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Prognostic Significance of Remote Myocardium Alterations Assessed by Quantitative Noncontrast T1 Mapping in ST-Segment Elevation Myocardial Infarction

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ABSTRACT

OBJECTIVES This study assessed the prognostic significance of remote zone native T1 alterations for the prediction of clinical events in a population with ST-segment elevation myocardial infarction (STEMI) who were treated by primary percutaneous coronary intervention (PPCI) and compared it with conventional markers of infarct severity.

BACKGROUND The exact role and incremental prognostic relevance of remote myocardium native T1 mapping alterations assessed by cardiac magnetic resonance (CMR) after STEMI remains unclear.

METHODS We included 255 consecutive patients with STEMI who were reperfused within 12 h after symptom onset. CMR core laboratory analysis was performed to assess left ventricular (LV) function, standard infarct characteristics, and native T1 values of the remote, noninfarcted myocardium. The primary endpoint was a composite of death, reinfarction, and new congestive heart failure within 6 months (major adverse cardiac events [MACE]).

RESULTS Patients with increased remote zone native T1 values (>1,129 ms) had significantly larger infarcts ($p = 0.012$), less myocardial salvage ($p = 0.002$), and more pronounced LV dysfunction ($p = 0.011$). In multivariable analysis, remote zone native T1 was independently associated with MACE after adjusting for clinical risk factors ($p = 0.001$) or other CMR variables ($p = 0.007$). In C-statistics, native T1 of remote myocardium provided incremental prognostic information beyond clinical risk factors, LV ejection fraction, and other markers of infarct severity (all $p < 0.05$). The addition of remote zone native T1 to a model of prognostic CMR parameters (ejection fraction, infarct size, and myocardial salvage index) led to net reclassification improvement of 0.82 (95% confidence interval: 0.46 to 1.17; $p < 0.001$) and to an integrated discrimination improvement of 0.07 (95% confidence interval: 0.02 to 0.13; $p = 0.01$).

CONCLUSIONS In STEMI patients treated by PPCI, evaluation of remote zone alterations by quantitative noncontrast T1 mapping provided independent and incremental prognostic information in addition to clinical risk factors and traditional CMR outcome markers. Remote zone alterations may thus represent a novel therapeutic target and a useful parameter for optimized risk stratification. (Effect of Conditioning on Myocardial Damage in STEMI [LIPSIA-COND]; NCT02158468) (J Am Coll Cardiol Img 2018;11:411-9) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CI = confidence interval

CMR = cardiac magnetic resonance

GBCA = gadolinium-based contrast agent

HR = hazard ratio

IQR = interquartile range

IS = infarct size

LV = left ventricular

MACE = major adverse cardiac event(s)

MS = myocardial salvage

MSI = myocardial salvage index

NRI = net reclassification improvement

MVO = microvascular obstruction

PPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

In patients with acute myocardial infarction (AMI), myocardial tissue injury and cardiac remodeling are not restricted to the territory supplied by the culprit artery, but they also affect the remote, noninfarcted myocardium (1). However, the exact role and clinical relevance of remote myocardium alterations remain incompletely understood. Animal studies have shown that myocardial tissue alterations, including diffuse fibrosis, may evolve in the noninfarcted myocardium early after AMI (2). However, studies in humans that have targeted changes in the remote myocardium have yielded conflicting results. Some investigators have demonstrated remote region dysfunction (3,4), whereas others have described no difference in contractility compared with control subjects (5). Importantly, data regarding remote myocardium alterations in patients with AMI are limited mainly because methods for a comprehensive in vivo evaluation of diffuse myocardial tissue disease have been missing.

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Advances in cardiac magnetic resonance (CMR) have recently paved the way for clinically feasible T1-mapping sequences, which allow quantification of absolute myocardial longitudinal relaxation (T1) times (6). T1-mapping is therefore increasingly used for better understanding of myocardial tissue pathology in a variety of cardiac diseases (7–12). In the setting of ST-segment elevation myocardial infarction (STEMI), T1-mapping not only allows the evaluation of infarct severity (10), but also allows depiction of diffuse tissue abnormalities that occur during the acute and chronic post-infarction period in the remote, noninfarcted myocardium (13–15). A study by Carrick et al. (15) suggested that early changes in remote zone native T1 values might be associated with the occurrence of early post-infarction remodeling, and in a secondary analysis, adverse outcome. However, this study did not evaluate whether remote zone native T1 values provided independent and incremental prognostic information over established CMR markers of infarct severity. Consequently, the promising role of remote zone native T1 for the prediction of hard clinical events, and especially its potential incremental prognostic value over other markers of infarct severity, remains uncertain. The aim of this study was to investigate T1 characteristics of the remote, noninfarcted myocardium and to comprehensively assess its prognostic value in a large STEMI population that was treated by primary percutaneous coronary intervention (PPCI).

METHODS

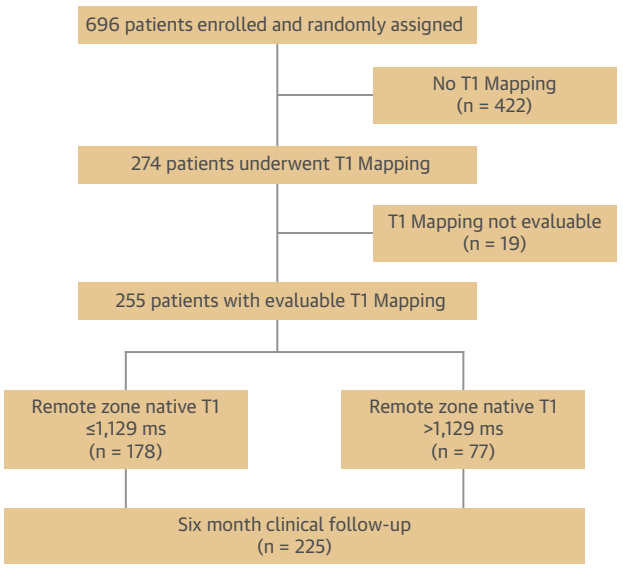
STUDY POPULATION AND CLINICAL ENDPOINTS. This was a CMR substudy of the prospective LIPSIA CONDITIONING (Effect of Conditioning on Myocardial Damage in STEMI) trial, a randomized, open-label, controlled trial conducted at the University of Leipzig–Heart Center between April 2011 and May 2014 (16). The trial is registered with ClinicalTrials.gov (NCT02158468). The detailed design and main results were recently published (16). Briefly, in LIPSIA CONDITIONING, patients with STEMI who had symptom onset at <12 h and who underwent PPCI were randomly assigned in a 1:1:1 ratio to: 1) combined intrahospital remote ischemic conditioning + post-conditioning in addition to PPCI; 2) post-conditioning in addition to PPCI; or 3) conventional PPCI. Exclusion criteria were age <18 years, previous fibrinolysis, pregnancy, cardiogenic shock, comorbidity with a limited life expectancy of <6 months, contraindication to CMR, and participation in another trial. The clinical endpoint (major adverse cardiac events [MACE]) was defined as a composite of death, reinfarction, and the occurrence of new congestive heart failure within 6 months. Only events occurring after CMR were included. The local ethics committee approved the study, and patients were required to provide written informed consent.

CMR IMAGING. CMR examinations were performed between days 2 and 5 after STEMI using a 1.5-T scanner. The detailed scan protocol and image analysis for the assessment of area at risk, myocardial salvage (MS), infarct size (IS), microvascular obstruction (MVO), and left ventricular (LV) ejection fraction were previously published (17,18). Blinded readers performed image evaluation with certified CMR post-processing software (cmr42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) at the CMR core laboratory. The core laboratory is highly experienced in CMR evaluation and has proven excellent reproducibility, as well as low interobserver and intraobserver variability for the determination of MS and IS (19). The measurements of the area at risk, IS, MS, and MVO were expressed as the percentage of LV volume (%LV) (17). T1-mapping was implemented in the CMR protocol after the beginning of patient recruitment and was performed in the final consecutive 274 patients of the study population (**Figure 1**). T1-mapping was acquired in 3 short-axis orientations (basal, midventricular, and apical) using single-slice breath-hold modified Look-Locker inversion recovery (MOLLI)

sequences. A MOLLI sequence variant was used with 8 single-shot balanced steady-state free precession readout trains (inversion, 3 readouts in consecutive RR intervals, re-inversion, 5 consecutive readouts, "3(3)5" scheme), in which the number in parentheses denotes the number of empty RR intervals before re-inversion (20). Typical sequence parameters were repetition time 2.9 ms, 8 echoes (3 to 5 scheme), flip angle of 50°, voxel size of 1.19 × 1.19 × 10 mm^3, 13 startup cycles to approach steady state, and effective inversion times between 167 and 5,472 ms. Native T1 values were derived by T1 assessment within the remote region of interest. The remote myocardium was defined as myocardium 180° from the infarcted zone with no signs of infarction, edema, or wall motion abnormalities (15). Special care was taken to have sufficient distance from the adjacent tissue, such as blood or lungs, to avoid partial volume artefacts (7).

STATISTICAL ANALYSIS. Continuous variables are presented as median (interquartile range [IQR]). Categorical variables are shown as frequencies with corresponding percentages. Differences between groups were tested using the Wilcoxon-Mann-Whitney U test. Proportions were compared by Fisher exact test or by the chi-square test. Event-free survival was depicted by the Kaplan-Meier method. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for binary outcomes. Univariable and stepwise multivariable Cox regression analysis was performed to identify predictors of MACE. To ensure statistical robustness of the Cox regression analysis with respect to our sample size and the number of MACE, we performed 2 separate models. All variables listed in **Table 1** (except for concomitant medication) and in **Table 2** were considered in univariate analysis for the first model (clinical risk factors). For the second model, we evaluated established CMR variables (17,21). Only variables with a p value <0.05 were entered into the multivariable analysis. To make the HR comparable, the continuous CMR variables that predicted MACE (LV ejection fraction, IS, MSI) were dichotomized according to the Youden index value. The potential incremental prognostic information of remote zone native T1 over clinical risk factors, LV ejection fraction, or CMR markers of infarct severity for the prediction of MACE was assessed with C-statistics. C-statistic results were compared as previously described (22). To further evaluate the incremental prognostic information of remote zone native T1 over established CMR predictors of MACE, net reclassification improvement (NRI) and integrated discrimination improvement were calculated by using R package PredictABEL (R Foundation, Vienna, Austria). Moreover, a CMR score for the prediction of MACE was created that assigned 1 point for each CMR parameter (IS, LV ejection fraction, MSI, and remote zone native T1; cutoff was determined by the receiver-operating characteristic), which resulted in a score range from 0 to 4 points. For these score points, we created the following risk classes: very low (0 points), low (1 point), intermediate (2 points), and high (3 to 4 points). All tests were 2-tailed, and the significance level was set at 0.05. Statistical analysis was performed with SPSS 22.0.0.1 (IBM, Armonk, New York), MedCalc Version 15.4 (Ostend, Belgium), and R 3.3.0 (R Foundation).

FIGURE 1 Study Flowchart



After exclusion of patients without or nonevaluable T1 mapping, a total of 255 patients were available for the present analysis.

RESULTS

STUDY POPULATION. Of 696 STEMI patients included in the randomized LIPSIA CONDITIONING trial, 274 patients underwent native T1-mapping (**Figure 1**). Nineteen patients had nonevaluable T1 maps (6.9%), mainly due to motion artefacts. Thus, the final study cohort consisted of 255 STEMI patients. Patients were dichotomized according to the Youden index value to assess the optimal cutoff value for the prediction of MACE by native remote zone T1: 1) remote zone native T1 values ≤1,129 ms (n = 178; 69.8%); and 2) remote zone native T1 values >1,129 ms

TABLE 1 Patient Characteristics

	Total (N = 255)	Remote Zone Native T1 ≤1,129 ms (n = 178)	Remote Zone Native T1 >1,129 ms (n = 77)	p Value
Age, yrs	63 (54–75)	63 (52–73)	69 (55–77)	0.09
Male	196 (77)	137 (77)	59 (77)	0.95
Body mass index, kg/m^2	27 (25–31)	27 (25–31)	27 (25–1)	0.85
Cardiovascular risk factors				
Current smoking	113 (44)	80 (45)	33 (43)	0.76
Hypertension	187 (73)	130 (73)	57 (74)	0.87
Hypercholesterolemia	116 (46)	77 (43)	39 (51)	0.28
Diabetes mellitus	52 (20)	38 (21)	14 (18)	0.56
Previous infarction	27 (11)	20 (11)	7 (9)	0.63
Previous PCI	29 (11)	21 (12)	8 (10)	0.75
Anterior infarction	113 (44)	62 (35)	51 (66)	<0.001
Time, min				
Symptom onset to PCI hospital admission	190 (123–338)	193 (125–338)	175 (117–338)	0.42
Door-to-balloon time	25 (21–31)	25 (20–30)	25 (21–34)	0.54
Killip class on admission				0.009
I	230 (90)	163 (92)	67 (87)	
II	21 (8)	15 (8)	6 (8)	
III or IV	4 (2)	0 (0)	4 (5)	
Concomitant medications at discharge				
Aspirin	252 (99)	178 (100)	74 (96)	0.008
Clopidogrel	52 (20)	33 (19)	19 (25)	0.26
Prasugrel	182 (71)	131 (74)	51 (66)	0.23
Ticagrelor	47 (18)	30 (17)	17 (22)	0.32
ß-blockers	245 (96)	173 (97)	72 (94)	0.16
ACE-I/ARB	243 (95)	172 (97)	71 (92)	0.13
Statins	245 (96)	172 (97)	73 (95)	0.49

Values are median (interquartile range) or n (%).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PCI = percutaneous coronary intervention.

(n = 77; 30.2%). Treatment strategies that were compared in the LIPSIA CONDITIONING trial were equally distributed in both groups (p = 0.58). In the remote zone ≤1,129 ms group, 57 (32%) patients received remote ischemic conditioning, 70 (39%) received remote ischemic post-conditioning, and 51 (29%) patients received both. In the remote zone >1,129 ms group, 27 (35%) patients received remote ischemic conditioning, 25 (33%) received remote ischemic post-conditioning, and 25 (33%) patients received both.

BASELINE AND PROCEDURAL CHARACTERISTICS. The baseline and procedural characteristics of the total study cohort and their relationships with remote zone native T1 groups are shown in Tables 1 and 2. Patients with increased remote zone native T1 values tended to be older (p = 0.09) and were significantly more likely to have an anterior wall infarction, a higher Killip class on admission, and a left anterior descending culprit lesion. Peak high-sensitive troponin T was higher in patients with increased remote zone native T1 (p = 0.043).

CMR FINDINGS. Patients underwent CMR imaging a median 3 days (IQR: 2 to 4 days) after the index event in both groups (estimated median difference 0 days [95% CI: 0 to 1 day]). CMR findings and their relation to native T1 are depicted in Table 3. The median remote zone native T1 value of the entire study cohort was 1,070 ms (interquartile range: 984 to 1,154). There was no association between native remote T1 values and time to CMR scan (r = −0.012; p = 0.851).

REMOTE ZONE NATIVE T1 VALUES AND CLINICAL OUTCOME. Sixteen patients (6.3%) experienced a MACE during follow-up (death, n = 5 [2%]; reinfarction, n = 3 [1.2%]; new congestive heart failure, n = 8 [3.1%]). Remote zone native T1 values were significantly higher in patients with MACE compared with those without MACE (Figure 2). Based on areas under the curve, remote zone native T1 values >1,129 ms best predicted MACE (areas under the curve: 0.78; 95% CI: 0.70 to 0.86; p < 0.001). The frequency of MACE was significantly higher in patients with remote zone native T1 values >1,129 ms (12 [15.6%] vs. 4 [2.2%]; p < 0.001) (Figure 3). The following CMR parameters were significantly associated with MACE in simple Cox regression analysis: LV ejection fraction <40.6% (HR: 7.4; 95% CI: 2.6 to 21.3; p < 0.001), IS >25.1%LV (HR: 5.8; 95% CI: 2.0 to 16.8; p = 0.001), MSI <28.2 (HR: 10.4; 95% CI: 2.9 to 37.0; p < 0.001), and remote zone native T1 >1,129 ms (HR: 7.4; 95% CI: 2.4 to 23.0; p = 0.001). Using stepwise multiple Cox regression analysis, LV ejection fraction, MSI, and remote zone native T1 emerged as independent predictors of MACE (Table 4). The inclusion of remote zone native T1 in addition to LV ejection fraction resulted in an increase of C-statistics from 0.79 to 0.85 (p = 0.012). Similarly, there was a significant increase of C-statistics when adding remote zone native T1 to infarct size (0.75 to 0.82; p = 0.006) or MSI (0.78 to 0.81; p = 0.038). In a reclassification analysis that applied risk levels of <1%, 1% to <6%, 6% to <12%, and ≥12%, the inclusion of remote zone T1 to a risk model that included LV ejection fraction, IS, and MSI led to an NRI of 0.82 (95% CI: 0.46 to 1.17; p < 0.001) and to an integrated discrimination improvement of 0.07 (95% CI: 0.02 to 0.13; p = 0.01) (Online Table 1). In detail, 40% of the cases and 7% of the noncases were reclassified upward, whereas 13% of the cases and 62% of the noncases were reclassified downward; therefore, 27% of the cases and 55% of the noncases were net correctly reclassified. The continuous NRI was 0.94 (95% CI: 0.48 to 1.41; p < 0.001). When using the risk levels determined by our scoring system (very low: 0% MACE; low: 1.5% MACE; intermediate: 10.5% MACE; and high: 28.9% MACE)

(Figure 4), the addition of remote zone T1 also led to a significant improvement in reclassification analysis of NRI of 0.49 (95% CI: 0.18 to 0.80; p = 0.002).

In addition to CMR variables, several baseline characteristics were associated with MACE in simple Cox regression analysis: anterior infarction (HR: 3.1; 95% CI: 1.1 to 8.9; p = 0.037), Killip class >1 (HR: 3.3; 95% CI: 1.1 to 10.2; p = 0.039), and ST-segment elevation resolution (HR: 0.98; 95% CI: 0.97 to 0.99; p = 0.028). Using stepwise multiple Cox regression analysis, Killip class >1, ST-segment elevation resolution, and remote zone native T1 >1,129 ms were identified as independent predictors of MACE (Table 5). Finally, 2 models using baseline risk factors and remote zone native T1 values for the prediction of MACE were created. The inclusion of remote zone native T1 in addition to Killip class resulted in a significant increase in C-statistics, from 0.58 to 0.79 (p < 0.001). Similarly, there was also a significant increase in C-statistics when adding remote zone native T1 in addition to ST-segment elevation resolution (0.66 to 0.79; p = 0.011).

TABLE 2 Angiographic, Procedural, ECG, and Biomarker Results

	Total (N = 255)	Remote Zone Native T1 ≤1,129 ms (n = 178)	Remote Zone Native T1 >1,129 ms (n = 77)	p Value
No. of diseased vessels				0.65
1	126 (49)	86 (48)	40 (52)	
2	84 (33)	58 (33)	26 (34)	
3	45 (17)	34 (19)	11 (14)	
Infarct-related artery				0.001
Left anterior descending	113 (44)	66 (37)	47 (61)	
Right coronary artery	112 (44)	90 (51)	22 (29)	
Left circumflex	30 (12)	22 (12)	8 (10)	
TIMI flow grade before PCI				0.37
0	134 (53)	99 (56)	35 (46)	
I	31 (12)	18 (10)	13 (17)	
II	55 (22)	38 (21)	17 (22)	
III	35 (14)	23 (13)	12 (16)	
TIMI flow grade after PCI				0.91
0	3 (1)	2 (1)	1 (1)	
I	3 (1)	2 (1)	1 (1)	
II	25 (10)	19 (11)	6 (8)	
III	224 (88)	155 (87)	69 (90)	
Stent implanted	247 (97)	173 (97)	74 (96)	0.81
Direct stenting	201 (79)	144 (81)	57 (74)	0.98
Aspiration thrombectomy	168 (66)	116 (65)	52 (68)	0.71
Peak troponin, ng/l	176 (46-562)	142 (41-528)	279 (89-634)	0.043
STR, %	72 (45-94)	74 (49-97)	69 (44-91)	0.50

Values are n (%) or median (interquartile range).
ECG = electrocardiography; STR = ST-segment elevation resolution; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

DISCUSSION

Our comprehensive CMR investigation demonstrated a strong association of native T1-mapping alterations of remote myocardium with future cardiovascular events in patients with reperfused STEMI, which was independent from the amount of damaged myocardium. The principle findings included: 1) native T1-values of remote myocardium assessed by quantitative noncontrast CMR imaging associated with adverse markers of myocardial damage and dysfunction; 2) remote zone native T1 that was independently predictive for MACE 6 months after STEMI; and 3) remote zone native T1 that added incremental prognostic information to clinical risk factors, LV ejection fraction, and markers of infarct severity for MACE prediction. Consequently, these findings might have significant future implications for the treatment of STEMI, including targeting the remote myocardium.

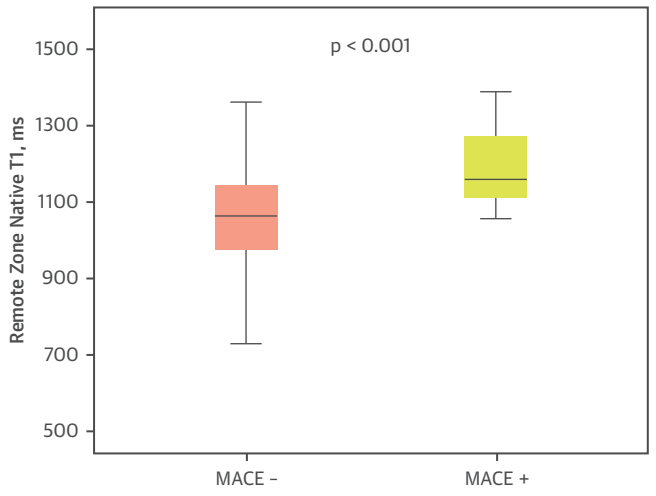
RISK STRATIFICATION BY MULTIPARAMETRIC CMR. Numerous studies demonstrated that the amount of infarcted tissue is strongly associated with cardiovascular outcome in STEMI survivors (21,23,24). Consequently, most efforts aimed to reduce the amount of infarcted tissue, and virtually no attention was given to alterations that occurred in the remote, noninfarcted myocardial tissue. Recently, the interest in myocardial tissue characterization by T1-mapping has rapidly grown due to important developments in imaging sequences and robustness (6). However, data for the prognostic value of native T1 in patients after myocardial infarction are scarce. Interestingly, changes in T1 values are detectable in the myocardium remote from the zone of infarction early after the acute event (13,15). In line with previous studies, we observed a significant association between remote zone native T1, LV ejection fraction,

TABLE 3 CMR Imaging Results

	Total (N = 255)	Remote Zone Native T1 ≤1,129 ms (n = 178)	Remote Zone Native T1 >1,129 ms (n = 77)	p Value
Area at risk, %LV	33 (25-42)	33 (24-41)	34 (26-43)	0.22
Infarct size, %LV	17 (7-26)	16 (7-25)	21 (12-29)	0.012
Myocardial salvage, %LV	15 (7-20)	15 (9-21)	12 (4-18)	0.011
Myocardial salvage index	45 (24-73)	50 (30-76)	34 (12-64)	0.002
Microvascular obstruction present	103 (40)	69 (39)	34 (44)	0.27
Microvascular obstruction, %LV	0 (0.0-1.1)	0 (0.0-1.0)	0 (0.0-1.3)	0.31
LV ejection fraction, %	48 (41-56)	49 (42-57)	46 (36-52)	0.011
LV end-diastolic volume, ml	137 (114-168)	135 (115-165)	140 (113-174)	0.60
LV end-systolic volume, ml	72 (54-93)	69 (53-91)	76 (55-110)	0.16

Values are median (interquartile range) or n (%).
CMR = cardiac magnetic resonance; LV = left ventricular.

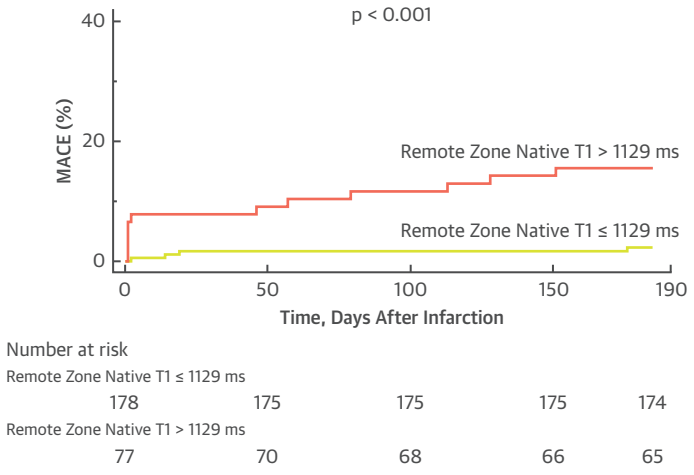
FIGURE 2 Remote Zone Native T1 Values and MACE



Box-and-whisker plots (**box**: 25th percentile, median, and 75th percentiles; **whisker**: minimum and maximum within 1.5 interquartile range of the lower and upper quartile, respectively) of remote zone native T1 values according to the presence or absence of major adverse cardiac events (MACE).

and infarct size (15). Carrick et al. (15) showed that remote zone native T1 was independently correlated with LV remodeling as detected by CMR at 6 months after STEMI. In a secondary analysis, these researchers also described an association of native remote zone T1 alterations and MACE. However, this study did not assess whether this association was independent from established CMR markers of infarct severity and whether the assessment of remote zone native T1 provided incremental prognostic information in addition to these infarct characteristics. Our study therefore confirmed and expanded these findings by demonstrating that native T1 measured in the remote myocardium was a strong independent predictor of hard clinical events post-STEMI. Importantly, we were also able to demonstrate an incremental prognostic value over and above clinical risk factors and CMR parameters of LV function and myocardial damage. Our data therefore highlighted that not only the amount of infarcted tissue, but that diffuse tissue abnormalities in the nonischemic areas were also of major prognostic importance.

FIGURE 3 Remote Myocardium Alterations by T1 Mapping and Prognosis After ST-Segment Elevation Myocardial Infarction



Kaplan-Meier curve showing the risk of MACE according to remote zone native T1 alterations. Abbreviation as in Figure 2.

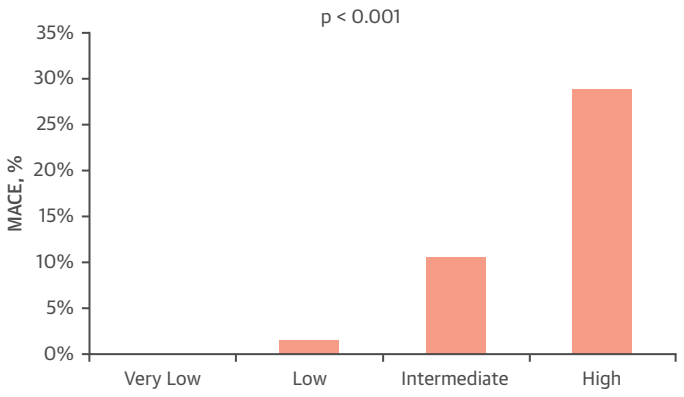
The pathophysiological mechanisms leading to increased T1 values in noninfarcted myocardium are not completely understood. The occlusion of the coronary artery and reperfusion of the injured myocardium triggers a robust local and systemic inflammatory response. In the remote myocardium, this response is associated with the activation of proinflammatory pathways and leukocyte infiltration (25). The magnitude of such an inflammatory response has been increasingly recognized as an important factor in the development of severe post-infarction remodeling (26). Accordingly, augmentation of remote zone native T1 during the acute phase after STEMI presumably represents myocardial edema and hypercellularity due to inflammation (15,25). However, T1 values are not only influenced by interstitial and intracellular water changes, but also by changes in the intravascular compartment (27). Altered vasodilator responsiveness as a consequence of an increase in oxygen consumption in remote regions might therefore also influence native T1 values. In contrast, increased native T1 could also reflect early diffuse myocardial fibrosis instead of a primary inflammatory response (2,8,13). Chan et al. (13) applied T1 mapping in a small cohort of patients with AMI (n = 25) and found shortened post-contrast T1 times in the remote myocardium, which was consistent with early extracellular matrix expansion (13). Contrary to this, there was no evidence of edema in the remote zone, which was in line with another study that observed no differences in T2 values between the remote myocardium of patients with AMI and the myocardium of healthy volunteers (28). Finally, changes in regional mechanical load that lead to compensatory cellular hypertrophy, hyperkinesis, and cellular dysfunction might represent another potential

TABLE 4 CMR Predictors of MACE in Univariable and Multivariable Cox Regression Analyses

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
LV ejection fraction <40.6%	7.4 (2.6–21.3)	<0.001	3.6 (1.2–11.0)	0.028
Infarct size >25.1 %LV	5.8 (2.0–16.8)	0.001	–	–
Myocardial salvage index <28.2	10.4 (2.9–37.0)	<0.001	4.9 (1.3–19.0)	0.020
Remote zone native T1 >1,129 ms	7.4 (2.4–23.0)	0.001	5.0 (1.6–15.9)	0.007

CI = confidence interval; MACE = major adverse cardiac event(s); other abbreviations as in Table 3.

FIGURE 4 CMR Score and Prognosis After ST-Segment Elevation Myocardial Infarction



Risk of MACE according to a cardiac magnetic resonance (CMR) score that assigned 1 point for each parameter above and/or below the optimal cutoff after application of a receiver-operating curve analysis (left ventricular ejection fraction, infarct size, myocardial salvage index, and remote zone native T1), which resulted in a score range from 0 to 4 points. Very low (0 points), low (1 point), intermediate (2 points), and high (3 to 4 points). Abbreviation as in Figure 2.

mechanism of T1 alteration (4,29,30). However, in the previous study by Carrick et al. (15), there was no association between native T1 and early natriuretic peptide levels, which suggested that LV wall stress was not a major determinant of native T1 in the acute setting.

CLINICAL IMPLICATIONS. The avoidance of an exogenous gadolinium-based contrast agent (GBCA) has important clinical implications. An association between GBCA and the occurrence of nephrogenic systemic fibrosis has been described in patients with severe renal dysfunction (31). Native T1-mapping is thus applicable in the broader range of patients with STEMI, including those with severe renal impairment. Moreover, there is some evidence regarding accumulation of GBCA in multiple tissues, including bone, kidneys, and brain, despite intact renal function (32). The clinical significance of such findings remains to be defined, but underscores the preference for non-contrast CMR techniques.

Our data also suggested that native T1-mapping was able to detect myocardial tissue abnormalities in the noninfarcted myocardium that otherwise would be missed by traditional late-gadolinium enhanced imaging. Consequently, a multiparametric approach by CMR for optimized risk stratification of the individual patient should include the assessment of remote zone native T1.

The early detection of diffuse myocardial tissue pathology in the noninfarcted myocardium in survivors of STEMI might also allow for the initiation of more timely disease-specific therapy. Interestingly, first experimental studies showed promising results for the treatment of remote myocardium alterations (33). Although, to the best of our knowledge, there is currently no clinical trial that has targeted remote zone native T1, our data suggested that quantification of native T1 might serve as an additional target in future studies that involve patients with STEMI.

STUDY LIMITATIONS. The sample size and number of MACE in our study was only moderate. Therefore, confirmation of our findings in larger studies is necessary. Nevertheless, the baseline characteristics, CMR results on infarct severity, and the incidence of MACE are comparable with other recent CMR studies (21). Different T1-mapping techniques are available, and further improvements have been made since the beginning of this study. The comparative value of different techniques and the optimal cutoff for T1 values remains to be defined. However, native T1-mapping by the MOLLI sequence, which was applied in this study, has been clinically approved and could be evaluated now. The post-STEMI inflammatory

TABLE 5 Clinical Predictors of MACE in Univariable and Multivariable Cox Regression Analyses

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Killip class, >1	3.3 (1.1–10.2)	0.039	3.9 (1.2–12.5)	0.024
STR, %	0.98 (0.97–0.99)	0.028	0.98 (0.96–0.99)	0.017
Anterior infarction, 1 yes	3.1 (1.1–8.9)	0.037	–	–
Remote zone native T1 >1,129 ms	7.4 (2.4–23.0)	0.001	6.6 (2.1–20.7)	0.001

Abbreviations as in Tables 2 and 4.

reaction, including myocardial edema, is dynamic; therefore, time to CMR scan might influence remote zone native T1 values (25,34). However, remote zone native T1 was not associated with time to CMR scan in our analysis. Comprehensive longitudinal studies covering the first weeks after infarction would be interesting to examine this issue in detail. Finally, risk of inclusion of partial voxel volume is higher in the lateral wall compared with the septal wall (7). Therefore, we preferred conservative intramyocardial placement of regions of interest in the remote myocardium in the present study, as suggested by others (35). Nevertheless, we could not exclude that this might have at least partially influenced the study results.

CONCLUSIONS

In patients who underwent PPCI for STEMI, increased remote zone native T1 values were associated with worse clinical outcomes. The prognostic value of native T1 is independent and incremental to conventional clinical risk factors, LV ejection fraction, and CMR markers of myocardial damage. Characterization of remote zone alterations by native T1-mapping might therefore be useful as an additional therapeutic target and important prognostic marker in patients with STEMI.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with revascularized STEMI, assessment of remote zone alterations by quantitative noncontrast T1-mapping proved a strong association with future cardiovascular events. Importantly, the prognostic information of remote zone native T1 was incremental in addition to established CMR outcome markers, including infarct size.

TRANSLATIONAL OUTLOOK: Characterization of remote zone alterations may be useful as an additional therapeutic target and important prognostic marker when caring for patients with STEMI. Additional studies are needed to validate the findings and evaluate whether therapeutic interventions that influence remote zone native T1 improve event-free survival after revascularized STEMI.

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APPENDIX For a supplemental table, please see the online version of this paper.