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ORIGINAL ARTICLE
Imaging

Reverse Remodeling and Non-Contrast T1 Hypointense Infarct Core in Patients With Reperfused Acute Myocardial Infarction

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Background: Non-contrast T1 hypointense infarct cores (ICs) within infarcted myocardium detected using cardiac magnetic resonance imaging (CMR) T1 mapping may help assess the severity of left ventricular (LV) injury. However, because the relationship of ICs with chronic LV reverse remodeling (LVRR) is unknown, this study aimed to clarify it.

Methods and Results: We enrolled patients with reperfused AMI who underwent baseline CMR on day-7 post-primary percutaneous coronary intervention (n=109) and 12-month follow-up CMR (n=94). Correlations between ICs and chronic LVRR (end-systolic volume decrease ≥15% at 12-month follow-up from baseline CMR) were investigated. We detected 52 (47.7%) ICs on baseline CMR by non-contrast-T1 mapping. LVRR was found in 52.1% of patients with reperfused AMI at 12-month follow-up. Patients with ICs demonstrated higher peak creatine kinase levels, higher B-type natriuretic peptide levels at discharge, lower LV ejection fraction at discharge, and lower incidence of LVRR than those without ICs (26.5% vs. 73.3%, P<0.001) at follow-up. Multivariate logistic regression analysis showed that the presence of ICs was an independent and the strongest negative predictor for LVRR at 12-month follow-up (hazard ratio: 0.087, 95% confidence interval: 0.017–0.459, P=0.004). Peak creatine kinase levels, native T1 values at myocardial edema, and myocardial salvaged indices also correlated with ICs.

Conclusions: ICs detected by non-contrast-T1 mapping with 3.0-T CMR were an independent negative predictor of LVRR in patients with reperfused AMI.

Key Words: Acute myocardial infarction; Cardiac magnetic resonance imaging; Native T1 mapping; Reverse remodeling; T1 hypointense infarct core

Left ventricular (LV) remodeling following acute myocardial infarction (AMI) affects clinical outcomes. LV remodeling consists of reverse remodeling (LVRR), defined as a decreased end-systolic volume (ESV), and adverse remodeling, defined as an increased end-diastolic volume (EDV).[1] Early reperfusion via percutaneous coronary intervention (PCI) and subsequent administration of β-blockers and renin-angiotensin system blockers improves the prognosis of patients with AMI complicated with heart failure and adverse LV remodeling.[2–7] Conversely, LVRR is associated with a favorable prognosis.[8] Therefore, early prediction of chronic cardiac remodeling after coronary reperfusion in patients with AMI is essential for clinical decision-making and may have benefit for the development of cardioprotective drugs, PCI procedures, and device therapy.

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Contrast cardiac magnetic resonance imaging (CMR) is a validated tool for an accurate and detailed evaluation of the severity of LV damage and the prognosis of patients with AMI. Patients with moderate to severe renal failure with contrast contraindications have a poor prognosis for cardiac events, and have been excluded from previous contrast CMR studies.[9] A recently developed T1-mapping CMR technique permits quantitative evaluation of myocardial tissue characteristics without using contrast agents.

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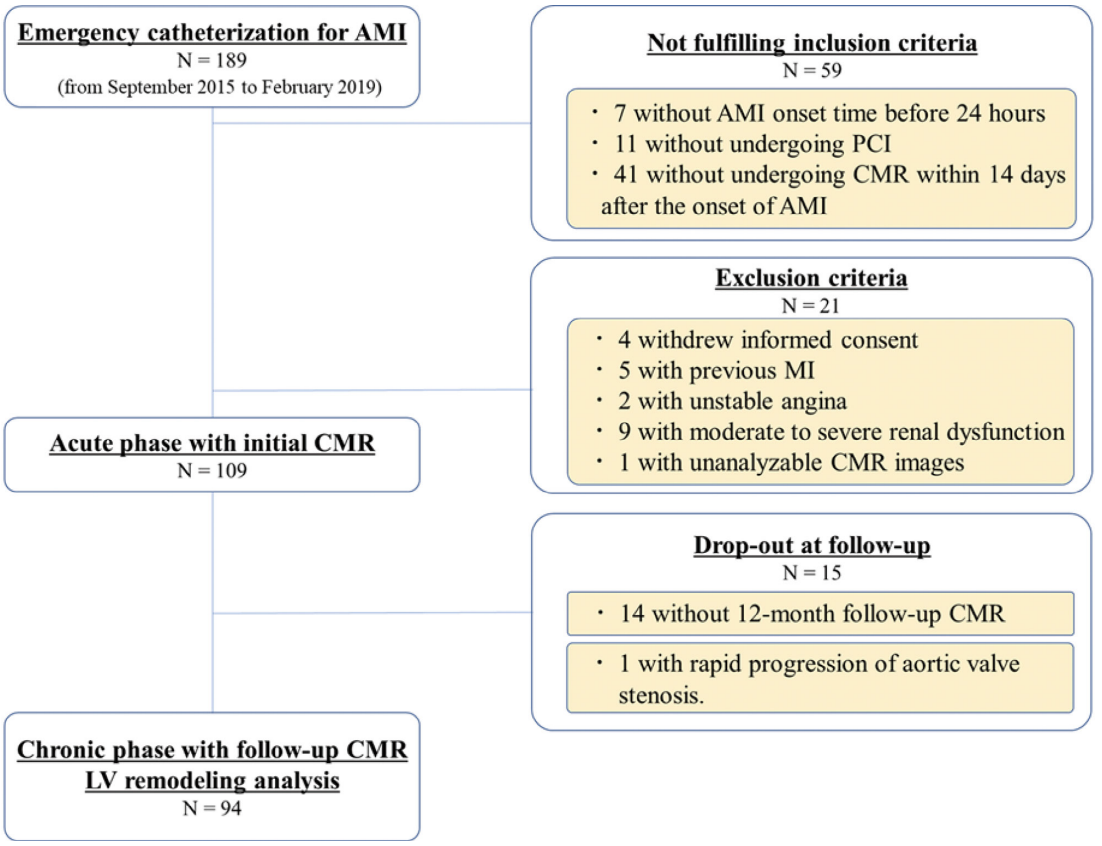

Figure 1. Study flowchart. ACS, acute coronary syndrome; AMI, acute myocardial infarction; CMR, cardiac magnetic resonance imaging; LV, left ventricular; PCI, percutaneous coronary intervention.

A previous animal study validated with histology showed that native T1 mapping, when compared with enhanced CMR, is a feasible alternative for detecting the extent and location of infarcted myocardium.[10] Moreover, the detection of hypointense infarct cores (ICs) on T1 imaging is a potential alternative for the evaluation of microvascular obstruction (MVO) and intramural hematoma. In a 1.5-T CMR cohort study, ICs were observed in 56% of patients, and low T1 values within the ICs were independently associated with adverse LV remodeling and heart failure occurrence.[11]

Only a few clinical cohort studies have been conducted with non-contrast T1 mapping technique and 3.0-T CMR. Additionally, the relationship between LVRR and T1 hypointense ICs on native T1 mapping has been rarely reported.[12–18] The primary aim of our study was to use 3.0-T CMR to evaluate the relationship of ICs to LV remodeling during the 1-year follow-up of patients with reperfused AMI. The secondary aims were to identify factors correlating with ICs (e.g., patient background, PCI procedure, and other CMR findings) and to clarify which marker is most predictive for chronic LVRR.

Methods

Study Population

This single-center, prospective, observational cohort study was conducted at the Department of Cardiovascular Medicine of Nara Prefecture Seiwa Medical Center. A total of 189 patients with AMI who underwent emergency PCI from September 2015 to February 2019 were screened for the inclusion and exclusion criteria. The inclusion criteria were: (1) diagnosed with AMI, defined as ischemic symptoms lasting ≥30 min with ST-segment elevation or depression (≥1 mm), elevated cardiac troponin I levels (≥0.1 ng/mL), and an onset-to-admission time <24 h; (2) underwent emergency PCI; and (3) underwent CMR within 14 days of AMI onset. The exclusion criteria were: (1) unable or unwilling to consent or commit to follow-up requirements; (2) standard contraindications to contrast agents or magnetic resonance imaging; and (3) history of MI. Finally, 109 patients were included in the baseline cohort, subdivided into those with and without ICs, and their background and CMR findings were compared. Of them, 14 patients did not undergo the 12-month follow-up CMR, and 1 patient had rapid progression of aortic valve stenosis; thus, 94 patients were eventually evaluated for chronic LV remodeling (**Figure 1**). The PCI procedure, such as aspiration thrombectomy, direct stenting, and pre- or post-dilatations, was chosen at the physician's discretion. The definitions of the clinical data are summarized in **Supplementary Methods 1**.

This study was approved by the Ethics Committee of Nara Prefecture Seiwa Medical Center (approval no. 58) and conducted following the standards outlined in the Declaration of Helsinki. Before commencing the baseline

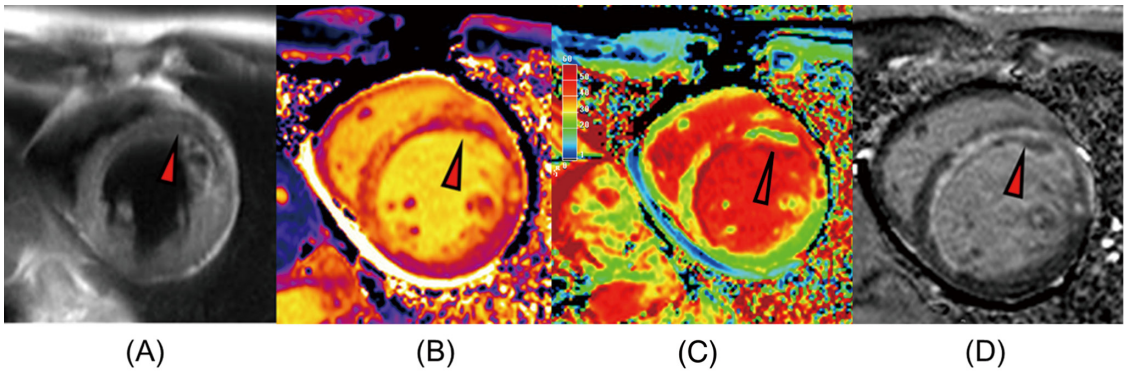

Figure 2. Representative CMR images of T1 hypointense infarct core in patients with reperfused AMI. (**A**) T2-weighted image: microvascular injury appears as a hypointense band at the anterior endomyocardium (arrowhead), but the border separating the infarcted area and normal myocardium is unclear. (**B**) Native T1 mapping: T1 hypointense infarct core is clearly visualized within the infarcted lesion (arrowhead). Native T1 mapping acquired using non-contrast imaging calculated by the modified Look-Locker inversion recovery protocol. (**C**) Extracellular volume mapping: microvascular injury appears as a hypointense area within the anterior myocardium (arrowhead). Image reconstructed using native and contrast-enhanced T1 mapping adjusted for the hematocrit. (**D**) Late gadolinium enhancement image: microvascular obstruction is detected as a low-intensity area within the enhanced myocardial tissue (arrowhead). AMI, acute myocardial infarction; CMR, cardiac magnetic resonance imaging.

CMR study, all participants provided written informed consent according to the study protocol.

Image Acquisition

Baseline CMR was performed using a 3.0-T scanner (MAGNETOM Skyra, Siemens, Erlangen, Germany) with an 18-element phased-array cardiac surface coil around 6 days after the primary PCI. The CMR protocol, details of dark blood-T2 weighted short tau inversion recovery (STIR), native T1 mapping, extracellular volume (ECV) mapping, cine imaging, and late gadolinium enhancement (LGE) images acquired for the analysis are provided in the **Supplementary Methods 2** and **Figure 2**.

Image Analysis

All images were analyzed using CVI42 software (Circle Cardiovascular Imaging, Calgary, Canada). The decision on the presence or absence of ICs was made by agreement of 2 cardiologists (Y.H. and S.O. with over 6 and 15 years of CMR experience, respectively) who were blinded to the patients' data. The reproducibility of the result for the presence of ICs was investigated for 30 randomly selected subjects from among the present cases. To calculate the intra-assay variation, a cardiologist (Y.H.) evaluated them again following a period of time from the initial analysis, and to calculate the inter-assay variation another cardiologist (A.S.) with 10 years' experience with CMR evaluated the presence and absence of ICs independently. The intra- and interobserver variabilities for the detection of ICs were excellent; Kappa value: 0.932, P<0.0001; McNemar-Bowker analysis: P=0.317, and Kappa value: 0.798, P<0.0001; McNemar-Bowker analysis: P=0.564, respectively.

The LV EDV, ESV, ejection fraction (EF), and mass were measured using cine images in the short-axis view. Adverse LV remodeling was defined as an increase in the EDV index ≥20% at follow-up from baseline. LVRR was defined as a decrease in the ESV index ≥15% at follow-up from baseline.[19]

T1 mapping was performed with breath-hold acquisitions and motion correction. The endocardial and epicardial borders were drawn manually. The myocardial area at risk (AAR) was defined as the region with T1 values >2 standard deviations (SDs) of the normal myocardium, that is, 1,186±24 ms in the mid-LV septal wall. This value was determined using data from 28 healthy volunteers without coronary risk factors, as per international consensus-based recommendations (19 men; median age, 47 [30–75] years). The area of salvaged myocardium was calculated by subtracting the area of infarcted myocardium from the AAR. The infarcted myocardium was defined as the region of contrast-enhanced myocardium with a signal intensity >5 SDs of that of the remote myocardium with good contractility on LGE images acquired 10–15 min after gadolinium injection. The infarcted myocardial area on native T1 mapping was matched using LGE, and its contours were subsequently copied and pasted to the native T1 mapping image while matching the slice positions. MVO was defined as the presence of a hypointense core within the infarcted myocardium on LGE images. Therefore, the MVO area was included in the infarcted myocardium. The calculated area and weight of each myocardial tissue were adjusted by body surface area and expressed in each index.

To identify ICs on native T1 mapping, we referred to the same slices of the T2-weighted STIR and LGE images, matching the lesion morphologies. The hypointense area within salvaged myocardium was excluded from ICs because it potentially represented residual viable myocardium. Infarcted myocardium was distinguished from ICs. To confirm the T1 value for each region of the myocardium, the region of interest was delineated meticulously with adequate margins to separate it from the adjacent myocardium, endocardium, and LV blood pool (**Supplementary Figure A**). The T1 values for each region of the myocardium with and without ICs are illustrated in **Supplementary Figure B**,**C**. Previous pathological studies have reported a correlation between high T1 values and intracellular or extracellular molecular alterations.[20–22] Our study showed that remote, edematous, and infarcted myocardium with

Table 1. Clinical Characteristics, PCI and CMR Findings of 109 Patients With Reperfused AMI With and Without ICs

	All patients (n=109)	With ICs (n=52)	Without ICs (n=57)	P value
Male	85 (78.0)	44 (84.6)	41 (71.9)	0.164
Age, years	65.1±12.2	63.8±1.7	66.3±1.6	0.196
Body mass index, kg/m²	24.4±3.8	24.77±0.52	24.12±0.50	0.245
Hypertension	64 (58.7)	28 (53.8)	36 (63.2)	0.338
Diabetes mellitus	28 (25.7)	15 (28.8)	13 (22.8)	0.516
Dyslipidemia	79 (72.5)	39 (75.0)	40 (70.2)	0.669
Current smoker	45 (41.3)	19 (36.5)	26 (45.6)	0.436
ST-elevation MI	100 (91.7)	51 (98.1)	49 (86.0)	0.033
Episodes of ischemic preconditioning	45 (41.3)	14 (26.9)	31 (54.4)	0.006
Statin therapy before admission	11 (10.3)	3 (5.9)	8 (14.3)	0.208
Antiplatelet loading before PCI	99 (90.8)	47 (90.4)	52 (91.2)	0.879
Laboratory tests				
Hct, %	36.5±4.9	36.3±0.68	36.7±0.65	0.730
Serum creatinine on admission, mg/dL	0.86±0.19	0.87±0.03	0.85±0.03	0.707
LDL-C on admission, mg/dL	132.2±40.6	134.8±40.8	129.8±40.6	0.685
L/H ratio	3.0±1.2	3.02±0.17	2.94±0.17	0.847
WBC 48 h after PCI, /μL	10,925.7±2,913.1	11,698.1±3,126.3	10,221.1±2,531.1	0.006
Monocytes, %	7.1 (5.7, 8.2)	6.8 (5.5, 8.2)	7.2 (5.9, 8.1)	0.430
CRP, mg/dL	5.6 (3.3, 8.7)	6.4 (3.5, 9.4)	4.8 (2.8, 8.1)	0.162
Peak CK, U/L	2,247 (1,157, 4,135)	4,134.5 (2,575.5, 5,522.5)	1,232 (695, 1,827)	<0.001
BNP on admission, pg/mL	29.7 (10.2, 79.2)	25.5 (10.1, 69.4)	33.9 (10.4, 83.0)	0.872
BNP at discharge, pg/mL	61.7 (37.3, 151.4)	108.9 (52.6, 200.4)	54 (30.5, 94.4)	<0.001
ECG ST resolution after primary PCI				
Complete resolution (>70%)	61 (61.0)	24 (47.1)	37 (75.5)	0.004
Medication at discharge				
Calperitide after primary PCI	70 (64.2)	37 (71.2)	33 (57.9)	0.166
Diuretics at discharge	19 (17.4)	16 (30.8)	3 (5.3)	<0.001
ACEI/ARB at discharge	107 (98.2)	52 (100.0)	55 (96.5)	0.496
Statin	103 (94.5)	47 (90.4)	56 (98.3)	0.101
SGLT2 inhibitor at discharge	4 (3.7)	4 (7.7)	0 (0)	0.046
β-blockers at discharge	89 (81.7)	47 (90.4)	42 (73.7)	0.028
Carvedilol equivalent at discharge, mg	5.27±3.63	5.66±3.69	4.82±3.55	0.207
Coronary angiography				
Culprit artery				0.117
LMT	2 (1.8)	1 (1.9)	1 (1.8)	
LAD	53 (48.6)	31 (59.6)	22 (38.6)	
LCX	9 (8.3)	2 (3.8)	7 (12.3)	
RCA	45 (41.3)	18 (34.6)	27 (47.4)	
No. of diseased arteries	1.73±0.80	1.83±0.83	1.65±0.77	0.264
LMT/LAD in culprit artery	55 (50.5)	32 (61.5)	23 (40.4)	0.035
Initial TIMI flow grade ≥2	19 (17.4)	3 (5.8)	16 (28.1)	0.002
Initial Rentrop grade 0	69 (63.3)	32 (61.5)	37 (64.9)	0.843
Final TIMI flow grade ≤2	22 (20.2)	17 (32.7)	5 (8.8)	0.004
Blush grade ≤1	8 (7.3)	7 (13.5)	1 (1.8)	0.026
Forrester classification				0.008
I	86 (78.9)	34 (65.4)	52 (91.2)	
II	19 (17.4)	14 (26.9)	5 (8.8)	
III	1 (0.9)	1 (1.9)	0	
IV	3 (2.8)	3 (5.8)	0	
Killip class 2–4	10 (9.2)	9 (17.3)	1 (1.8)	0.006

(**Table 1** continued the next page.)

	All patients (n=109)	With ICs (n=52)	Without ICs (n=57)	P value
PCI procedure				
Onset to balloon time, min	197.5 (137.3, 311.8)	177.5 (129.8, 267.8)	215.5 (143.8, 351.8)	0.168
Thrombectomy	81 (74.3)	46 (88.5)	35 (61.4)	0.002
Distal protection	9 (8.3)	6 (11.5)	3 (5.3)	0.305
Post-balloon dilatation	57 (52.3)	25 (48.1)	32 (56.1)	0.446
Post-balloon dilatation, mm	3.14±0.53	3.11±0.56	3.17±0.51	0.626
Stentless PCI	7 (6.4)	4 (7.7)	3 (5.3)	0.707
Stent diameter, mm	3.16±0.46	3.19±0.43	3.14±0.49	0.675
Stent length, mm	21.3±7.4	22.3±8.7	20.4±5.9	0.366
IABP	33 (30.3)	20 (38.5)	13 (22.8)	0.096
Duration of hospitalization, days	14.0 (11.0, 16.0)	15.5 (13.0, 18.0)	13.0 (10.5, 15)	<0.001
CMR LV/RV functional findings at baseline				
LVEF, %	51.7±12.5	46.4±12.2	56.5±10.8	<0.001
LV end-diastolic volume index, mL/m^2	67.0±19.1	73.2±18.1	61.3±18.4	0.001
LV end-systolic volume index, mL/m^2	33.4±15.4	40.0±15.0	27.4±13.3	<0.001
LV mass index, g/m^2	69.3±13.0	71.9±13.1	66.9±71.9	0.022
T1/ECV mapping and other CMR findings at baseline				
Baseline native T1 values in remote myocardium, ms	1,169.9±39.7	1,189.6±33.4	1,151.9±33.4	<0.001
Baseline native T1 value in edematous myocardium, ms	1,321.8±56.3	1,338.9±45.8	1,306.2±60.68	0.006
Baseline native T1 value in infarcted myocardium, ms	1,499.7±66.3	1,498.6±66.3	1,500.7±66.8	0.660
Baseline ECV value in remote myocardium, %	26.96±2.87	27.74±2.84	26.24±2.72	0.005
Microvascular obstruction	51 (46.8)	51 (98.1)	0 (0)	<0.001
ECV value in remote myocardium, %	26.96±2.87	27.74±2.84	26.24±2.72	0.005
ECV value in edematous myocardium, %	34.65±4.45	35.6±4.2	33.8±4.5	0.085
ECV value in infarcted myocardium, %	49.05±9.97	51.0±9.0	47.3±10.5	0.048
AAR index, mm^2/g/m^2	20.15±9.34	25.0±9.2	16.4±7.4	<0.001
MSA index, mm^2/g/m^2	8.93±6.78	7.7±4.8	10.7±6.4	0.013
Myocardial salvage index, %	47.5±24.2	30.7±16.3	62.9±19.5	<0.001
Transmural extent of LGE >75%	73 (67.0)	52 (100)	21 (36.8)	<0.001
Infarct index, mm^2/g/m^2	9.66 (4.35, 16.46)	16.46 (12.10, 22.57)	4.95 (3.02, 7.98)	<0.001

Missing data: time from symptom onset to reperfusion, n=5; HbA1c, n=5; LDL-C on admission and LDL-C/HDL-C ratio, n=2; monocyte, n=10; BNP at discharge, n=2; high-potency statin before admission, n=2. Data are mean±SD, median (interquartile range), or n (%). β-blockers included carvedilol or bisoprolol, and the doses of bisoprolol were considered to be equivalent to 4-fold of the doses of carvedilol. Diseased artery was defined as the coronary artery with stenosis >50%. % area of infarct or salvaged myocardium was calculated by the infarct area or MSA (mm^2) divided by the total myocardial mass (g)×100 (%). Myocardial salvage index was calculated by the MSA divided by the AAR×100 (%). AAR, area at risk; ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CK, creatine kinase; CMR, cardiac magnetic resonance imaging; CRP, C-reactive protein; ECG, electrocardiogram; ECV, extracellular volume; Hct, hematocrit; IABP, intra-aortic balloon pumping; ICs, infarct cores; LGE, late gadolinium enhancement; L/H, low-density lipoprotein/high-density lipoprotein; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density-lipoprotein cholesterol; LMT, left main trunk; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MSA, myocardial salvage area; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell count.

and without ICs could be distinguished using native T1 values (median: 1,197 vs. 1,336 vs. 1,490 ms, respectively, in patients with ICs and median: 1,156 vs. 1,321 vs. 1,495 ms, respectively, in those without ICs). In contrast, we found no difference in T1 values between ICs and remote myocardium with ICs.

Statistical Analysis

Continuous variables are expressed as mean±SD and median (25th–75th percentile) for normally and non-normally distributed data, respectively. Categorical data are presented as absolute numbers and percentages. The Wilcoxon rank-sum and chi-square tests were used to compare variables between patients with and without ICs, and patients with and without LVRR. The statistical analysis of T1 values between the remote myocardium of patients with AMI with and without ICs and normal myocardium of healthy volunteers was adjusted for age. Univariate and multivariate logistic regression analyses were performed for covariables with $P<0.05$ in the comparative analyses, to identify factors associated with the occurrence of ICs and LVRR. The forward stepwise selection method was adopted for multivariate logistic regression analysis using appropriate candidate factors (that were previously reported) with $P<0.05$ in the univariate logistic regression analysis.[12–18] Receiver-operating characteristic (ROC) curves were drawn to determine the peak threshold creatine kinase (CK) value predictive of ICs. The intra- and interobserver

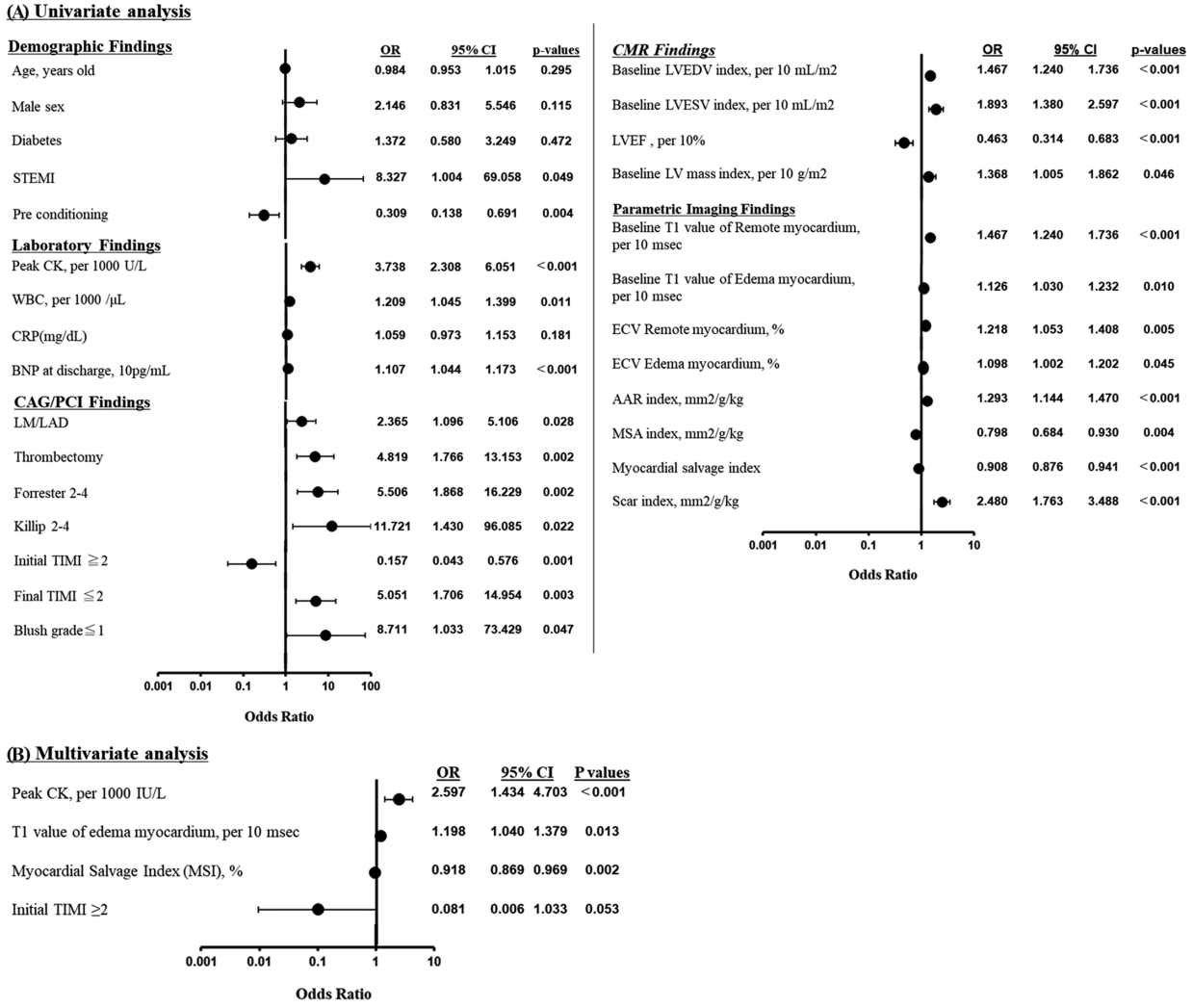

Figure 3. Logistic regression analyses for IC prediction in 109 patients with reperfused AMI. (**A**) Univariate analysis; (**B**) multivariate analysis. Data are presented as P values and odds ratios (ORs) with 95% confidence intervals (CI). Multivariate analysis was performed by forward stepwise logistic regression analysis with the following covariates: age, male sex, diabetes, and serum C-reactive protein (CRP) level (as reported in a previous study[12–18]), as well as 24 covariates with P<0.05 in the univariate analysis to predict the presence of ICs. The stopping criterion was adopted at P=0.10. Finally, the peak creatine kinase (CK) level after reperfusion therapy, initial TIMI flow grade >2, T1 value of myocardial edema, and MSI were selected as input covariates for multivariate analysis. AAR, area at risk; AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance imaging; CRP, C-reactive protein; ECV, extracellular volume; IC, infarct core; LVEF, left ventricular ejection fraction; LVEDSV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; MSA, myocardial salvage area; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell count.

variabilities for the detection of IC were assessed by Kappa Coefficient and McNemar-Bowker test.

All statistical analyses were performed using JMP® version 13.0.0 (SAS Institute Inc., Cary, NC, USA). P<0.05 was considered statistically significant.

Results

Clinical Characteristics and PCI Procedures of Patients With and Without ICs

The clinical characteristics, PCI findings, and CMR findings at baseline of the 109 patients with reperfused AMI and at follow-up of the 94 patients are shown in **Table 1** and the **Supplementary Table**. Baseline CMR findings revealed ICs in 52 (47.7%) patients with reperfused AMI. Of these, LGE images revealed MVO in 51 (98.1%) patients. Patients with ICs had a lower incidence of non-ST-segment elevation MI (non-STEMI) and fewer episodes of ischemic preconditioning (P=0.033 and P=0.006, respectively), as well as significantly higher peak CK values, white blood cell counts, and B-type natriuretic peptide (BNP) levels at discharge (P<0.001, P=0.006, and P<0.001, respectively), compared with those without ICs. Patients with ICs had a lower incidence of non-left main trunk (LMT)/left anterior descending artery (LAD) lesions in the culprit artery (P=0.035), initial TIMI flow grade ≥2 (P=0.002), final TIMI flow

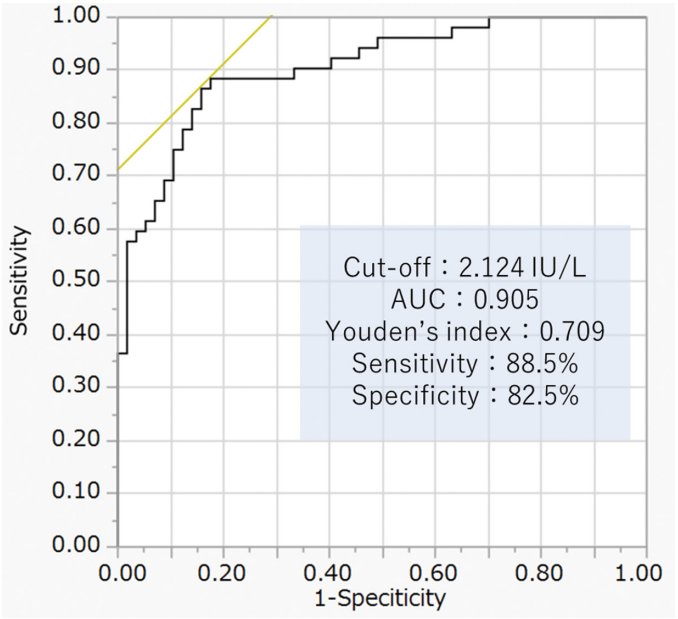

Figure 4. ROC curves for predicting the presence of ICs with peak creatinine kinase after primary percutaneous coronary intervention plotted for the 109 patients with reperfused AMI. The optimal cutoff value of peak creatine kinase for predicting the presence of ICs was 2,124 U/L with a sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index of 88.5%, 82.5%, 83.5%, 87.8%, and 0.709, respectively. The area under the curve (AUC) was 0.905. AMI, acute myocardial infarction; IC, infarct core; ROC, receiver-operating characteristic.

grade 3 (P=0.004), poor blush grade score (P=0.026), Forrester class 1 (P=0.008), and Killip class 1 (P=0.006), compared with those without ICs. Thrombectomy was more commonly performed in patients with ICs (P=0.002). There was no remarkable difference in the backgrounds of the patients at baseline and at follow up.

CMR Findings of Patients With and Without ICs

The CMR findings are shown in **Table 1**. Patients with ICs had significantly larger LV volumes and lower LVEFs than those without ICs (P<0.001 and P<0.001, respectively). Moreover, there was a higher incidence of a transmural extent of LGE >75% (P<0.001), a higher percentage of infarcted myocardium and myocardial AAR (P<0.001 and P<0.001, respectively), and a smaller percentage of salvaged myocardium and myocardial salvage index (MSI) (P=0.013 and P<0.001, respectively) in patients with ICs than in those without ICs. Native T1 values and ECV in the remote myocardium were higher in patients with ICs than in those without ICs at baseline (P<0.001 and P=0.017, respectively), akin to ECV at follow-up CMR (P<0.001) (**Supplementary Table**).

Predictors of ICs

The absence of ischemic preconditioning, STEMI, LMT/LAD lesions, thrombectomy, poor initial and final TIMI flow grades, higher peak CK values, and high Forrester class were positively correlated with the presence of ICs in the univariate logistic analysis (**Figure 3**). We performed forward stepwise selection to determine candidate factors for multivariate analysis to predict the presence of ICs using 29 covariates. Of these, 24 covariates showed P<0.05 in the univariate analysis, and 5 covariates (age, sex, C-reactive protein level, blood glucose level on admission, and diabetes) were added, as they were reportedly relevant to adverse clinical outcomes and MVO. Finally, 3 variables (peak CK level, T1 value of myocardial edema, and MSI) were independently correlated with ICs among patients with reperfused AMI in the multivariate analysis (odds ratio [OR]: 2.597, 95% confidence interval [CI]: 1.434–4.703, P<0.001; OR: 1.198, 95% CI: 1.040–1.379, P=0.013; and OR: 0.918, 95% CI: 0.869–0.969, P=0.002, respectively). ROC curve analysis to predict IC occurrence suggested that peak CK >2,124 U/L after reperfusion therapy can be used to stratify patients without ICs (area under the curve, 0.905). The sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index were 0.885, 0.825, 0.835, 0.878, and 0.709, respectively (**Figure 4**).

Chronic Cardiac Remodeling in Patients With Reperfused AMI

Among the 94 patients who underwent 12-month follow-up CMR, LV adverse and reverse remodeling were observed in 14 (14.9%) and 49 (52.1%) patients, respectively. Their characteristics and PCI procedures are shown in **Table 2**. Episodes of ischemic preconditioning and the administration of a high-potency statin before admission were more common in patients with LVRR than in those without LVRR (P=0.038 and P=0.027, respectively). The peak CK level was significantly lower and the Killip class was significantly better in patients with reverse remodeling than in those without reverse remodeling (P=0.003 and P=0.026, respectively). The use of diuretics at discharge was lower in patients with reverse remodeling than in those without reverse remodeling (P=0.010). Among 24 patients with diabetes, dipeptidyl peptidase-4 inhibitors were more commonly administered in patients with reverse remodeling than in those without reverse remodeling (P=0.019). Patients with reverse remodeling had a lower incidence of LMT/LAD lesions in the culprit artery, blush grade ≤1, and Killip class ≥2 than those without remodeling (P=0.042, P=0.022, and P=0.026, respectively).

CMR Findings of Patients With and Without LVRR

Patients with LVRR showed significantly lower incidences of ICs, MVO, and transmural extent of LGE >75%, as well

as a lower infarct index and higher MSI at baseline, than those without remodeling (P<0.001, P<0.001, P=0.009, P=0.002, and P=0.015, respectively). Additionally, significant improvements in both LV and right ventricular function and size were observed in patients with LVRR compared with those without remodeling. Patients with LVRR showed a significantly lower follow-up ECV in myocardial edema (P=0.002); of the 14 patients (14.9%) with adverse LV remodeling, none had LVRR (**Table 2**).

ICs and LVRR

Previous episodes of ischemic preconditioning, peak CK values, peak monocyte counts, BNP level at discharge, LMT/LAD lesions, thrombectomy, Killip class, administration of diuretics, the presence of ICs, LGE transmurality, MSI, and the percent area of infarcted myocardium were significantly related to chronic LVRR in the univariate analysis (**Figure 5**). We performed forward stepwise selection to determine candidate factors for the multivariate analysis to predict LVRR using 17 covariates. Of these, 13 covariates had P<0.05 in the univariate analysis, to which we added 4 covariates (age, sex, initial TIMI coronary flow, and T1 value in edematous myocardium) because they were reportedly relevant to adverse clinical outcomes. The latter 2 strongly correlated with the occurrence of ICs in this study. Consequently, multivariate logistic regression analysis revealed that the presence of ICs and LMT or LAD lesions were independent negative predictors of LVRR (OR: 0.180, 95% CI: 0.040–0.770, P<0.001; and OR: 0.311, 95% CI: 0.104–0.923, P=0.035, respectively), and the peak monocyte count within 48 h after reperfusion was an independent positive predictor (OR: 1.352, 95% CI: 1.025–1.784, P=0.033).

Table 2. Clinical Characteristics, PCI and CMR Findings of 94 Patients With and Without LVRR at Baseline and 12-Month Follow-up

	Follow-up (n=94)	With LVRR (n=49)	Without LVRR (n=45)	P value
Male	77 (81.9)	37 (75.5)	40 (88.9)	0.113
Age, years	65.4±10.8	64.8±1.5	66.1±1.6	0.736
Body mass index, kg/m²	24.4±3.5	24.7±0.5	24.1±3.8	0.520
Hypertension	54 (57.4)	30 (61.2)	24 (53.3)	0.532
Diabetes mellitus	24 (25.5)	16 (32.7)	8 (17.8)	0.155
Dyslipidemia	70 (74.5)	37 (75.5)	33 (73.3)	0.818
Current smoker	38 (40.4)	24 (49.0)	15 (36.8)	0.095
ST-elevation MI	86 (91.5)	44 (51.2)	42 (48.8)	0.716
Episodes of ischemic preconditioning	40 (42.6)	26 (65.0)	14 (35.0)	0.038
Statin before admission	6 (6.5)	6 (12.5)	0 (0)	0.027
Antiplatelet loading before PCI	85 (90.4)	46 (93.9)	39 (86.7)	0.303
Laboratory findings				
Hematocrit, %	36.7±5.0	36.8±4.6	36.5±5.4	0.803
Serum creatinine, mg/dL	0.87±0.20	0.84±0.17	0.91±0.22	0.110
Blood glucose level on admission, mg/dL	141 (119, 178)	144 (118, 186)	141 (124, 172)	0.835
HbA1c, %	6.2±1.1	6.4±1.2	6.0±1.0	0.373
LDL-C on admission, mg/dL	132.0±41.2	133.0±42.4	131.0±39.9	0.941
Peak WBC within 48 h after PCI, /μL	10,918.1±2,556.4	10,702.0±2,682.9	11,153.3±2,410.8	0.172
Monocytes, %	7.1 (5.8, 8.2)	7.6 (5.9, 8.4)	6.3 (5.6, 7.7)	0.057
CRP, mg/dL	5.7 (3.4, 8.6)	5.8 (3.1, 9.9)	5.6 (3.5, 7.9)	0.714
Peak CK, U/L	2,186 (1,129, 4,134)	1,589 (912, 2,874)	2,978 (1,536, 4,931)	0.003
BNP on admission, pg/mL	25.6 (10.1, 80.1)	33.3 (10.2, 83.7)	25.4 (9.3, 74.1)	0.575
BNP at discharge, pg/mL	58.1 (36.2, 127.3)	54.8 (37.1, 85.3)	61.1 (33.6, 199.4)	0.190
BNP at follow-up, pg/mL	29.4 (16.1, 56.5)	25.2 (14.7, 42.4)	44.2 (17.4, 74.1)	0.006
ECG ST resolution after primary PCI				
Complete resolution (>70%)	54 (62.8)	29 (65.9)	25 (59.5)	0.540
Medications following primary PCI				
Statins after primary PCI	88 (93.6)	48 (98.0)	40 (88.9)	0.101
β-blockers	78 (83.0)	40 (81.6)	38 (84.4)	0.788
Equivalent doses with carvedilol, mg				
At discharge	5.26±3.73	5.41±3.72	5.10±3.75	0.601
At follow-up	6.89±4.90	7.25±5.17	6.51±4.60	0.529
Carperitide after primary PCI	61 (64.9)	28 (57.1)	33 (73.3)	0.131
Loop diuretics at discharge	15 (16.0)	3 (6.1)	12 (26.7)	0.010
ACEI/ARB at discharge	94 (100)	49 (100)	45 (100)	1.000
SGLT2 inhibitor at discharge	3 (3.2)	2 (4.1)	1 (2.2)	1.000
Duration of hospitalization, days	14 (11, 16)	13 (11, 15)	15 (12, 17)	0.060

(**Table 2** continued the next page.)

	Follow-up (n=94)	With LVRR (n=49)	Without LVRR (n=45)	P value
Angiographic findings				
LMT/LAD of culprit artery	48 (51.1)	20 (41.7)	28 (58.3)	0.042
Number of diseased arteries	1.7±0.8	1.67±0.11	1.78±0.12	0.715
Initial TIMI ≥2	18 (19.1)	12 (24.5)	6 (13.3)	0.198
Final TIMI ≤2	19 (20.2)	7 (14.3)	12 (26.7)	0.198
Blush grade ≤1	5 (5.3)	0 (0)	5 (11.1)	0.022
Initial Rentrop grade 0	59 (62.8)	29 (49.2)	30 (50.9)	0.524
LVEDP, mmHg	18.2±6.5	17.4±5.4	19.1±7.7	0.332
Forrester class >II	21 (22.3)	8 (16.3)	13 (28.9)	0.215
Killip class >2	8 (8.5)	1 (2.0)	7 (15.6)	0.026
PCI procedure				
Time from symptom onset to reperfusion, min	215 (142, 320)	215 (145, 345)	216 (131, 302)	0.580
Thrombectomy	70 (74.5)	32 (45.7)	38 (54.3)	0.057
Post-balloon dilatation	51 (54.3)	25 (51.0)	26 (57.8)	0.540
Post-balloon dilatation, mm	3.16±0.55	3.19±0.46	3.13±0.63	0.969
Stentless PCI	6 (6.4)	3 (50.0)	3 (50.0)	1.000
Distal protection	6 (6.4)	3 (6.1)	3 (6.7)	1.000
IABP	30 (31.9)	13 (26.5)	17 (37.8)	0.274
CMR LV/RV findings				
Baseline LVEF (%)	51.9±12.1	52.7±11.1	51.0±13.1	0.568
Baseline LV end-diastolic volume index, mL/m^2	66.7±19.2	68.3±17.0	64.9±21.4	0.515
Baseline LV end-systolic volume index, mL/m^2	32.9±14.7	32.5±12.6	33.4±16.6	0.997
Baseline LV mass index, g/m^2	69.2±12.9	68.4±13.4	70.0±12.4	0.429
Follow-up LVEF, %	55.90±12.20	62.26±9.53	48.97±14.57	<0.001
Follow-up LV end-diastolic volume index, mL/m^2	64.77±19.44	56.80±15.57	73.44±22.93	<0.001
Follow-up LV end-systolic volume index, mL/m^2	30.44±18.72	22.00±9.50	39.64±21.82	<0.001
Follow-up LV mass index, g/m^2	64.01±11.21	63.46±10.43	64.61±12.01	0.714
Adverse LV remodeling	14 (14.9)	0 (0)	14 (31.1)	<0.001
CMR T1/ECV mapping and other findings at baseline and follow-up				
Native T1 values at remote myocardium, ms	1,170.2±37.5	1,167.8±33.9	1,172.8±41.0	0.222
Native T1 value at myocardial edema, ms	1,500.6±67.0	1,498.8±69.4	1,502.6±64.2	0.759
Native T1 value at infarct myocardium, ms	1,319.5±56.8	1,317.5±56.1	1,321.7±57.6	0.596
Native T1 value at IC, ms	1,175.0 (1,075.8, 1,261.4)	1,179.1 (1,031.2, 1,269.1)	1,170.9 (1,031.2, 1,333.1)	0.961
Microvascular obstruction on LGE image	45 (47.9)	13 (26.5)	32 (71.1)	<0.001
Hypointense IC on native T1 map (IC)	46 (48.9)	13 (26.5)	33 (73.3)	<0.001
Baseline ECV value at remote myocardium, %	226.9±2.8	26.9±2.7	26.8±2.9	0.747
Baseline ECV value at myocardial edema, %	49.0±10.0	47.6±9.8	50.4±10.0	0.222
Baseline ECV value at infarct myocardium, %	34.5±4.7	34.5±4.8	34.6±4.5	0.985
Baseline AAR index, mm^2/g/m^2	20.3±9.1	18.5±8.3	22.3±9.9	0.061
Baseline MSA index, mm^2/g/m^2	9.0±5.9	9.5±6.3	8.4±5.4	0.489
Baseline myocardial salvage index, %	46.1±23.9	51.6±22.8	40.2±23.8	0.015
Baseline transmural extent of LGE >75%	62 (66.0)	26 (53.1)	36 (80.0)	0.009
Baseline infarct index, mm^2/g/m^2	10.2 (4.8, 16.8)	7.3 (4.0, 11.8)	12.6 (8.1, 19.6)	0.002
Follow-up ECV value in remote myocardium, %	26.12±3.74	25.46±3.27	26.71±4.11	0.375
Follow-up ECV value in myocardial edema, %	47.68±13.43	42.06±8.82	52.74±16.49	0.002
Follow-up ECV value in infarct myocardium, %	31.74±7.24	31.61±6.42	31.86±7.90	0.713

Missing data: body mass index, n=12; time from symptom onset to reperfusion, n=5; HbA1c, n=4; LDL-C on admission and LDL-C/HDL-C ratio, n=2; monocyte, n=9; BNP at discharge, n=1; Statins before admission, n=2. LV end-diastolic volume, n=17; baseline ECV data, n=1. LVRR, left ventricular reverse remodeling. Other abbreviations as in Table 1.

Discussion

We investigated the significance of hypointense ICs on non-contrast myocardial T1 mapping using 3.0-T CMR to predict the occurrence of chronic LV remodeling among patients with reperfused AMI. The main findings of this study were: (1) ICs detected in 47.7% of patients with reperfused AMI; (2) close association of the presence of ICs with AMI-related (e.g., peak CK level, Killip class, Forrester class, etc.) severity indices of LV damage, such

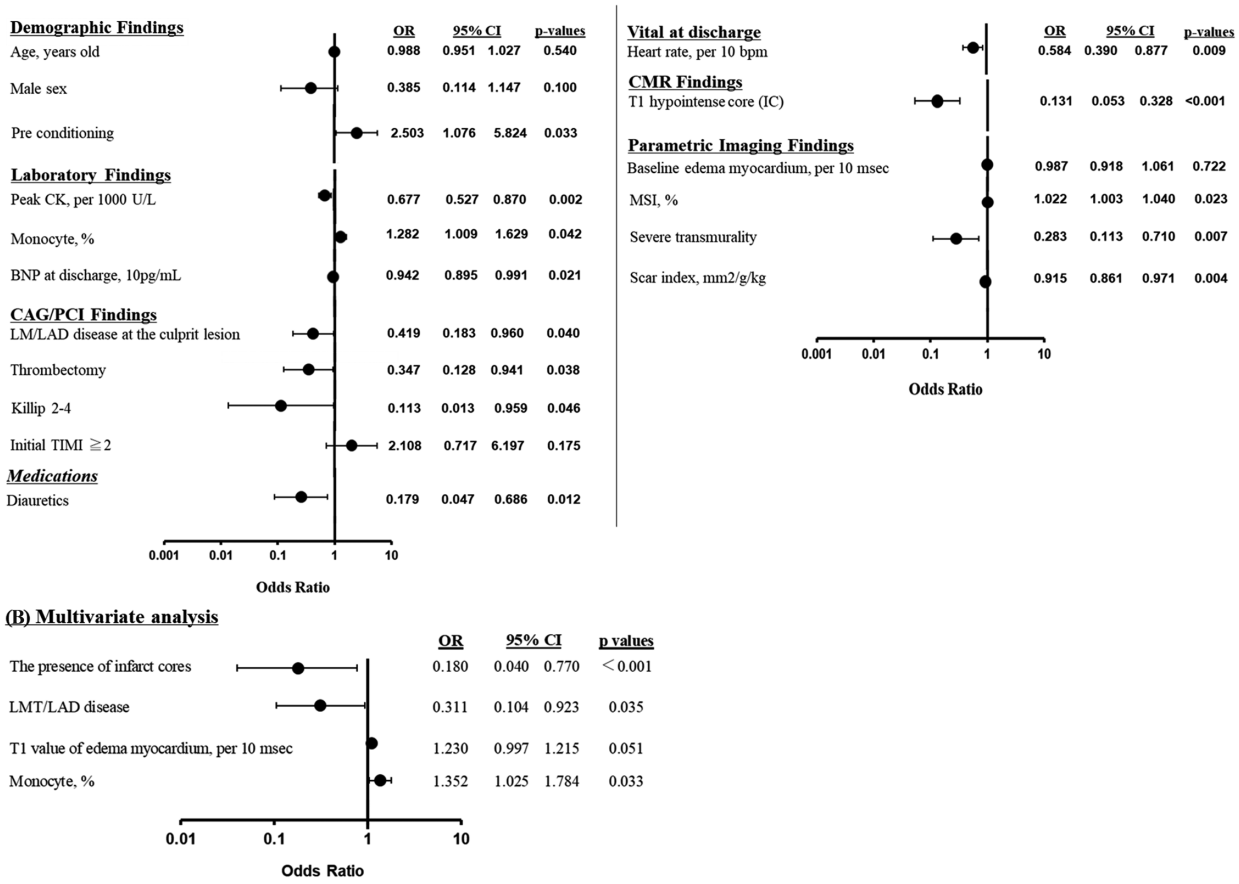

Figure 5. Logistic regression analyses to predict reverse left ventricular remodeling. (**A**) Univariate analysis; (**B**) multivariate analysis. Data are presented as in Figure 3. This multivariate analysis was performed by forward stepwise logistic regression analysis with the following covariates: age, male sex, 13 covariates with P<0.05 in the univariate analysis to predict reverse remodeling, and 2 covariates that were independent predictors of ICs (TIMI coronary flow and T1 value in edematous myocardium). The stopping criterion was adopted at P=0.10. Finally, left main trunk (LMT)/left anterior descending (LAD) artery disease at the culprit lesion, monocyte (%) after reperfusion therapy, the presence of infarct cores (ICs), and T1 value of myocardial edema were selected as input covariates for multivariate analysis. bpm, beats/min; BNP, B-type natriuretic peptide; CI, confidence interval; CK, creatine kinase; CMR, cardiac magnetic resonance imaging; MSI, myocardial salvage index; TIMI, Thrombolysis in Myocardial Infarction.

as exacerbation of acute LV function and dilatation; (3) a higher peak CK value, lower MSI, and higher T1 value at myocardial edema by native T1 mapping as independent predictors of ICs; and 4) the presence of ICs as the strongest independent negative predictor of chronic LVRR.

Detection and Significance of ICs

Our study demonstrated that ICs were detected using non-contrast T1 mapping in 47.7% of patients with reperfused AMI. T1 mapping has the following advantage: reduced patient breath-holding and scan times, resulting in a lower frequency of uninterpretable images compared with conventional analyses using T2* and spin-echo imaging.[14] All patients were analyzed by native T1 mapping; however, some patients who underwent T2-weighted or ECV imaging had uninterpretable images due to motion artifacts. Interestingly, the T1 values of ICs were more widely distributed, with a median of 1,181 ms (1,095–1,260 ms), than those of other myocardial tissues. Low T1 values in the widely distributed ICs may reflect the presence of hemorrhage within the MVO because iron deposits after myocardial hemorrhage shorten T1 values. Conversely, the higher water content due to inflammation prolongs T1 values.

Carrick et al[11] conducted a CMR study involving 267 patients with reperfused AMI using a 1.5-T scanner. They suggested that the lower the T1 value in the ICs, the higher the risk of adverse remodeling, all-cause death, or first hospitalization for heart failure post-discharge. They also implied that it was feasible to identify ICs using non-contrast T1 mapping; moreover, its prognostic value was comparable to that of MVO revealed via LGE imaging.[11] Notably, ICs detected by 3.0-T CMR native T1 mapping had better conformity with MVO detected by contrast-enhanced CMR images compared with ICs detected using 1.5-T CMR. Our 3.0-T CMR had better sensitivity, specificity, and accuracy than 1.5-T CMR in MVO detection (sensitivity: 0.981 vs. 0.856; specificity: 1.000 vs. 0.938; accuracy: 0.991 vs. 0.892).

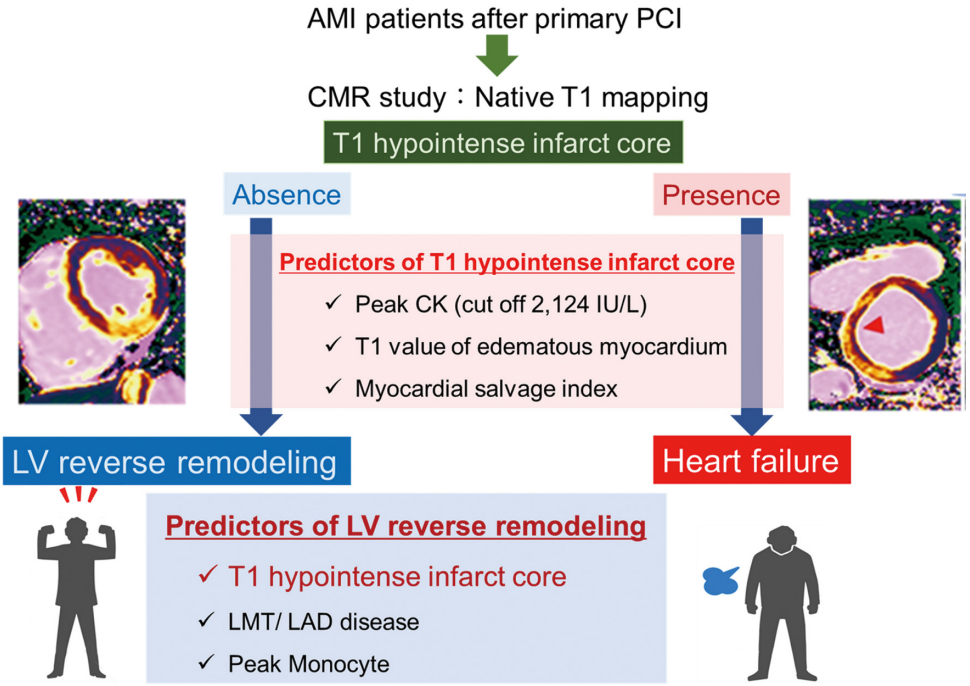

Figure 6. Predictive potential of T1 hypointense infarct cores (ICs). It was the strongest negative predictor for LV reverse remodeling at the 12-month follow-up. CK, creatine kinase; left main trunk (LMT)/left anterior descending (LAD) artery disease.

In this study, patients with ICs had higher peak CK levels and smaller areas of salvaged myocardium. The presence of ICs reflected more severe AMI, even after primary PCI. As a result, patients with ICs showed lower EFs, larger LV dilatations, and higher BNP levels at discharge, as well as a lower incidence of chronic LVRR than those without ICs. The early detection of ICs is essential to stratify patients with poor prognoses.

T1 Hypointense ICs and MVO

In our study using 3.0-T CMR, MVO was detected in 47.2% of patients with reperfused AMI, and 98.1% of patients with T1 hypointense ICs had MVO. A previous study using 1.5-T CMR showed that 145 (50.3%) of 288 patients with reperfused AMI had MVO, and 137 (85.6%) of 160 patients with ICs had MVO.[11] Our study showed a better concordance between IC and MVO occurrence, probably because of the higher resolution of 3.0-T CMR on T1 mapping and the timing of CMR.

MVO size and hemorrhage quantity markedly change over time after reperfusion. Fernandez et al reported that the quantity of myocardial hemorrhage increased from day 4 to day 7.[23] In the study by Carrick et al,[11] CMR images were obtained 2 days after reperfusion therapy; thus, MVO size and myocardial hemorrhage quantity might have been underestimated in their results.

ICs and LVRR

It is essential to predict the occurrence of chronic LVRR because reverse remodeling correlates with favorable long-term clinical outcomes in patients with AMI.[24] In our study, several discriminators were discovered that predict such occurrence in patients with reperfused AMI. Among them, the presence of ICs was the strongest negative predictor for LVRR at the 12-month follow-up. In addition, patients without ICs showed smaller infarct sizes and larger areas of salvaged myocardium after reperfusion therapy. Therefore, LV dysfunction and LV enlargement rarely occurred during the follow-up of patients without ICs. Conversely, we found that the peak CK level, which is a well-established predictor of death and myocardial recovery,[25] was not a predictor of LVRR. One possible reason is that elevated CK levels ordinarily reflect the spread and extent of "damaged" myocardium but not necessarily the extent of severe transmural infarction or the presence of microvascular injury. Using contrast-enhanced CMR, we demonstrated that patients with chronic LVRR had less transmural myocardial damage and MVO. Therefore, the simple, objective and noninvasive detection of ICs via native T1 mapping may help predict the improvement of acute LV dysfunction and enlargement in the chronic phase of AMI for all patients with reperfused AMI, including those with renal dysfunction and contrast allergy (**Figure 6**).

ICs and Clinical Outcomes

The association between ICs and clinical adverse events in this cohort may not show in this study because the number of patients with major adverse clinical outcomes, which are a composite of cardiac death, MI, and unplanned rehospitalization for heart failure, was extremely small (n=3, 3.2% in patients with ICs vs. none in those without), though there was a worse trend of the incidence of major adverse clinical outcomes in patients with ICs in the Kaplan-Meier curve statistically analyzed by the log rank test (P=0.07).

Study Limitations

Our study had several limitations. First, it was a prospective cohort single-center study with a small sample size, so several analyses might have been statistically underpowered. The incidence of clinical adverse events could not be discussed in this report due to the small number of cases. Second, the strategies for PCI and medication administration after coronary reperfusion depended on the physician. Third, although native T1 mapping was assessed without contrast enhancement, the infarcted area, salvaged area, AAR, and ECV map were evaluated using contrast-enhanced CMR. Thus, patients with renal dysfunction were excluded and such patients may show different results.

Conclusions

Non-contrast T1 mapping detected hypointense ICs in 47.7% of patients with reperfused AMI, and the presence of T1 hypointense ICs was the most valuable predictor of LVRR after 12 months of follow-up.

Acknowledgments

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Conflicts of Interest / Funding

None.

IRB Information

The Ethics Committee of Nara Prefecture Seiwa Medical Center (approval no. 58).

Data Availability

✓ The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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