been shown to be reliable markers of interstitial myocardial fibrosis, edema, and inflammation. The aim of this study was to evaluate myocardial involvement in acute phase Takotsubo syndrome using native and post-contrast T1 mapping, ECV fraction, and T2 mapping.

Material and methods: We investigated 14 patients with acute Takotsubo syndrome and 14 healthy controls. CMR included cine imaging, black-blood STIR imaging, early and late gadolinium enhancement imaging, native and post-contrast T1 mapping, and T2 mapping. Wall motion, T2 ratio, early gadolinium enhancement ratio, extracellular volume fraction, T1 and T2 relaxation times were analyzed.

Results: Patients had significantly impaired left ventricular function (46 ± 10%) and acute wall motion abnormalities compared with controls (62 ± 2%). Native T1 and T2 values, T2 ratio, and ECV fraction were significantly higher in patients compared with controls. In patients, native T1 and T2 values as well as T2 ratio were significantly higher in segments with abnormal wall motion compared with normokinetic segments. Native T1 values, T2 relaxation times, T2 ratio, and ECV fraction were significantly higher, post-contrast T1 relaxation times significantly lower in segments with abnormal wall motion compared with segments of controls; except for T2 ratio and post-contrast T1 relaxation times this also held true for patients' segments with normal wall motion.

Conclusions: Native T1 and T2 mapping, as well as ECV fraction, discriminate between visually affected vs. unaffected segments in patients with acute Takotsubo syndrome and reveal significant T1 and T2 tissue changes even in visually unaffected segments. Thus, mapping may allow for better detection in convalescent stages of disease and additionally may have the potential to serve as a marker of disease progress. These preliminary findings warrant further investigation in a larger patient cohort.

1. Introduction

Takotsubo syndrome (TTS) is an acute, but usually reversible, heart failure syndrome predominantly affecting postmenopausal women. Precipitated by either emotional (primary) or physical (secondary) stress, most patients present with acute onset of symptoms comparable with ST-segment elevation myocardial infarction (STEMI) or non- ST-segment elevation myocardial infarction (NSTEMI), yet without evidence of hemodynamic relevant coronary artery disease as underlying cause. Excessive catecholamine release with subsequent sympathetic activation, resulting in myocardial stunning, appear to have a central role in the pathophysiology of this rare disease, however the exact pathophysiological mechanisms have not been fully clarified [1]. Previous studies suggest that 1–2% of patients presenting with acute coronary syndrome are ultimately diagnosed with TTS [2,3]. The most common anatomical variant of TTS is characterized by hypo-/a- or dyskinesia of the apical and midventricular left ventricular (LV) segments accompanied with basal hypercontractility and thus resulting in the typical appearance of "apical ballooning" [4]. Cardiovascular magnetic resonance imaging (CMR) is particularly suitable for the evaluation of TTS, as it not only allows for precise quantification of left and right ventricular function, but because it also helps to differentiate TTS from acute cardiac conditions with similar clinical presentation such as myocarditis or myocardial infarction [5].

Besides visual assessment of the distinct kinetic morphology of disease, detection and evaluation of the extent of myocardial edema play a pivotal role. T2-STIR-imaging is the gold standard for assessment of myocardial edema in current clinical practice and has proven to

* Corresponding author.
E-mail addresses: darius.dabir@ukbonn.de (D. Dabir), julian.luetkens@ukbonn.de (J. Luetkens), daniel.kuetting@ukbonn.de (D.L.R. Kuetting), andreas.feisst@ukbonn.de (A. Feisst), alexander.isaak@ukbonn.de (A. Isaak), hans.schild@ukbonn.de (H.H. Schild), daniel.thomas@ukbonn.de (D. Thomas).

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reliably detect edema in most diverse cardiac conditions [6–8]. However, T2-STIR-imaging is hampered by limitations including susceptibility to signal drop outs, slow-flow artifacts, arrhythmia, and breathing artifacts. In addition, for relative T2 ratios a reference region of interest (ROI), usually placed within the adjacent skeletal musculature, is needed.

T1, T2 mapping, and extracellular volume (ECV) fraction have shown to reliably differentiate between healthy and diseased myocardium in most diverse cardiac diseases, often revealing superior diagnostic value compared against standard CMR markers [9–12]. Thus, the aim of this study was to evaluate the diagnostic value of T1, T2 mapping, and ECV fraction compared with standard CMR markers of disease and especially regarding STIR imaging in CMR assessment of acute phase TTS.

2. Material and methods

2.1. Study population

This study complies with the Declaration of Helsinki and the research protocol was approved by the local ethics committee. Informed consent was obtained from each patient.

According to the recently proposed ESC International Expert Consensus Criteria, patients had an overall high probability for TTS at the time of their hospitalization (InterTAK score = 76 (72–80) [13,14]. Further, all patients fulfilled diagnostic criteria for TTS based on the 2015 Heart Failure Association of the European Society of Cardiology Takotsubo Syndrome Diagnostic Criteria [1]: (1) transient regional wall motion abnormalities of LV or RV myocardium preceded by a stressful trigger and (2) extending beyond a single epicardial vascular distribution; (3) absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed; (4) new and reversible electrocardiography (ECG) abnormalities (ST-segment elevation, ST depression, LBBB, T-wave inversion, and/or QTc prolongation) during acute phase; (5) significantly elevated serum natriuretic peptide (BNP or pro BNP) during acute phase; (6) positive but relatively small elevation in cardiac troponin measured with a conventional assay; (7) recovery of ventricular systolic function on cardiac imaging at follow-up.

Exclusion criteria included contraindications to contrast enhanced CMR as described previously [15].

2.2. CMR protocol

CMR was performed within a mean of 4 days (1–8 days) after onset of symptoms. Image acquisition was performed on a whole-body 1.5 T MR scanner (Ingenia, Philips Healthcare, Best, Netherlands) using a 32-channel torso coil with digital interface for signal reception.

Image acquisition was performed according to the Updated Society of Cardiac Magnetic Resonance recommendations [16].

Functional imaging consisted of ECG-gated steady state free precession images acquired during breath hold in horizontal long axis (HLA), vertical long axis (VLA), left ventricular outflow tract, and short axis (SA) view, the latter covering the whole left ventricle from apex to base. For *detection of edema*, black-blood T2 short tau inversion recovery sequences were acquired in transverse, VLA, and SA views. Early gadolinium enhancement ratio (EGEr) for the assessment of *inflammation induced myocardial hyperemia* was investigated using transverse free-breathing T1 weighted images prior and < 1 min after intravenous injection of a single dose (0.1 mmol per kilogram body weight) of extracellular contrast agent (Gadovist, Bayer Healthcare, Leverkusen, Germany) as previously described [17]. Immediately after image acquisition, a second single dose of contrast agent was administered for the assessment of myocardial fibrosis and scarring using the late gadolinium enhancement technique (LGE). LGE imaging was performed 10–15 min after injection of the second contrast agent bolus using T1 weighted segmented inversion-recovery gradient-echo sequences acquired in HLA, VLA and SA. The correct inversion time was determined using the Look-Locker technique.

In addition to the standard CMR protocol native and post-contrast T1 mapping and T2 mapping were performed. T2 maps were acquired prior to contrast agent injection in end-diastole in 3 short axis slices (apical, mid, basal) using a multiecho dataset based on two established MR techniques (GraSE), as previously described [18]. Before and 10 min after administration of contrast agent T1 maps were obtained in end-diastole in 3 short axis slices (apical, mid, basal) using a steady-state free precession based 3-3-5 modified Look-Locker inversion recovery scheme [19].

2.3. Image analysis

Left ventricular function including ejection fraction (LVEF), end-diastolic volume (LVEDV), and intraventricular septal thickness (IVST) was evaluated offline, using a dedicated software (ViewForum, Philips Healthcare). Functional analysis was performed using the standard method by manually tracing endocardial contours. Papillary muscles were included in the left ventricular volume. Additionally, wall motion abnormalities were assessed visually and graded as normal, hypo-, a-, or dyskinetic.

Presence of myocardial edema was evaluated by comparing the signal intensity of the LV myocardium in STIR-weighted SA images against the signal intensity of a reference region within adjacent skeletal muscle in the same slice (T2 ratio), as previously described [20]. EGEr was measured as previously described [17]. For both, T2 ratio and EGEr, the mean value of 2 measurements was used for statistical analysis.

T1 and T2 maps were evaluated using a dedicated Software (Philips IntelliSpace 9, Philips Healthcare, Best, Netherlands). Automatic motion correction was performed prior to analysis in all maps, irrespective of presence of motion artifacts. T1 and T2 relaxation times were measured within the complete apical, midventricular, and basal short axis slice, tracing endo- and epicardial contours and taking care to exclude epicardial fat, pericardium, and blood from analysis (Figs. 1 and 2).

2.4. Statistical analysis

Statistical analysis was performed using SPSS Software Version 24 (SPSS Inc., Chicago, IL, USA). Descriptive data are presented as means ± standard deviation or as absolute frequency. Continuous variables were checked for normal distribution. Continuous variables between two groups were compared by using the unpaired Student *t*-test Dichotomous variables were compared using the Chi-squared test. Correlation analysis was performed by using Pearson correlation coefficient. A P value less than 0.05 indicated statistical significance.

3. Results

3.1. Population characteristics

14 patients (12 female) with a mean age of 67 ± 18 years were included into this study. Patients' characteristics are summarized in Table 1. The control group consisted of 14 healthy subjects (3 female; mean age 43 ± 13 years) without medical history of cardiac disease, normal ECG, and normal CMR (mean LVEDV: 158 ± 34 ml, mean IVSD: 10 ± 1 mm). Patients had significantly impaired left ventricular function and acute wall motion abnormalities compared with controls (46 ± 10% vs. 62 ± 2%; $p < 0.001$). Further, patients had significantly smaller LVEDVs compared to controls ($p = 0.001$). No significant differences could be revealed between patients and controls regarding IVSD ($p = 0.952$). Late gadolinium enhancement was not observed in any of the patients. 13 patients (93%) showed myocardial

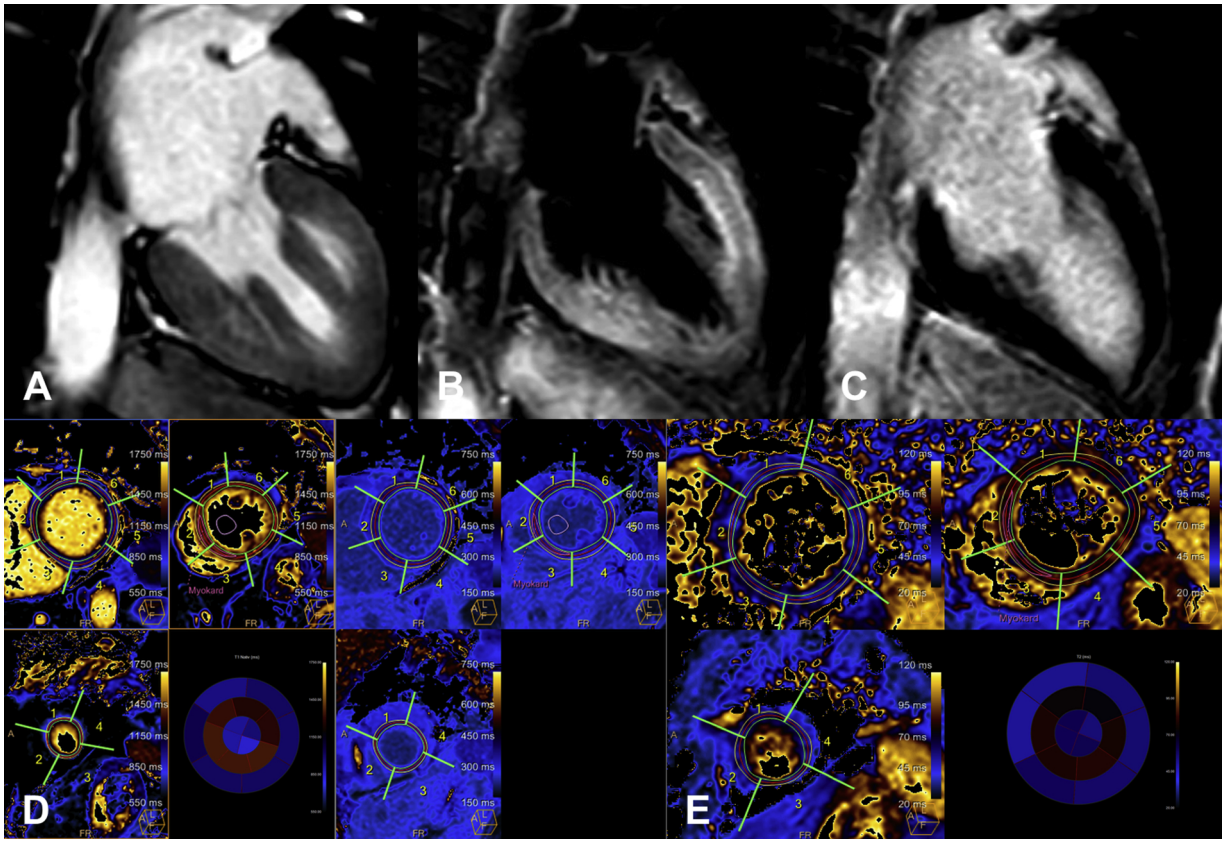

Fig. 1. 52-year-old patient with mid left ventricular variant of TTS. (**A–C**) Images in VLA orientation show midventricular ballooning in endsystole (**A**; SSFP-Cine) and corresponding myocardial edema (**B**; T2 STIR) but no LGE (**C**; T1 IR). (**D** + **E**) Corresponding color encoded T1 (**D**) and T2 (**E**) maps.

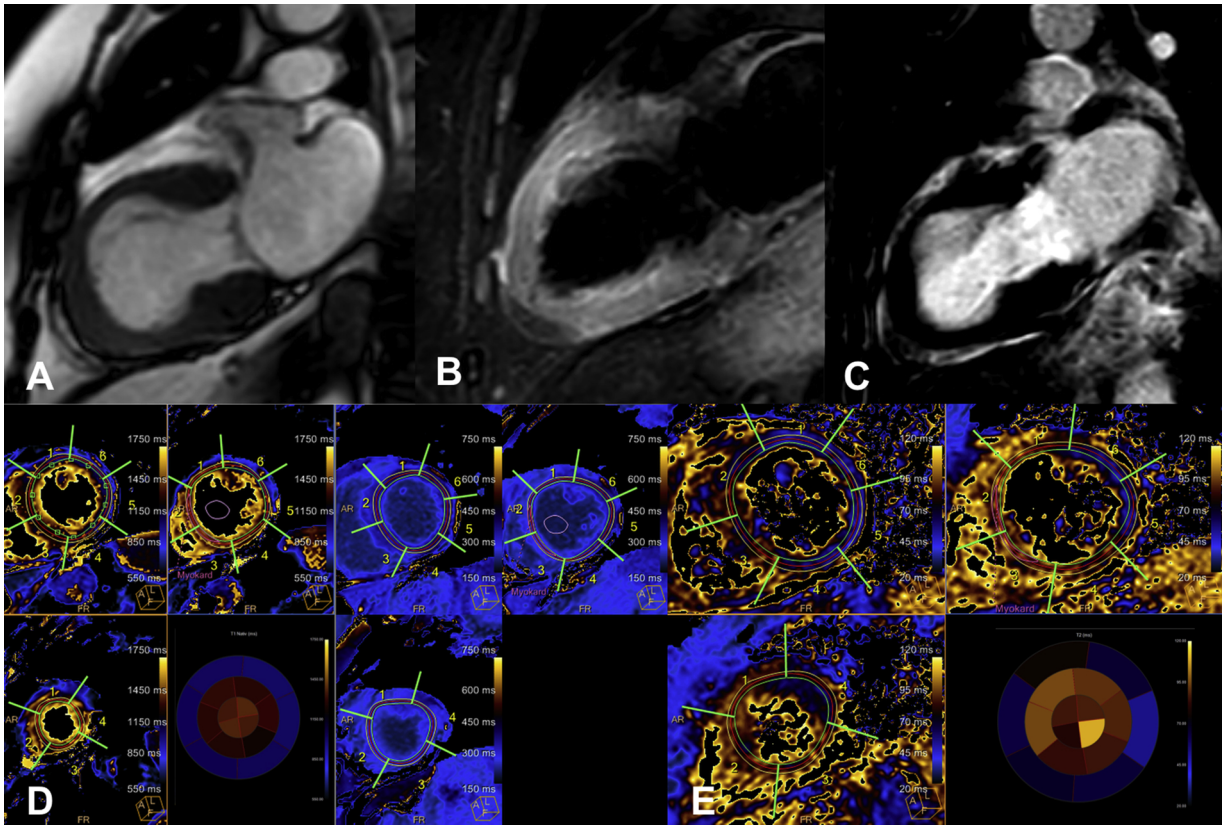

Fig. 2. 83-year-old patient. (**A–C**) Images in VLA orientation with typical apical and midventricular ballooning in endsystole (**A**; SSFP-Cine) and corresponding myocardial edema (**B**; T2 STIR) but no LGE (**C**; T1 IR). (**D** + **E**) Corresponding color encoded T1 (**D**) and T2 (**E**) maps.

Table 1
Patients' characteristics.

Patient #	Age (y)	Sex	Symptoms	Time to CMR (d)	EF (%)	LVEDV (ml)	IVST	Edema	Wall motion abnormality	ECG –abnormalities	TnI max. (ng/ml)
1	77	F	PS	6	38	123	11.5	7-17	7-17 HK	LBBB	n/a
2	72	F	PS (ACP, P, D, N)	5	41	148	11	7,8, 12-17	7-17 AK	Long QT	11.40
3	44	F	PS (ACP, P)	1	33	138	8	7-17	7-17 AK	Long QT	5.19
4	69	M	PS (ACP, D)	6	47	83	11	7-17	7-17 AK	Long QT	10.20
5	79	F	PS (ACP, D)	6	57	83	10.3	13-17	13-17 HK	ST depression	2.91
6	50	F	PS (ACP, D)	8	23	90	7.2	n/A	7 AK 8-17 HK	Long QT	0.74
7	75	F	PS (ACP)	3	43	120	12.1	13-17	7-17 HK	Long QT	0.12
8	85	F	ES (D)	2	45	120	11	7-10 13-17	7-10 AK 13-17 HK	ST depression	16.30
9	55	F	ES (ACP, N)	6	52	112	7	13-17	13-17 AK	ST depression	1.71
10	87	F	PS (D)	3	46	114	11.3	7-17	7-17 HK	ST depression	0.52
11	85	F	ES (ACP)	5	57	106	11	13-17	13-17 HK	LBBB	4.13
12	52	F	PS (ACP, D)	5	59	130	9	7-12	7-12 HK	Long QT	3.26
13	83	F	ES (ACP, D)	5	49	105	8	7-17	7-17 HK	Long QT	0.85
14	31	M	ES (ACP, P)	1	56	172	11	13-17	13-17 HK	ST elevation	13.10

PS = physical stress, ES = emotional stress, ACP = acute chest pain, P = palpitations, D = dyspnea, N = nausea, LBBB = left bundle branch block, Long QT = long QT syndrome.

edema. 2 patients showed increased EGEr (3.59 ± 3). One patient showed the mid left ventricular variant of disease (Fig. 1), whereas all other patients presented with the classical distribution pattern (Fig. 2). Except for one patient who was hospitalized due to acute heart failure, patients presented with ACS-like symptoms.

3.2. Results of quantitative and conventional CMR parameters

Results for T1 and T2 mapping as well as T2 ratio, ECV fraction, and EGEr are listed in Table 2. Native T1 ($p < 0.001$) and T2 values ($p < 0.001$), T2 ratio ($p = 0.017$), and ECV fraction ($p = 0.004$) were significantly higher in patients compared with controls (Fig. 3). In patients, native T1 ($p < 0.001$) and T2 relaxation times ($p < 0.001$) as well as T2 ratio ($p < 0.001$) were significantly higher in segments with abnormal wall motion compared with segments with normal wall motion (Fig. 4). Native T1 relaxation times ($p < 0.001$), T2 relaxation times ($p < 0.001$), T2 ratio ($p < 0.001$), and ECV fraction ($p < 0.001$) were significantly higher, post-contrast T1 relaxation times ($p = 0.019$) significantly lower in segments with abnormal wall motion compared with midventricular segments of controls; except for T2 ratio ($p = 0.835$) and post-contrast T1 relaxation times ($p = 0.754$) this also held true for patient segments with normal wall motion (Fig. 5). No significant difference could be revealed regarding global relative enhancement between patients and controls ($p = 0.177$). Both patients and controls showed higher T1 relaxation times within the sepal segments compared with lateral segments (patients: 1148 ms vs. 1106 ms; controls: 975 ms vs. 941 ms), however without reaching statistical significance ($p = 3.996$ and $p = 0.05$, respectively).

Table 2
Measurement results for native and post-contrast T1 mapping, T2 mapping, ECV, T2 ratio, and relative enhancement including significances between groups and regarding wall motion abnormalities.

	Controls	Takotsubo	p-value
T1 native (ms)			
Normal wall motion	956 ± 27	1071 ± 78	$p < 0.001$
Abnormal wall motion	n/a	1199 ± 125	
Global left ventricular	956 ± 27	1132 ± 82	$p < 0.001$
T1 post contrast (ms)			
Normal wall motion	347 ± 25	347 ± 56	$p = 0.754$
Abnormal wall motion	n/a	317 ± 46	
Global left ventricular	347 ± 25	322 ± 40	$p = 0.066$
T2 (ms)			
Normal wall motion	52 ± 2	60 ± 6	$p < 0.001$
Abnormal wall motion	n/a	75 ± 8	
Global left ventricular	52 ± 2	67 ± 7	$p < 0.001$
ECV (%)			
Normal wall motion	28 ± 4	34 ± 8	$p = 0.007$
Abnormal wall motion	n/a	40 ± 8	
Global left ventricular	28 ± 4	36 ± 9	$p = 0.004$
STIR (T2 ratio)			
Normal wall motion	1.59 ± 0.17	1.58 ± 0.27	$p = 0.835$
Abnormal wall motion	n/a	2.25 ± 0.36	
Global left ventricular	1.59 ± 0.17	1.92 ± 0.46	$p = 0.017$
Relative Enhancement			
Global	2.34 ± 2	3.59 ± 2.65	$p = 0.177$

3.3. Correlation of CMR markers

Native T1 and T2 relaxation times showed excellent correlation in patients and controls ($r = -0.93$, $p < 0.001$). Native T1 ($r = -0.59$), T2 relaxation times ($r = -0.71$), ECV ($r = -0.68$), and T2 ratio ($r = -0.49$; $p = 0.008$) showed good correlation with LVEF (all $p < 0.001$). No significant correlation could be revealed between relative enhancement and LVEF ($r = -0.21$, $p = 0.323$).

3.4. Results of clinical markers

All patients presented with ECG-abnormalities. The maximum troponin level during hospitalization accounted for 5.42 ng/ml (0.12–16.30 ng/ml; Table 1). Patients underwent follow-up about 50 days after CMR comprising ECG and echocardiography showing full recovery of all, ECG-abnormalities, LVEF (67 ± 8%), and wall motion abnormalities.

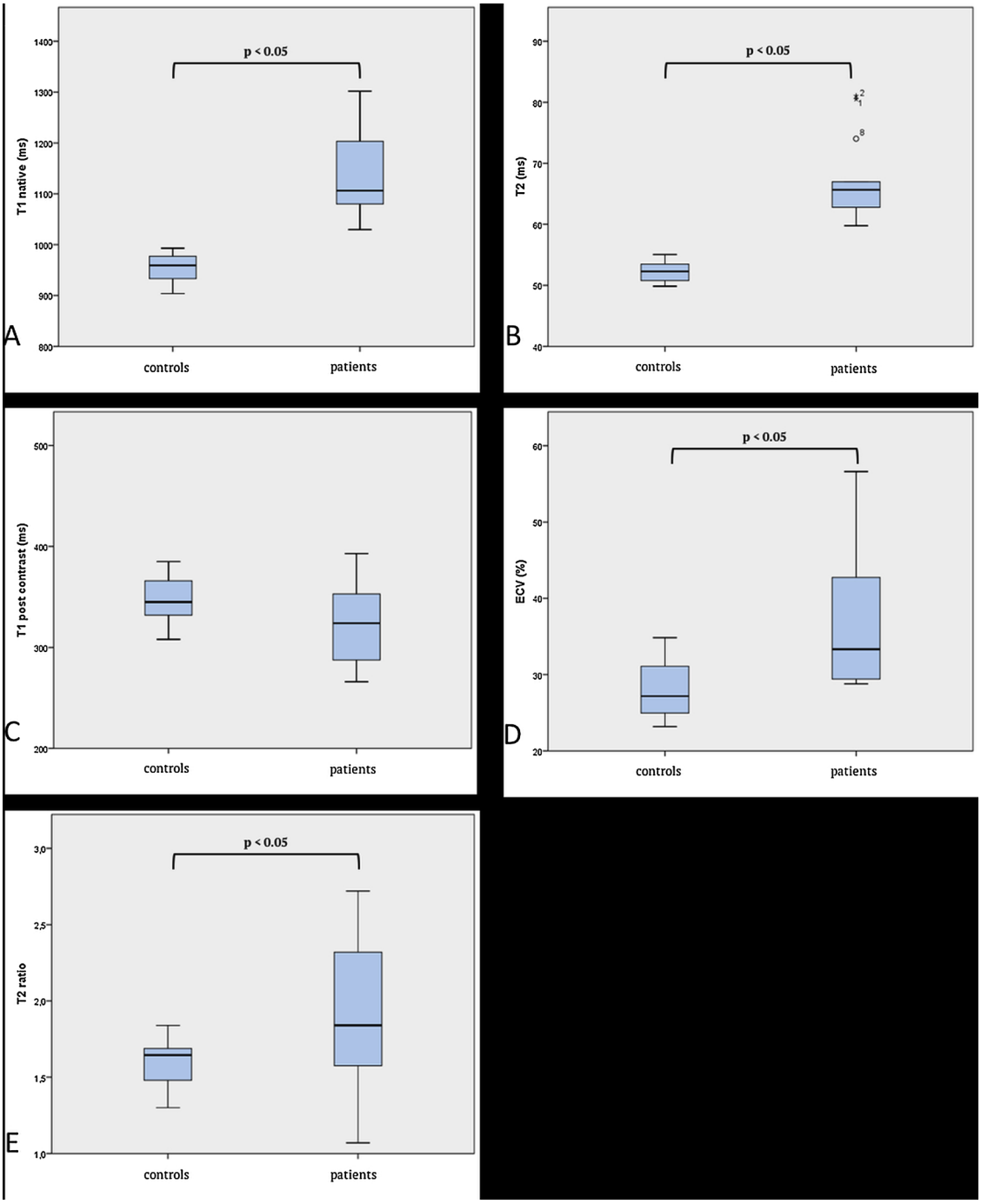

Fig. 3. Boxplots showing results for native T1 (A) and T2 (B) mapping, post-contrast T1 mapping (C), ECV fraction (D) and T2 ratio regarding controls and patients.

4. Discussion

The diagnostic performance of native T1 and T2 mapping in detecting acute edema compared with STIR-imaging has previously been investigated with results in favor of the mapping techniques [21,22]. Furthermore, preliminary data on T2 mapping and native and post-contrast T1 mapping investigating nine patients with acute TTS have recently been published [23]. While native T1 and T2 mapping revealed significantly higher values in patients' segments with wall motion abnormalities, post-contrast T1 values were not significantly different in abnormal segments compared with normokinetic segments.

Results in the present study were in accordance with aforementioned findings: patients revealed significantly higher native T1 and T2 times, ECV, and T2 ratio compared with controls. Further, native T1 and T2 relaxation times were significantly increased in patients' segments with abnormal wall motion compared with normokinetic segments. In addition to the previously mentioned studies, we also calculated the ECV fraction. Compared with post-contrast T1 values, which tend to vary depending on many factors (e.g. time and dosing of contrast agent injection, body fat percentage, renal function), ECV fraction represents a physiological value. It is calculated from pre- and post-contrast T1 relaxation times of myocardium and blood-pool and corrected for hematocrit, making it a more robust and reliable parameter. Consequently, and in accordance with native T1 and T2 relaxation times, also ECV fraction was significantly higher in patients´ segments with abnormal wall motion compared with the normokinetic

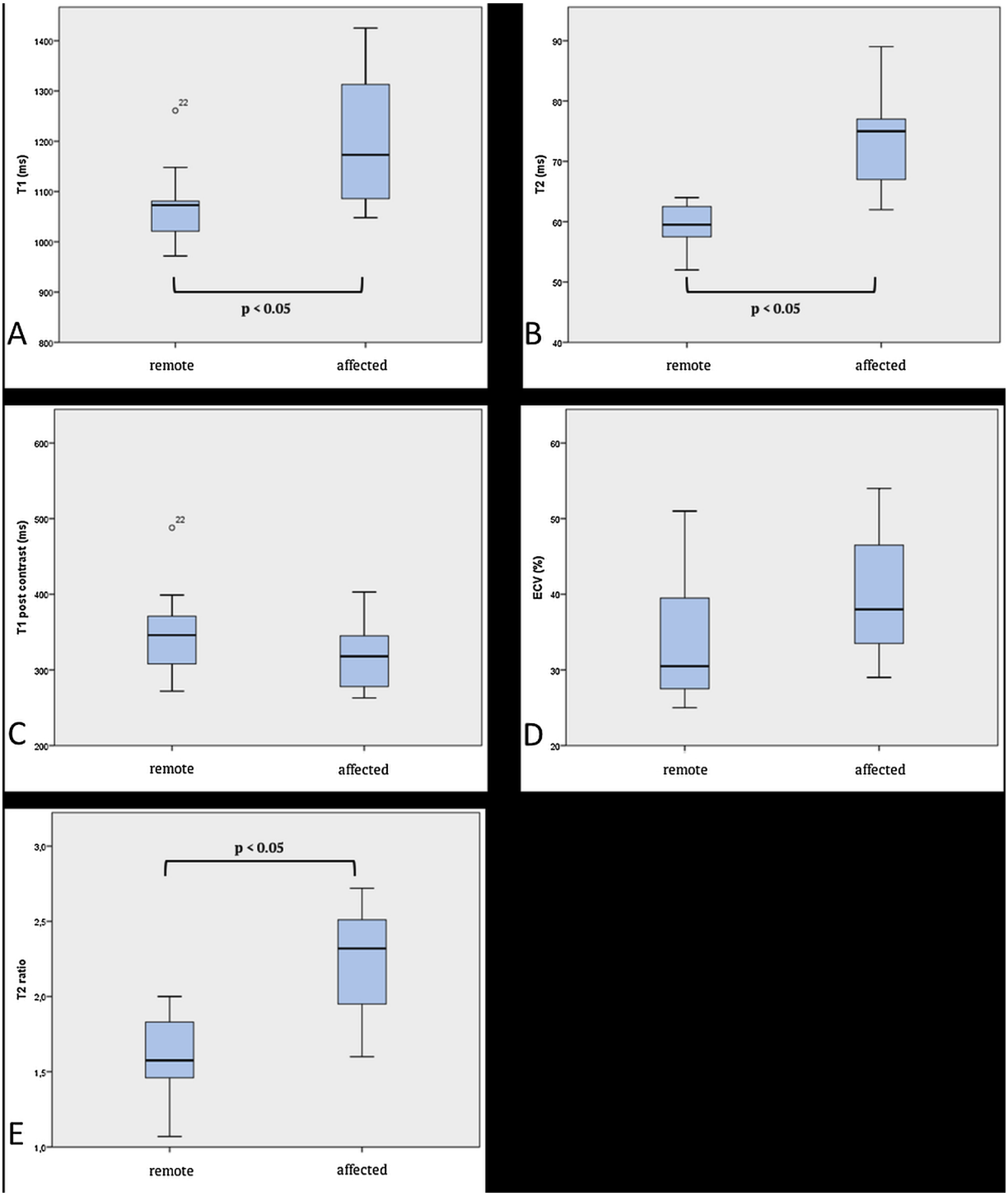

Fig. 4. Boxplots showing results for native T1 (A), T2 (B), post-contrast T1 mapping (C), ECV fraction (D), and T2 ratio (E) in affected and remote segments of patients.

myocardium.

As has been described by other authors, native T1 relaxation times showed regional differences within the left ventricular myocardium with extremes between septal and lateral segments [24–26]. According to previous results, both patients and controls in the underlying study showed regional differences in T1 relaxation times with higher values within the sepal segments compared with lateral segments. However, the differences between pathological and normal segments exceeded regional segmental differences by far and thus should not have influence on the findings of the study.

The most crucial finding in the underlying study, however, was revealed by comparing patients' segments with and without wall motion abnormalities to control segments: unlike T2 ratio, native T1 and T2 values as well as ECV were significantly elevated in patients segments with normal wall motion. Thus, this is the first study to show that mapping, unlike conventional CMR parameters, detects myocardial involvement in acute TTS in otherwise unsuspicious segments. Whereas this finding may not have an impact on the diagnosis of acute phase TTS, it emphasizes the potential of quantitative CMR imaging to allow for detection of disease in convalescent stages where myocardial edema

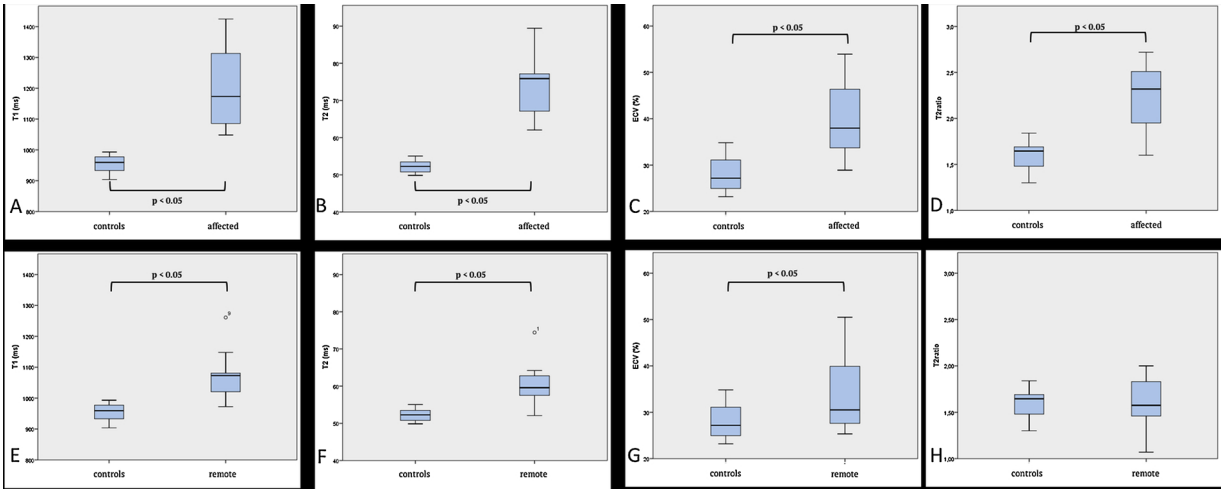

Fig. 5. Boxplots showing results for native T1 and T2 mapping, ECV fraction and T2 ratio in affected patient segments vs. control segments (A–D) and remote patient segments vs. control segments (E–H) respectively.

might not be present anymore, as shown in patients with myocarditis [27]. Also, in clinical routine CMR is frequently performed at a later stage during the course of disease where remainder subtle pathologies in left ventricular contractility and detection of myocardial edema might be missed by conventional CMR sequences.

In contrast to T2 ratio and relative enhancement, native T1 and T2 relaxation times, as well as ECV showed good correlation with LVEF, which serves as a marker for severity of cardiac disease. The fact that the quantitative approaches revealed the best agreement with LVEF once again emphasizes the potential of quantitative imaging techniques compared with conventional semiquantitative approaches.

While the exact pathophysiological mechanism of TTS has not been ascertained yet, histology based studies suggest that both, catecholamine-mediated microcirculatory disturbance inducing ischemia and direct toxicity of catecholamines may be the underlying cause for the temporal morphological alterations within the myocardium. Further, it was postulated that myocardial inflammation might be an issue due to histological proof of focal mononuclear inflammatory areas of fibrotic response in TTS patients [28]. This hypothesis was emphasized by CMR results revealing increased CMR-derived inflammatory signs in a majority of patients with acute phase TTS [29]. In the present study two patients showed increased EGEr in addition to myocardial edema as an indicator of myocardial inflammation and thus underlining aforementioned hypotheses.

5. Conclusions

Native T1 and T2 mapping as well as ECV fraction not only discriminate between visually affected vs. unaffected segments in patients with acute TTS but also reveal significant involvement of otherwise unaffected myocardial segments. Thus, mapping may allow for better detection in convalescent stages of disease and additionally may have the potential to serve as a marker of disease progress. These preliminary findings warrant further investigation in a larger patient cohort.

5.1. Limitations

This study has several limitations. Owing to the rareness of the disease, the study comprises a relatively small sample size; however, the severity of disease at the time of examination and an overall high sensitivity of sequences used in this study were able to achieve statistical significance between groups. One of the proposed Heart Failure Association diagnostic criteria for acute TTS was not met as brain natriuretic peptide was not included in the patients' blood work. The control group examined in this study was neither age nor gender matched to the patient group. While native T1 relaxation times acquired using the 3-3-5 MOLLI scheme are neither age or gender related, gender related differences regarding T2 relaxation times using the GraSe sequence have previously been described in young adults (< 35years). Further, age related T2 differences have been revealed between healthy subjects younger and older than 35 years respectively [15,30]. Although, both our patients and controls apply to the aforementioned older age group, age cannot be completely excluded as a possible confounding factor in the underlying study.

Although T1 and T2 mapping are proven reliable markers of myocardial fibrosis and edema respectively, both methodologies are not completely free of limitations. Both sequences still reveal vendor and site specific values. Planning of the slice orientation requires experience to avoid through-plane motion. However, using the GraSe and MOLLI sequences, the most robust sequences were used in this study and special care was taken regarding sequence planning.

Consensus reading was not performed in this study as inter- and intraobserver variability of T1 and T2 mapping in patients with myocardial edema have previously been evaluated extensively and shown excellent results. Also, all measurements were performed by an investigator with > 9 years of experience in cardiovascular imaging.

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Declaration of interest

None declared.

Conflict of interests

The authors declare that there is no conflict of interest.

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of any part of the work are appropriately investigated and resolved.

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