学位論文

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in Takotsubo Cardiomyopathy
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相川　幸生
Yukio Aikawa

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

指導教員

安田　聡　教授
熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

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著 者 名 ：　相 川 幸 生
（単名）　Yukio Aikawa

指導教員名 ： 熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学　安田　聡教授

審査委員名 ： 生体機能薬理学担当教授　光山　勝慶
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Clinical impact of native T1 mapping for detecting myocardial impairment in takotsubo cardiomyopathy

Yukio Aikawa[1,2], Teruo Noguchi[1]*, Yoshiaki Morita[3], Emi Tateishi[3], Atsushi Kono[3], Hiroyuki Miura[1], Yoshiaki Komori[4], Yasuhide Asaumi[1], Tetsuya Fukuda[3], and Satoshi Yasuda[1,2]

[1]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan; [2]Department of Advanced Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan; [3]Department of Radiology, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan; and [4]Research and Collaboration Department, Siemens Healthcare K.K., Gate City Osaki West Tower, 1-11-1, Osaki Shinagawa-ku, Tokyo 141-8644, Japan

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Aims To investigate the clinical impact of T1 mapping for detecting myocardial impairment in takotsubo cardiomyopathy (TTC) over time.

Methods and results In 23 patients with the apical ballooning type of TTC, the following 3T magnetic resonance (MR) examinations were performed at baseline and 3 months after TTC onset: T2-weighted imaging, T2 mapping, native T1 mapping, extracellular volume fraction (ECV), and late gadolinium enhancement. Eight healthy controls underwent the same MR examinations. Serial echocardiography was performed daily for ≥7 days and monthly until 3 months after onset. The median time from onset to MR examination was 7 days. During the acute phase, patients had, relative to controls, higher native T1 (1438 ± 162 vs. 1251 ± 90 ms, $P < 0.001$), ECV (35 ± 5% vs. 29 ± 4%, $P < 0.001$), and T2 (90 ± 34 vs. 68 ± 12 ms, $P < 0.001$) for the entire heart. Per-region analysis showed that higher native T1 and T2 in the basal region were correlated with lower left ventricular ejection fraction ($r = -0.599$, $P = 0.004$ and $r = -0.598$, $P = 0.003$, respectively). Receiver operator characteristic analysis showed that the area under the curve for native T1 (0.96) was significantly larger than that for T2 (0.86; $P = 0.005$) but similar to that for ECV (0.92; $P = 0.104$). At 3-month follow-up, native T1, ECV, and T2 in the apical region remained significantly elevated in all patients with TTC. The number of left ventricular (LV) segments with elevated native T1 (cut-off value 1339 ms) was significantly correlated with prolonged LV wall motion recovery time ($r = 0.494$, $P = 0.027$).

Conclusion Characterization of myocardium with native T1 mapping is a promising method for predicting LV wall motion restoration in TTC.

Keywords magnetic resonance imaging • T1 mapping • takotsubo cardiomyopathy

Introduction

Takotsubo cardiomyopathy (TTC) is a transient form of left ventricular (LV) dysfunction in the absence of significant coronary artery disease associated with a distinctive contraction pattern. TTC is commonly believed to have a rapid course with complete resolution of wall motion abnormalities. However, more detailed evaluations with T2-weighed imaging (T2WI) have detected persistent myocardial abnormalities in areas with prolonged myocardial oedema.[1] In addition, there is increasing evidence that physiological abnormalities persist after contractile abnormalities have returned to normal macroscopically.[2–4]

Recently, T1 mapping, which includes native T1 and extracellular volume fraction (ECV) measurements,[5–7] has emerged as a quantitative technique for detecting acute myocardial oedema and extracellular matrix abnormalities in several myocardial diseases.[8–12] In patients

* Corresponding author. Tel: +81 (6) 6833 5012; Fax: +81 (6) 6872 7486. E-mail: tnoguchi@ncvc.go.jp

with TTC, although T1 mapping has been reported to be superior to conventional T2WI for detecting myocardial oedema,[13] chronological changes in native T1 values have not been fully evaluated. In particular, there is little information regarding ECV changes in TTC. Therefore, this study was designed to investigate whether the extent of myocardial oedema detected by T1 mapping may affect the restoration of LV wall motion and the clinical course from the acute to the chronic phase of TTC.

Methods

Study population

Between April 2014 and March 2017, we studied 23 consecutive patients with TTC. The diagnosis of TTC was based on the Mayo Clinic criteria.[14] All patients underwent invasive coronary angiography with ergonovine maleate provocation testing to exclude significant coronary artery stenosis (>50% diameter stenosis) and vasospastic angina pectoris. Patients with myocarditis, hypertrophic cardiomyopathy, secondary cardiomyopathy, valvular heart disease, and hypertensive heart disease were excluded. Because two patients had difficulty staying still during cardiac magnetic resonance (CMR) and three patients had estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, only native T1 analysis were available for those five patients. Of note, three patients who experienced complications of TTC underwent late gadolinium enhancement (LGE). As a comparison group for patients with TTC, we selected eight controls who were sex-matched and of a similar age as patients with TTC (female, 88%; mean age, 61 years). Controls had normal electrocardiographic (ECG) findings and no history of cardiac disease or known cardiac risk factors such as a history of hypertension, dyslipidaemia, diabetes mellitus, and smoking. None of the control patients had positive LGE or biventricular morphological abnormalities on CMR (*Table 1*). This prospective observational study was approved by the institutional review board. All study participants gave written informed consent.

CMR protocol

CMR examinations were performed with a 3T MR clinical scanner (MAGNETOM Verio, Siemens Healthcare GmbH, Erlangen, Germany). LV function and volumes were assessed using fast cine imaging with a steady-state free precession sequence (true-FISP) [echo time (TE) 1.53 ms, repetition time (TR) 3.43 ms, flip angle 50°, slice thickness 5 mm, gaps 5 mm, in-plane resolution 1.7 × 1.3 mm]. T2-weighted spin-echo images were acquired using half-Fourier acquisition single shot turbo spin-echo (HASTE) sequence before contrast injection with black blood pulse and fat suppression in the same position as the cine images (TR 2 RR intervals, TE 76 ms, slice thickness 5 mm, gaps 5 mm, in-plane resolution 2.5 × 1.8 mm^2). LGE with segmented inversion–recovery (IR) prepared true-FISP at 10 min after the administration of 0.125 mmol/kg body weight of gadolinium diethylene triamine penta-acetic acid. LGE data were obtained during the mid-diastolic phase with an inversion time of 350 ms (TE 1.13 ms, TR 2.75 ms, slice thickness 8 mm, gaps 2 mm, in-plane resolution 1.9 × 1.5 mm^2). T1 measurements were obtained from a Modified Look-Locker Inversion-recovery (MOLLI) sequence with a 3(3)5 scheme[15] on short-axial slices at the base, mid-ventricle, and apex before and 21 min after gadolinium administration.[16] In the MOLLI 3(3)5 scheme, three images are acquired after the first IR pulse and five images are acquired after the second IR pulse, with three recovery beats to allow for more complete T1 recovery between IR pulses. A T1 map was reconstructed using eight source images with different inversion times. Imaging parameters were as follows: TE 1.1 ms, TR 2.5 ms, flip angle 35°, slice thickness 8 mm, and in-plane resolution 3.1 × 1.7 mm^2. T2 mapping was based on a conventional multi-echo fast spin-echo sequence with a TR of two RR intervals. Three different TEs were acquired: 5.3, 32, and 58 ms. T2 mapping was calculated from three different TE points using T2 relaxation curve fitting. Images were acquired with a slice thickness of 6 mm and in-plane resolution of 2.7 × 1.3 mm^2 in the same slice position as for T1 mapping.[17] All images were acquired with ECG triggering and performed during suspended respiration.

Figure 1 shows a representative case of TTC. On cine CMR, apical ballooning was evident at end-systolic phase compared to end-diastolic phase (*Figure 1A* and *B*). On dark-blood T2WI, hyperenhancement was observed in the area with apical ballooning (*Figure 1C*). Agreement between T2WI hyperenhancement and elevated native T1 and ECV were detected (*Figure 1D* and *F*). No LGE was observed in this case (*Figure 1E*).

Image analysis

Evaluation of LV function

For quantification of LV volumes and left ventricular ejection fraction (LVEF), we manually traced the LV endocardial contours in end-systolic and end-diastolic frames on cine imaging using a dedicated software programme (Argus system®, Siemens Healthcare GmbH). Matching short-axis slices were compared across cine, native T1, ECV, T2, and T2WI. Short-axis images were divided into six segments per slice using anterior right ventricular–left ventricular insertion point as reference and for comparing segments amongst sequences. On cine CMR, segments were graded as: normal = 1, hypokinetic = 2, akinetic = 3, or dyskinetic = 4. We defined hypokinetic, akinetic, and dyskinetic segments as abnormal wall motion area. Qualitative analysis of the presence or absence of hyperenhancement on T2WI and LGE in patients with TTC was determined by consensus from two experienced radiologists who were blinded to clinical data.

Native T1 and ECV measurement

After pre-contrast T1 mapping, the LV myocardium was contoured and divided into 16 segments (six for the basal and mid-ventricular slices and four for the apical slice) based on the American Heart Association classification system. Native T1 was calculated as the average of T1 from all pixels for each segment using a dedicated software programme (Qmass®, Medis, Leiden, the Netherlands).

Evaluation of extracellular volume with T1 mapping

We quantified ECV using the following formula from recent publications:

Extracellular volume fraction = λ*(1 - haematocrit)

where $\lambda = \Delta R1_{myocardium}/\Delta R1_{blood\ pool}$ and R1 = 1/T1

Each ECV measurement in a short-axis slice location was derived from a native T1 acquisition and a post-contrast acquisition occurring 21 min after the contrast bolus using automated analytic software (Mapmaker®, Medis). To obtain ECV in each short-axis slice (basal, mid-ventricular, and apical), we averaged segments belong to each slice. To obtain entire heart of ECV, we averaged all 16 segments in each patient. Of 32 segments of apical slices in eight controls, 4 (12.5%) segments were avoided due to partial volume averaging. Haematocrit was assessed within 1 h after CMR scanning.

Dark-blood T2WI

For assessment of myocardial oedema with T2WI, the ratio of mean signal intensity (SI) of myocardium to skeletal muscle was used (T2 SI ratio). The T2 SI ratio was calculated as previously described.[13,18]

Reproducibility and agreement analysis

Inter-observer and intra-observer reproducibility were performed for all patients and controls by two independent operators who measured native T1, ECV, T2, and T2 SI ratio in each of the 16 myocardial segments.

Table 1 Characteristics of patients with TTC and controls

	TTC ($n = 23$)	Controls ($n = 8$)	*P* value
Age (years)	63 ± 11	61 ± 9	0.75
Female	21 (91)	7 (88)	0.84
Hypertension	17 (74)	4 (50)	0.23
Hyperlipidaemia	13 (57)	4 (50)	0.76
Diabetes mellitus	6 (26)	0 (0)	0.11
Smoking	3 (13)	4 (50)	0.032
CKD (eGFR <45 mL/min/1.73 m^2)	3 (13)	0 (0)	0.16
Body mass index (kg/m^2)	20 ± 3.5	21 ± 2.9	0.73
Heart rate (/min)	70 ± 11.5	67 ± 9.4	0.078
Chest pain and/or dyspnoea	21 (91)		
Laboratory data			
Creatine kinase (IU/L)	238 ± 203	72 ± 26	0.030
Elevated cardiac troponin T[a]	19 (83)	0 (0)	<0.001
eGFR (mL/min/1.73 m^2)	63 ± 25	73 ± 18	0.33
Haematocrit (%)	36 ± 4	41 ± 3	0.004
ECG change at presentation	23 (100)	0 (0)	<0.001
ST elevation	17 (74)	0 (0)	<0.001
T-wave inversion	4 (17)	0 (0)	0.18

Values are expressed as mean ± SD, *n* (%), or medians (interquartile range).
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TTC, takotsubo cardiomyopathy.
[a]Cardiac troponin T: normal range, <0.1 ng/mL.

Laboratory electrocardiography, and echocardiography measurements

Upon admission and every 6 h until a peak level was confirmed, measurements of creatine kinase (CK), CK-MB, and high-sensitivity cardiac troponin T were measured. ECG was performed daily during the acute phase (at least 7 days). Transthoracic echocardiography was performed daily during the acute phase and then monthly until 3 months after the onset of symptoms. Echocardiographic measurements were performed twice, according to American Society of Echocardiography guidelines,[19] by an expert reader blinded to the patient's clinical history.

Statistical analysis

All continuous variables are presented as mean ± standard deviation. Differences between data during acute presentation and follow-up were examined using the paired *t*-test or Wilcoxon matched-pairs signed-rank test as appropriate. Patient data at follow-up were compared with those of control subjects using unpaired tests (unpaired *t*-tests or Mann–Whitney *U* test). Analysis of variance was used to compare means across multiple groups. Categorical variables are presented as frequencies or percentages and were compared using the χ^2 test. The Tukey–Kramer test was used to compare continuous variables and the χ^2 test with Bonferroni correction was used to compare categorical variables. Receiver operator characteristic (ROC) analysis was performed to identify cut-off values for native T1, ECV, T2, and T2 SI ratio that distinguish between normal and affected myocardial segments. Myocardial segments in patients with TTC were considered to be affected by oedema if there were acute wall motion abnormalities (wall motion score >1), while segments in controls with normal wall motion were considered unaffected. Since segments with normal wall motion may or may not be affected by oedema, these segments were not included in the ROC analysis[13] in order to identify optimal cut-off values for native T1 mapping, ECV, T2 mapping, and T2WI. Area under the curve (AUC) values were compared using an algorithm described by Delong *et al.*[20] Pairwise comparisons of AUCs were conducted using the roccomp command in Stata. Inter-observer and intra-observer reproducibility of native T1, ECV, and T2 were assessed using the Bland–Altman method. All statistical tests were two-sided, and *P* values <0.05 were considered statistically significant. Statistical analysis was performed with JMP version 9.0.2 (SAS Institute, Cary, NC, USA) and Stata version 12 (StataCorp LP, College Station, TX, USA).

Results

Clinical characteristics of the study participants

The baseline clinical characteristics of the study patients are summarized in *Table 1*. All 23 patients underwent coronary catheterization and left ventriculography on admission, which confirmed the LV apical ballooning pattern. Epicardial coronary artery stenosis of ≥50% was not observed. We performed ergometrine maleate provocation testing, which was negative for coronary spasm criteria in all 23 patients.

Patient-based analysis at baseline

Table 2 shows the comparison of CMR parameters between patients with TTC and controls. In patients with TTC, CMR imaging was performed a median of 7.0 days (IQR 5.0–8.5 days) after the onset of symptoms. Compared to controls, patients with TTC had significantly higher native T1 (1251 ± 90 ms vs. 1438 ± 162 ms; $P < 0.001$), T2 (68 ± 12 ms vs. 90 ± 34 ms; $P < 0.001$), ECV (29 ± 4% vs. 35 ± 5%;

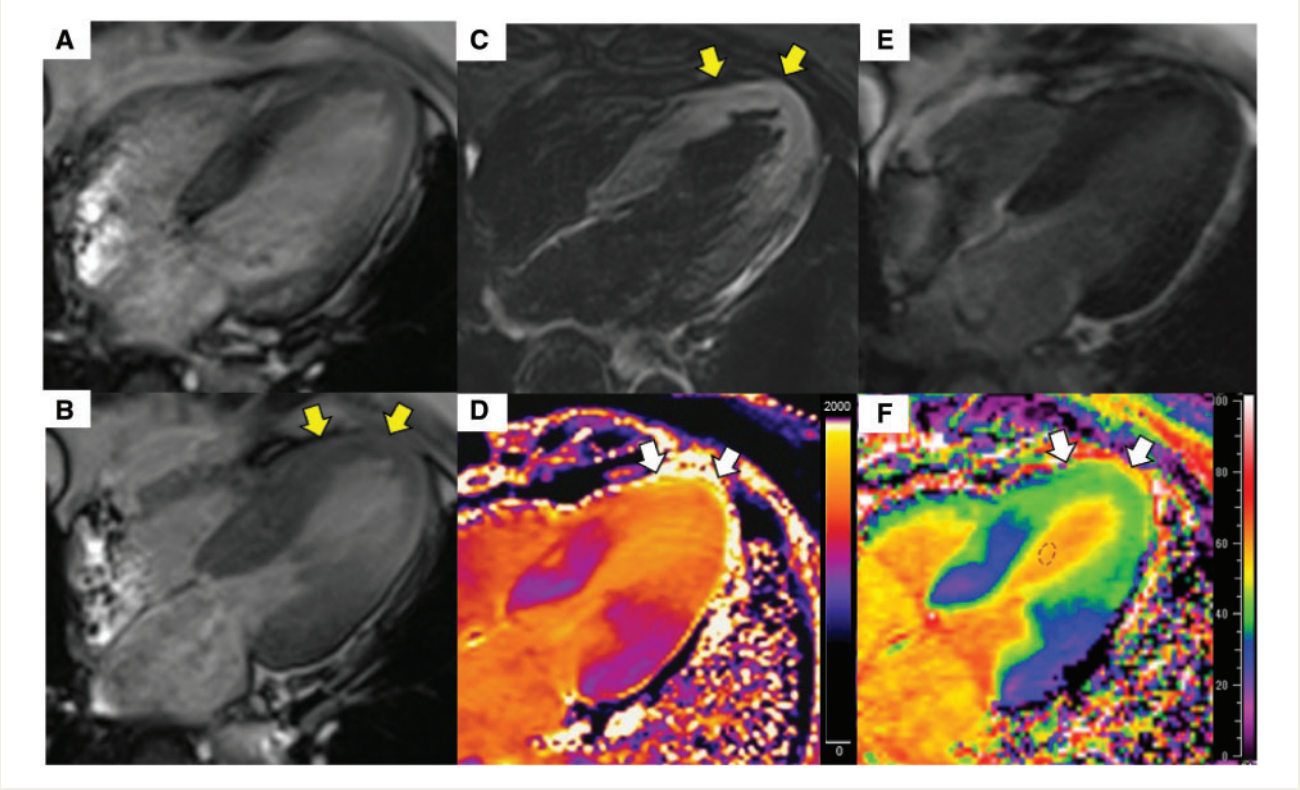

Figure 1 Representative CMR images of takotsubo cardiomyopathy. (*A* and *B*) Each of end-diastolic and end-systolic phases of cine-CMR on four-chamber view. (*B*) Typical left ventricular apical ballooning in TTC (yellow arrows). The abnormal wall motion area at apical region was visualized as hyperintense region by T2-weighted image (*C*, yellow arrows), as high T1 by native T1 map (*D*, white arrows), and as high ECV by ECV map (*F*, white arrows). Late gadolinium enhancement was not observed in the affected apical region (*E*). Orange increased native T1 (*D*). Green increased ECV (*F*). CMR, cardiac magnetic resonance; ECV, extracellular volume fraction; TTC, takotsubo cardiomyopathy.

$P < 0.001$), and T2 SI ratio (1.3 ± 0.4 vs. 1.5 ± 0.7; $P = 0.004$) on analysis based on the entire heart. Myocardial oedema detected by conventional T2WI was visible in 18 of 23 patients (78%). None of the patients with TTC had LGE.

Segment and region-based analysis at baseline

In patients with TTC, the mid-ventricular and apical regions had significantly higher native T1, ECV, T2, and T2 SI ratio than the basal region ($P < 0.001$, respectively) (*Figure 2A–D*). Interestingly, native T1, ECV, and T2 in the basal region (assumed to be remote myocardium) were also significantly higher in patients with TTC than in controls ($P < 0.05$, respectively) (*Figure 2A–C*).

Figure 3 shows correlations between native T1, ECV, T2, T2 SI ratio, and LVEF at baseline. There were significant negative correlations between native T1 (r = -0.599, $P = 0.004$), ECV (r = -0.532, $P = 0.041$), and T2 (r = -0.598, $P = 0.003$) of the entire heart and baseline LVEF (*Figure 3A–C*). In per-region analysis, native T1 (r = -0.602, $P = 0.003$), T2 (r = -0.613, $P = 0.002$), and T2 SI ratio (r = -0.530, $P = 0.013$) in the basal region were correlated with LVEF (Supplementary data online, *Figure S1A, C*, and *D*), whereas ECV values in the basal region were not significantly correlated with LVEF (Supplementary data online, *Figure S1B*). Similarly, significant negative correlations were observed between native T1, ECV, T2, and LVEF (Supplementary data online, *Figure S1E–G*) in the mid-ventricular region. Conversely, no significant correlations were observed between native T1, ECV, T2, T2 SI ratio, and LVEF in the apical region (Supplementary data online, *Figure S1I–L*).

ROC analysis for detecting impaired myocardium and diagnostic accuracy of T1 mapping compared with T2 mapping and T2 SI ratio

The optimal cut-off point, sensitivity, specificity, and AUC for native T1 mapping, ECV, T2 mapping, and T2WI to differentiate segments with oedema from normal segments were as follows: native T1, 1339 ms, 91%, 84%, and 0.96; ECV, 35%, 73%, 94%, and 0.92; T2, 76 ms, 74%, 83%, and 0.86; T2WI: 1.38, 68%, 64%, and 0.70. ROC analysis showed that native T1 had a significantly higher AUC than T2 (0.96 vs. 0.86, $P = 0.005$) and T2WI (0.96 vs. 0.70, $P < 0.001$). However, the AUCs for native T1 and ECV (0.96 vs. 0.92, $P = 0.104$) were similar for the detection of regional oedema (Supplementary data online, *Figure S2*). We defined an area as having myocardial oedema according to the native T1 cut-off value of 1339 ms. *Figure 4A* shows the relationship between myocardial oedema and LVEF at baseline. There was a significant negative correlation between the number of

Table 2 CMR findings in each region of left ventricle

	TTC at baseline ($n = 23$)	Controls ($n = 8$)	*P*-value
CMR parameters			
Onset to CMR examination (days)	7 (5.0–8.5)	NA	NA
LVEF (%)	46 ± 8	62 ± 2	<0.001
LVEDVI (mL/m^2)	73 ± 23	78 ± 12	0.57
LVESVI (mL/m^2)	39 ± 16	31 ± 6	0.19
RVEF (%)	50 ± 7	50 ± 5	0.90
Native T1 (ms)			
Whole heart	1438 ± 162	1251 ± 90	<0.001
Basal	1336 ± 104	1247 ± 88	<0.001
Mid	1444 ± 148	1256 ± 99	<0.001
Apical	1581 ± 143	1246 ± 77	<0.001
ECV (%)			
Whole heart	35 ± 5	29 ± 4	<0.001
Basal	31 ± 4	29 ± 3	0.002
Mid	35 ± 4	29 ± 4	<0.001
Apical	40 ± 5	30 ± 3	<0.001
T2 (ms)			
Whole heart	90 ± 34	68 ± 12	<0.001
Basal	79 ± 31	66 ± 12	0.008
Mid	90 ± 35	70 ± 14	<0.001
Apical	106 ± 45	71 ± 4	<0.001
T2 signal intensity ratio			
Whole heart	1.5 ± 0.7	1.3 ± 0.4	0.004
Basal	1.1 ± 0.6	1.2 ± 0.4	0.60
Mid	1.5 ± 0.7	1.3 ± 0.4	0.040
Apical	1.9 ± 0.7	1.4 ± 0.5	<0.001
T2-weighted imaging, *n* (%)	18 (78)	0 (0)	<0.001
Late gadolinium enhancement, *n* (%)	0 (0)	0 (0)	

CMR, cardiac magnetic resonance; ECV, extracellular volume fraction; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; NA, not applicable; RVEF, right ventricular ejection fraction.

segments with myocardial oedema and baseline LVEF ($r = 0.406$, $P = 0.037$).

Follow-up

During hospitalization, three of 23 patients with TTC experienced adverse clinical events: oozing cardiac rupture ($n = 1$), LV thrombus ($n = 1$), and cardiac tamponade ($n = 1$). Interestingly, the patient with oozing cardiac rupture had the highest native T1 value in the apical region (1835 ms). The other two patients also had significantly higher native T1 values, which are beyond the 75th percentile of native T1 values observed (1716 and 1758 ms, respectively).

CMR imaging was performed in all 23 patients at a median of 96 days after the onset of symptoms. *Table 3* shows changes in CMR parameters between baseline and follow-up. Follow-up echocardiography and CMR imaging showed normalization of LVEF in all patients. Native T1 and ECV of the entire heart also decreased significantly (native T1 values, from 1438 ± 162 to 1314 ± 101 ms, $P < 0.001$; ECV, from 35 ± 5 to 33 ± 5%, $P < 0.001$), but did not normalize by the 3-month follow-up. *Figure 4B* shows that the number of segments with myocardial oedema was positively correlated with LV wall motion recovery time ($r = 0.494$, $P = 0.027$). In addition, there was a significant positive correlation between baseline native T1, ECV, T2, T2 SI ratio of the entire heart, and time to recovery of LV wall motion (Supplementary data online, *Figure S3A–D*). In per-region analysis, native T1 and T2 in the basal and mid-ventricular regions were positively correlated with time to recovery of LV wall motion (Supplementary data online, *Figure 3E, G, I, and K*).

Reproducibility and agreement analysis

There were excellent correlation and agreement for native T1, ECV, T2, and T2 SI ratio between the two blinded operators ($r = 0.97$, $r = 0.95$, and $r = 0.92$, respectively). The Bland–Altman analysis of inter-observer variability showed that the percentage difference for T1 was ±0.1% (±2.1 ms) and the 95% confidence interval (CI) for differences was ±0.5% of the mean (±7.8 ms). For ECV, the percentage difference was ±0.7% (±0.2%) and the 95% CI for differences was ±1.1% of the mean (±0.4%). For T2, the percentage difference in T2 was ±2.4% (±1.8 ms) and the 95% CI for differences was ±2.6% of the mean (±2.0 ms). The percentage difference in intra-observer variability for native T1 was ±0.3% (±4.7 ms) and the 95% CI for

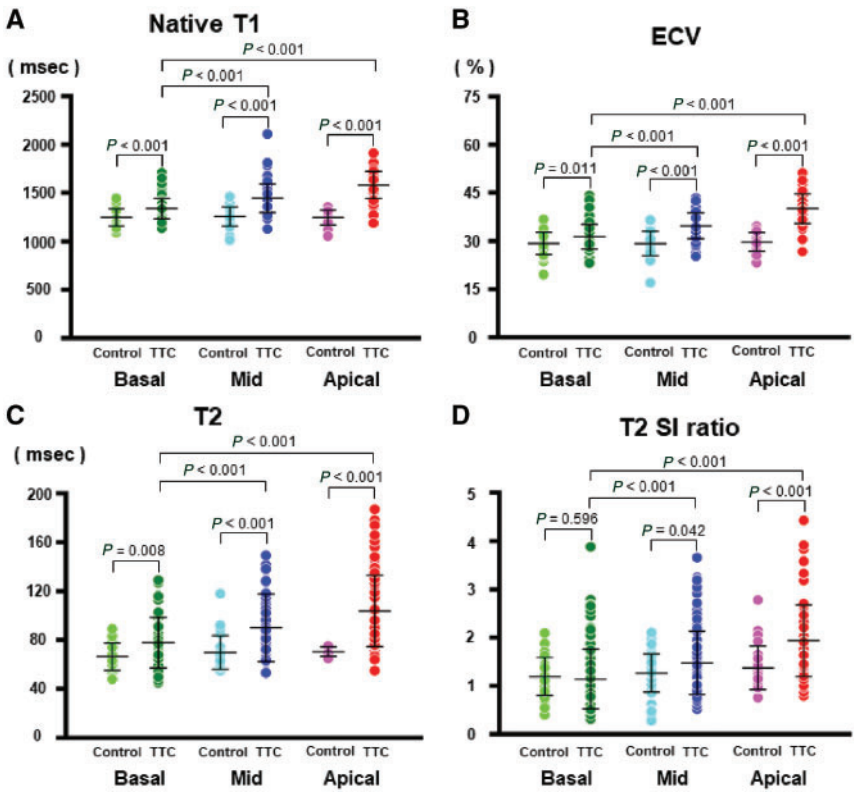

Figure 2 Comparisons of native T1, ECV, T2, and T2 SI ratio in each region of the left ventricle in patients with TTC and controls. (*A–D*) Native T1, ECV, T2, and T2 SI ratio, respectively. In areas with abnormal wall motion (mid-ventricle, blue points; apex, red points), patients with TTC had significantly higher native T1, ECV, T2, and T2 SI ratio than controls. Among patients with TTC, native T1, ECV, T2, and T2 SI ratio in the mid-ventricular and apical regions were significantly higher than in basal myocardium (green points). ECV, extracellular volume fraction; TTC, takotsubo cardiomyopathy; T2 SI, T2 signal intensity.

differences was ±0.5% of the mean (±6.8 ms). For ECV, the percentage difference was ±0.3% (±0.1%) and the 95% CI for differences was ±1.4% of the mean (±0.5%). For T2, the percentage difference in T2 was ±1.3% (±1.0 ms) and the 95% CI for differences was ±2.8% of the mean (±2.2 ms).

Discussion

This is the first report documenting the chronological changes in myocardial native T1, ECV, and T2 in patients with TTC. In particular, native T1 in remote myocardium, but not in the affected region, was significantly correlated prolonged LV wall motion recovery. In addition, we demonstrated that native T1 mapping outperformed conventional T2 mapping for detecting myocardial oedema and the feasibility of serial native T1 mapping to assess changes in myocardial characteristics in the underline disease.

CMR techniques for detecting myocardial oedema in TTC

CMR techniques for detecting myocardial oedema in TTC have focused on detecting increased hyper-enhancement through T2WI.[21,22] In addition, Neil *et al.*[1] identified that elevated T2 SI ratio in even remote myocardium of apparent normality in TTC. Although interruption of traditional T2WI remains subjective or semiquantitative approach,[18,21,22] Thavendiranathan *et al.*[23] identified myocardial impairment in TTC using quantitative T2-mapping so that elevation of T2 values in the affected regions as well as remote myocardium. On the other hand, Ferreira *et al.*[13] demonstrated for the first time that the elevation of non-contrast T1 mapping in affected myocardium as well as even in normal wall motion in TTC and a negative correlation between baseline LVEF and native T1. Consequently, native T1 mapping has emerged as a promising technique for detecting myocardial oedema in TTC. However, data using this technique, such as ECV findings and longitudinal evolution of these native T1 and ECV in TTC are sparse.

Native T1 as imaging marker of myocardial impairment in TTC

Consistent with previous studies,[1,13,23] our results showed that even in remote myocardium (LV basal region), which presents as a hyperdynamic area in the acute phase of TTC, native T1 and T2 were significantly higher than those in controls (*Table 2*). On the other hand, we demonstrated first time that ECV was highest in the affected apical region and decreased gradually from the apical to basal regions

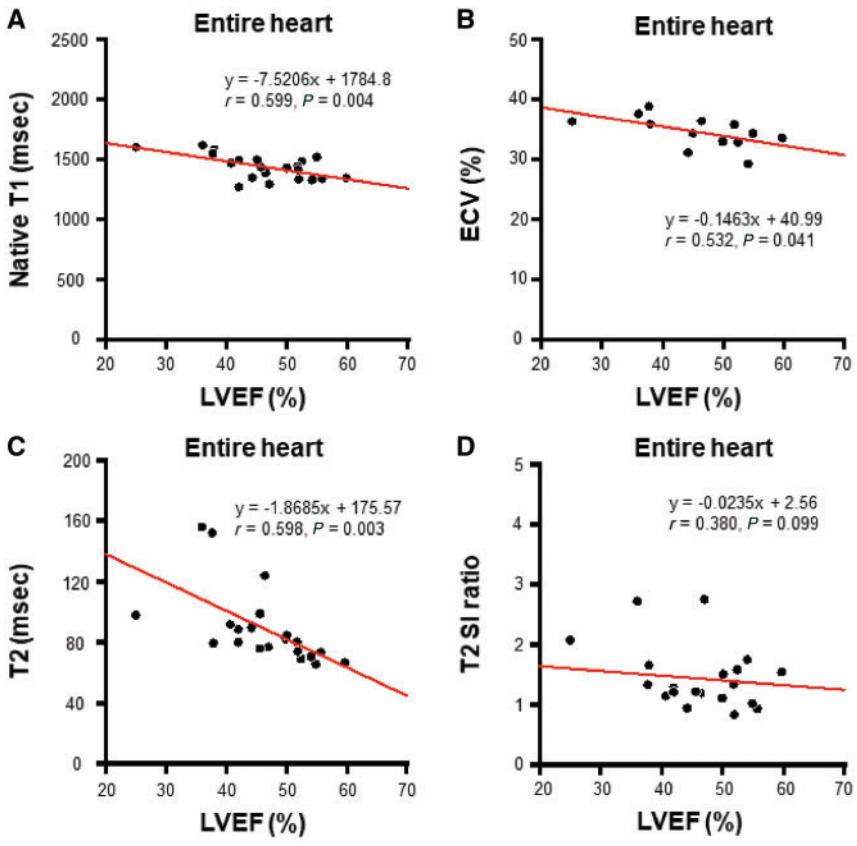

Figure 3 Correlations between baseline native T1, ECV, T2, T2 SI ratio, and LVEF. (*A–D*) The relationship between native T1, ECV, T2, T2 SI ratio (entire heart), and LVEF at baseline. ECV, extracellular volume fraction; LVEF, left ventricular ejection fraction; TTC, takotsubo cardiomyopathy; T2 SI, T2 signal intensity.

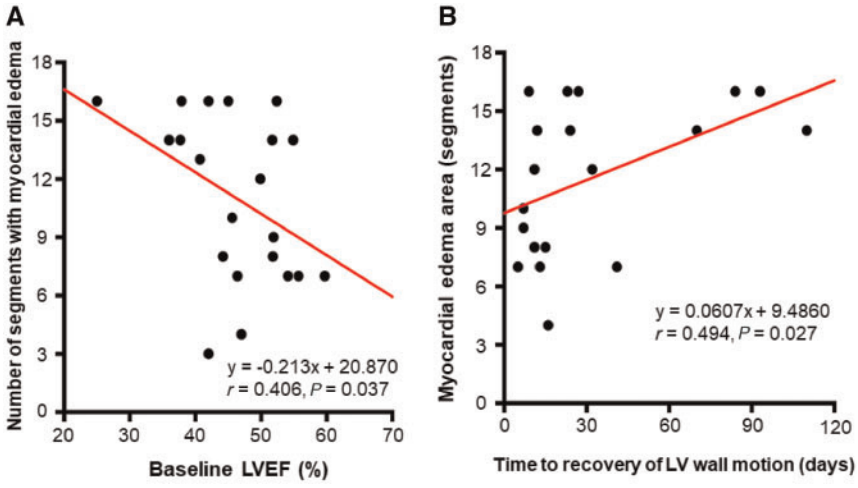

Figure 4 Correlations between myocardial oedema and LVEF at baseline, and time to recovery of LV wall motion. (*A*) Relationship between myocardial oedema area and LVEF at baseline. Myocardial oedema area had significantly good correlation with LVEF at baseline ($r = 0.406$, $P = 0.037$). (*B*) Relationship between myocardial oedema area and recovery time of cardiac function. Broader myocardial oedema area correlated with longer recovery time of cardiac function ($r = 0.494$, $P = 0.027$). Segments with a native T1 value greater than 1339 ms were defined as areas of myocardial oedema on the basis of ROC analysis (Supplementary data online, *Figure S2*). LVEF, left ventricular ejection fraction.

Table 3 Changes in CMR parameters between baseline and follow-up in patients with TTC

	Baseline	Follow-up	*P*-value
CMR parameters			
LVEF (%)	46 ± 8	59 ± 4	<0.001
LVEDVI (mL/m^2)	73 ± 23	71 ± 18	0.268
LVESVI (mL/m^2)	39 ± 16	30 ± 10	0.002
RVEF (%)	50 ± 7	50 ± 4	0.84
Native T1 (ms)			
Whole heart	1438 ± 162	1314 ± 101	<0.001
Basal	1336 ± 104	1286 ± 81	<0.001
Mid	1444 ± 148	1297 ± 78	<0.001
Apical	1581 ± 143	1393 ± 111	<0.001
ECV (%)			
Whole heart	35 ± 5	33 ± 5	<0.001
Basal	31 ± 4	31 ± 4	0.705
Mid	35 ± 4	32 ± 4	<0.001
Apical	40 ± 5	35 ± 5	<0.001
T2 (ms)			
Whole heart	90 ± 34	75 ± 24	<0.001
Basal	79 ± 31	69 ± 17	0.204
Mid	90 ± 35	75 ± 26	0.006
Apical	106 ± 32	82 ± 26	0.005
T2 signal intensity ratio			
Whole heart	1.5 ± 0.7	1.2 ± 0.4	<0.001
Basal	1.1 ± 0.6	1.0 ± 0.4	0.070
Mid	1.5 ± 0.7	1.1 ± 0.4	<0.001
Apical	1.9 ± 0.7	1.4 ± 0.5	<0.001

CMR, cardiac magnetic resonance; ECV, extracellular volume fraction; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; RVEF, right ventricular ejection fraction.

(*Figure 2B*). Interestingly, elevated basal native T1 and T2 were inversely correlated with lower LVEF (Supplementary data online, *Figure S1A*, *C*, and *D*), whereas ECV in those regions were not correlated with LVEF (Supplementary data online, *Figure S1B*). In addition, there were no significant correlations between apical native T1, ECV, and T2 and LVEF (Supplementary data online, *Figure S1I–L*). Since the apical region is most severely affected in patients with apical TTC, often with akinesia or dyskinesia during the acute phase, LVEF mostly reflects the wall motion of the remote myocardium (basal region). Therefore, although apical native T1, ECV, and T2 were highest among LV regions, they were not correlated with LVEF. Thus, focusing on just the apical slices may fail to distinguish the more minor TTC from the more severe TTC.

On the other hand, the precise mechanism for the discrepancy of correlations between basal native T1 and ECV with LVEF are not known. Possibilities include that changes in native T1 and ECV within the myocardium are dependent in different mechanisms leading to increased T1 relaxation and ECV in TTC. Since native T1 are prolonged by excess free water content and ECV increases with expansion of the interstitial space[24] due to acute oedema or inflammation, these findings suggest that TTC adversely affects not only the interstitial space but also myocytes, and that some degree of myocardial oedema occurs diffusely, even in remote myocardium. In addition, Dass *et al.*[25] suggested that since T1 are strongly correlated with impaired myocardial energetics, native T1 may detect functional changes in the myocardium prior to the development of fibrosis as evaluated by ECV. Therefore, native T1 measures signal from the interstitium as well as the myocytes, native T1 but not ECV could be affected by additional changes such as intramyocellular water distribution in TTC (Supplementary data online, *Figure S2*). Further study is needed to evaluate the mechanism of increased in ECV and native T1 in patients with TTC.

At follow-up, elevated native T1 of the entire heart and each LV region were positively correlated with prolonged LV wall motion recovery time (Supplementary data online, *Figure S3A–D*). Moreover, the number of segments with increased native T1 (areas of myocardial oedema), which was defined based on ROC analysis, was significantly correlated with prolonged LV wall motion recovery time (*Figure 4B*). Chronological changes in native T1, T2, and ECV showed that the broader myocardial oedema detected by T1 and T2 mapping during the acute phase was associated with decreases in global LV systolic function and prolongs the time needed for normalization.

Diagnostic accuracy of native T1 and ECV compared to T2 mapping

Consistent with a previous study,[13] our results demonstrated that native T1 and ECV mapping outperformed T2WI with superior sensitivity and excellent specificity in detecting changes in reversible myocardium in TTC (Supplementary data online, *Figure S2*). Despite superior diagnostic accuracy for myocardial oedema (AUC > 0.90), ECV examination is not recommended in patients with eGFR <45 mL/min/1.73 m^2 due to the risk of nephrogenic systemic fibrosis associated with gadolinium exposure. Indeed, we excluded 5 (22%) patients with TTC who met this exclusion criterion. Thus, this study demonstrates the feasibility of serial native T1 mapping to assess changes in myocardial characteristics in patients with TTC.

Study limitations

Although slices of at least 10 mm are recommended in T2WI to maximize the signal-to-noise ratio (SNR),[18] we employed thin slices (5 mm) in this study. Therefore, thin slices of T2WI might result in decreased SNR compared to thicker slices and may affect the cut-off value of the T2WI signal for detecting myocardial oedema compared to previous studies.[13,22] While histological examination was not performed in our cohort, it is highly likely that segments with acute wall motion abnormalities might have features of acute oedema. In this study, we used the MOLLI 3(3)5 scheme for T1 quantification of the myocardium.[16] The original MOLLI 3(3)3(3)5 scheme sequence, as described by Messroghli *et al.*,[26] provides a high-resolution T1 map of the myocardium in native and post-contrast settings within a 17-heartbeat breath hold. However, long breath holds often limit its clinical application in patients due to motion artefact and heart rate variability. The MOLLI 3(3)5 scheme was implemented as a two-inversion recovery sequence with the first of three and the second of five consecutive image acquisitions, decreasing the acquisition time and reliability for T1 estimation.[27] It yields results very close to the original MOLLI sequence.[26] Previous studies have shown that a

reduced breath-hold MOLLI T1-mapping protocol using methods similar to those in this study leads to similar results as the conventional MOLLI technique.[16,28]

Conclusion

Native T1 mapping offers high diagnostic performance, detection of myocardial oedema, and prediction of LV wall motion restoration in patients with TTC.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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