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Original Article

Quantification of Myocardial Injury and Evaluation of Viability by Cardiac MRI in Acute Myocardial Infarction

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SUMMARY

Background: Late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) is a standard for imaging of myocardial infarction (MI). However, it has been reported the usefulness of quantification of the T1 relaxation time for the characterization of old MI. Our aim is to quantitatively assess myocardial injury and viability without contrast mediums in acute MI.
Methods: Twenty patients with acute MI underwent CMR within 1 month after reperfusion therapy. We assessed the native and post-contrast T1 mappings, native T2 mappings, and LGE in cross section. MIs were classified as "transmural" (> 75% of the area was transmural) and "non-transmural" (< 75% of the area was transmural). Transmural MIs were further classified into endocardial or epicardial types, while non-transmural MIs were classified into infarcted, salvaged, and remote. We defined 50% on the epicardial side of the region with high T2-weighted imaging as epicardial 50% area.
Result: In non-transmural MI, the native T1 and T2 values of the infarcted and salvaged areas were higher than the remote area. Additionally, native T1 value of the infarcted area was higher than the salvaged area. However, there was no significant difference between transmural MI types for any variables. Last, native T1 value of the epicardial 50% area was significantly prolonged in transmural MI than in non-transmural MI.
Conclusion: Native T1 value is useful for myocardial injury evaluation. Furthermore, transmural and non-transmural MI could be detected by T1 mapping of epicardial 50% areas without contrast mediums in the acute phase of MI.

1. Introduction

The distinction between reversible and irreversible myocardial injury is important in the pathophysiology of coronary artery disease. Cardiac magnetic resonance (CMR) visualizes myocardial necrotic and fibrotic areas, while late gadolinium enhancement (LGE) provides high spatial resolution and tissue contrast with chronic myocardial infarction (MI). Specifically, using LGE in the acute phase (4 to 12 wk after onset) helps predict myocardial survival rates in patients with acute MI (AMI); though, if the MI has more than 75% enhancement, no improvement in wall motion is expected.[1] In addition, T2-weighted imaging (T2WI) in CMR is useful for evaluating the area at risk of post-reperfusion, and can discriminate between acute and chronic Mis.[2] T2WI reveals the presence of myocardial edema within 30 min after the onset of ischemia, and the absence of LGE suggests reversible myocardial injury.[3,4] Therefore, LGE and T2WI-CMR are used as complementary techniques to assess irreversible and reversible injuries, salvageable area at risk, and scar burden in AMI.[5] In AMI, edema that is recognized with T2WI has been reported to continue up to 1 mo after its onset.[6] CMR is mainly a qualitative (visual) evaluation; however, it has become possible to quantitatively evaluate myocardial injury using mapping in order to quantify the T1 and T2 relaxation times. For patients with AMI, the T1 and T2 relaxation times provide quantitative evaluation of myocardial injury.[7,8]

The aims of this study were to quantitatively evaluate the myocardial injury in patients with AMI using T1 and T2 mapping, and to test the hypothesis that native T1 and T2 values are different in the myocardium of infarcted, salvaged, and remote areas of patients with AMI. Providing evidence for this hypothesis would enable the evaluation of myocardial viability without contrast media. We further hypothesized that the viability of the myocardium can be predicted by measuring the native T1 value of the epicardial areas.

2. Methods

2.1. Protocol

Among the patients with AMI who visited our hospital between October 2015 and February 2017, those who underwent urgent revascularization were included. MI was defined and managed according to the current guidelines. Exclusion criteria were as follows: 1) hemodynamic instability, 2) significant arrhythmias, 3) congenital heart disease, 4) previous coronary bypass surgery, 5) LGE patterns

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of myocarditis, and 6) standard CMR contraindications. We identified 42 underwent urgent revascularization patients, and 22 patients excluded. As a result, 20 patients (mean age: 66.6 ± 11 y) were deemed eligible and were prospectively registered. The patients underwent CMR with pre- and post-contrast T1 mapping, native T2 mapping, and LGE in cross section within 1 mo after the reperfusion therapy. We also observed T2WI as an index of myocardial edema. Patient characteristics are described in Table 1. The timing of magnetic resonance imaging (MRI) was determined by the attending physician (mean duration: 11.5 ± 5.4 d). Patients signed written informed consent before participation in the study. The procedures for informed consent and enrollment were in accordance with the detailed regulations that were approved by the Institutional Review Board at Saiseikai Matsuyama Hospital.

2.2. CMR sequences

CMR imaging was performed using 3T (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany) with an 18-element surface coil. After the acquisition of scout images, dark-blood T2W short-axis images of the left ventricle were obtained using a turbo spin echo sequence.

A gadolinium-based contrast agent (gadopentetate dimeglumine, Magnevist; Bayer Schering, Berlin, Germany) was administered intravenously at 0.1 mmol/kg body weight. LGE images were obtained using a phase-sensitive inversion recovery (PSIR) single-shot true fast imaging with steady state precession (also known as TrueFISP) sequence approximately 10 min after administration of the contrast.

T1 maps were obtained from three short-axis images (basal, mid, and apical) of the left ventricle using single-shot TrueFISP, based on the modified look-locker inversion-recovery (MOLLI) sequence. T2 maps were obtained from the same locations as the T1 maps, using a fast low angle shot (also known as FLASH) sequence with T2 preparation pulses.

2.3. CMR examination

To ensure consistent slice positioning and infarct analysis between the time points, MOLLI T1 mapping, tissue tagging, and acquisition of T2WI, LGE, and wall motion cine images were performed in three identical short-axis positions by acquiring the central three slices of five parallel short-axis slices spaced equally from the mitral annulus to the left ventricle apical cap. In addition, LGE and cine imaging were performed using a contiguous stack of short-axis slices covering the entire left ventricle. The same slice geometry, position, and 10-mm SL were used for all sequences. LGE image mapping was performed 10 min after contrast administration, and post-contrast T1 was performed after 20 min. For native T1 and T2 values, we cooperated with healthy volunteers and set the following facility standards: native T1, 1250 ms and native T2, 35 ms.

Extracellular volume (ECV) was measured from the property of the gadolinium contrast agent that was non-specifically distributed in the extracellular fluid, and was used to quantitatively measure the T1 value of myocardial tissue and left ventricular lumen blood before and after administration of the contrast agent (i.e., pre- and post-contrast T1) with correction of hematocrit level in the blood.[9]

2.4. Image analysis

Regions of interest (ROIs) were placed in the infarcted, salvaged, and remote myocardium. The infarcted myocardium was defined as areas of LGE based on the feature analysis and combined thresholding computer algorithm, which was validated using histopathology. Infarcted myocardium was subclassified as non-transmural or transmural based on whether the radial transmural extents of LGE were less or more than 75%, respectively. In the non-transmural infarctions, the salvaged myocardium was defined as the area from the non-LGE myocardium epicardial region to the infarcted myocardium. Transmural infarcts were further classified into endocardial (infarct-endo) and epicardial (infarct-epi) regions. The areas of microvascular obstruction (MVO) were defined as areas of hypo-enhancement within the hyper-enhanced areas on the LGE images. Care was taken to exclude areas of MVO in the infarcted ROIs. Remote myocardium was defined as having no LGE of a different myocardial territory from the infarction. Fifty percent of the epicardium side of the myocardial region where edema was observed from T2WI was defined as the epicardial 50% area (Figure 1).

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA) software. Continuous variables are expressed as mean ± standard deviation if the variable was normally distributed, or median (interquartile range) if not, and groups were

Table 1
Patient characteristics.

	Total (n = 20)	Transmural infarction (n = 10)	Non-transmural infarction (n = 10)	p value
Age (years)	66.6 ± 11.2	63.5 ± 11.3	69.6 ± 12.1	ns
Men, n (%)	13 (65)	7 (70)	6 (60)	ns
Body mass index (kg/m^2)	23.9 ± 2.7	24.2 ± 2.1	23.6 ± 3.4	ns
Hypertension, n (%)	11 (55)	6 (60)	5 (50)	ns
Dyslipidaemia, n (%)	6 (30)	4 (40)	2 (20)	ns
Diabetes, n (%)	4 (20)	1 (10)	3 (30)	ns
Current smoker, n (%)	8 (40)	5 (50)	3 (30)	ns
Previous stable angina, n (%)	2 (10)	1 (10)	1 (10)	ns
Microvascular obstruction, n (%)	8 (40)	8 (80)	0 (0)	< 0.05
Culprit vessel, n (%)				
Left anterior descending artery, n (%)	9 (45)	6 (60)	3 (30)	ns
Left circumflex artery, n (%)	2 (10)	0 (0)	2 (20)	ns
Right coronary artery, n (%)	8 (40)	3 (30)	5 (50)	ns
Left main trunk artery, n (%)	1 (5)	1 (10)	0 (0)	ns
TIMI flow 0 before reperfusion, n (%)	12 (60)	7 (70)	5 (50)	ns
TIMI flow 3 after reperfusion, n (%)	19 (95)	10 (100)	9 (9)	ns
Peak creatine kinase levels (IU/L)	2098 (1217–4521)	2951 (1676–8493)	1295 (642–2818)	< 0.05
Door to reperfusion time (min)	75 (59–115)	80 (72–156)	62 (53–76)	< 0.05
Onset-MRI (days)	11.5 ± 5.4	11.0 ± 3.8	13.5 ± 6.4	ns

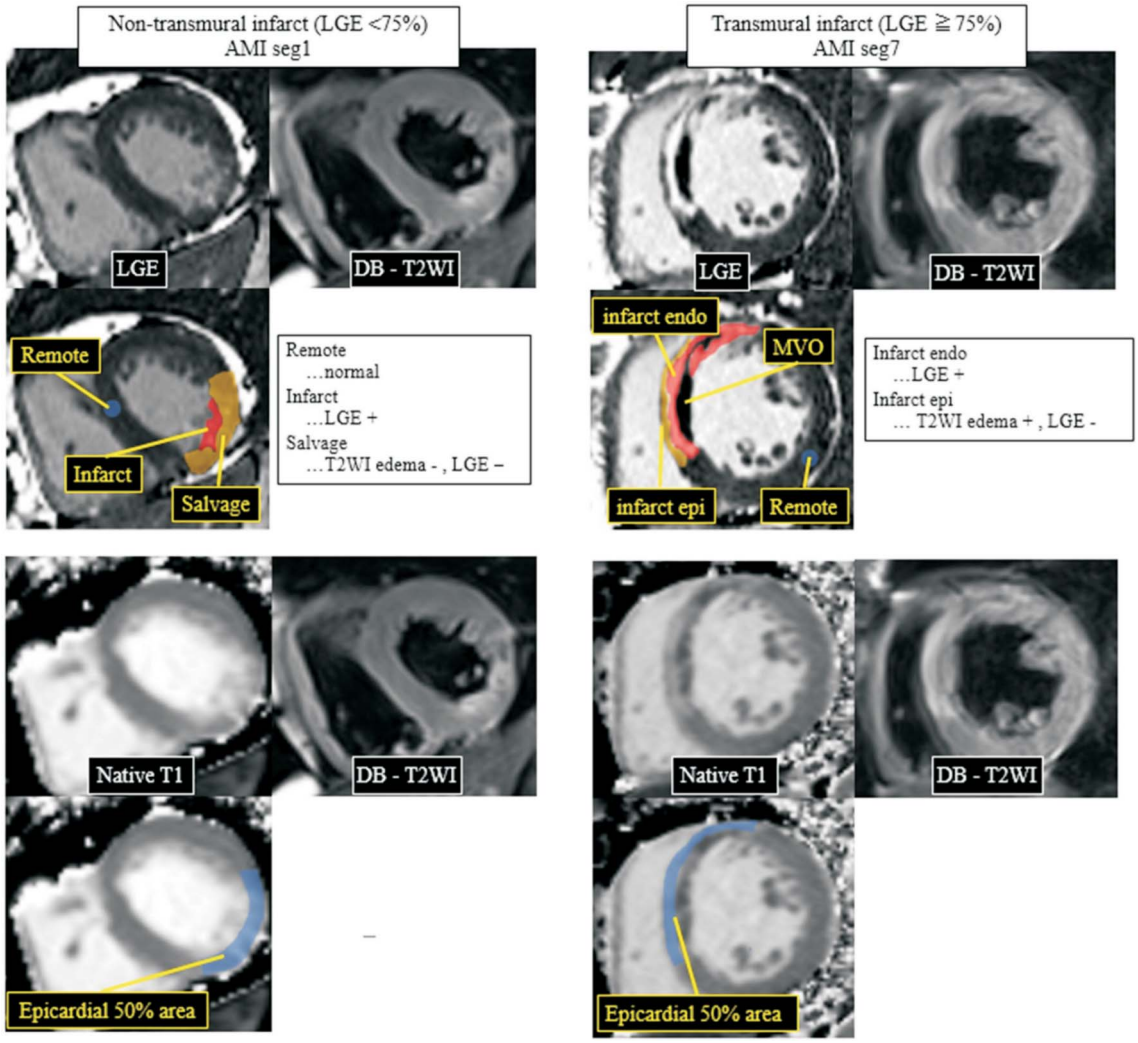

Figure 1. Infarcts were classified as transmural or non-transmural. Non-transmural infarcts were further classified into remote, salvaged, and infarcted areas. Transmural infarcts were also divided into endocardial (infarcted-endo) and epicardial (infarcted-epi) areas. Epicardial 50% area was defined as 50% on the epicardial side of the area with high T2.

compared using Student's t-test or Wilcoxon test for continuous values, and chi-squared test for categorical data, as appropriate. Shapiro-Wilk's test was used to assess whether data were normally distributed or not. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

3. Results

Of the 20 patients included in this study, 10 were transmural infarctions and 10 were non-transmural infarctions. All patients had evidence of AMI using LGE and T2WI during the initial scan. The two characteristics are described Table 1. It was noted that MVO was only observed in the transmural infarctions.

3.1. Native T1 values and ECV

In the non-transmural infarction, native T1 values and ECV of infarcted myocardium were significantly greater than that of the salvaged myocardium (1602.8 ± 68.5 vs. 1451.2 ± 62.6 ms, 45.0 ± 5.1 vs. 35.2 ± 2.5%; $p < 0.05$, respectively). Further, salvaged myocardium had a significantly greater native T1 values and ECV than the remote myocardium (1451.2 ± 62.6 and 1232.5 ± 63.6 ms, 35.2 ± 2.5 vs. 23.6 ± 2.7%; $p < 0.05$, respectively) (Figure 2). In the transmural infarction, there was no significant difference between infarct-endo and infarct-epi (1619.1 ± 80.3 and 1565.4 ± 95.2 ms, 45.9 ± 5.2 and 40.1 ± 4.0%, respectively), but both were significantly greater than the remote myocardium (1232.5 ± 63.6 ms, 23.0 ± 3.1%; $p < 0.05$ for both, respectively) (Figure 3).

3.2. Native T2 values

In the non-transmural infarction, native T2 values in the infarcted myocardium were similar to those in the salvaged myocardium (69.8 ± 6.9 and 53.0 ± 6.1 ms), but significantly greater than those of the remote myocardium (41.0 ± 4.6 ms; $p < 0.05$) (Figure 2). In the transmural infarction, the native T2 values in the infarct-endo were similar to the infarct-epi (54.7 ± 6.3 and 54.6 ± 5.7 ms), but significantly greater than those of the remote myocardium (40.4 ± 2.8 ms; $p < 0.05$) (Figure 3).

3.3. Epicardial 50% area

There was a significantly higher value for native T1 of the transmural infarction compared to that of the non-transmural infarction (1597.3 ± 77.5 vs. 1480.2 ± 58.1 ms; $p < 0.05$). In addition, the result obtained by dividing the native T1 value of the epicardial 50% area by the native T1 value of the remote area was significantly higher in the transmural infarction than the non-transmural infarction (1.28 ± 0.06 vs. 1.14 ± 0.08%; $p < 0.05$) (Figure 4).

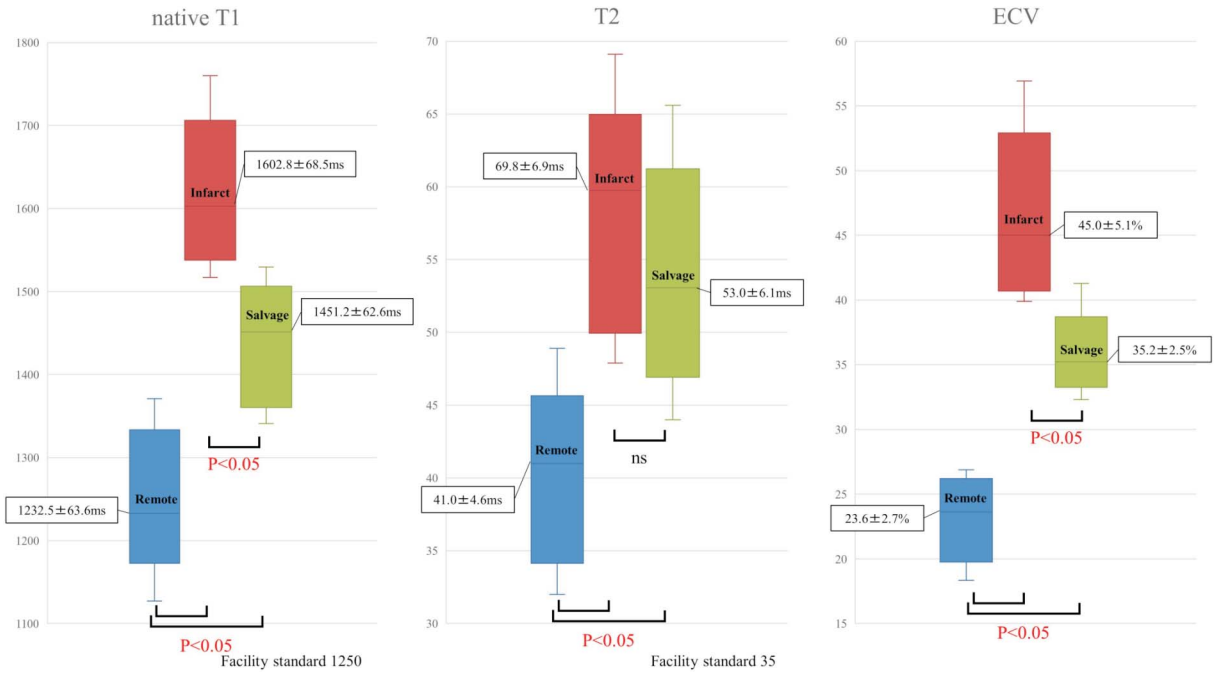

Figure 2. Significantly higher values were observed for native T1 and ECV of the infarcted and salvaged myocardium compared to that of the remote myocardium, and a significantly higher value was observed in the infarcted myocardium compared to the salvaged myocardium. Similarly, a significantly higher value was observed for native T2 of the infarcted and salvaged myocardium compared to that of the remote myocardium; no significant difference was observed between the infarcted and salvaged myocardium.

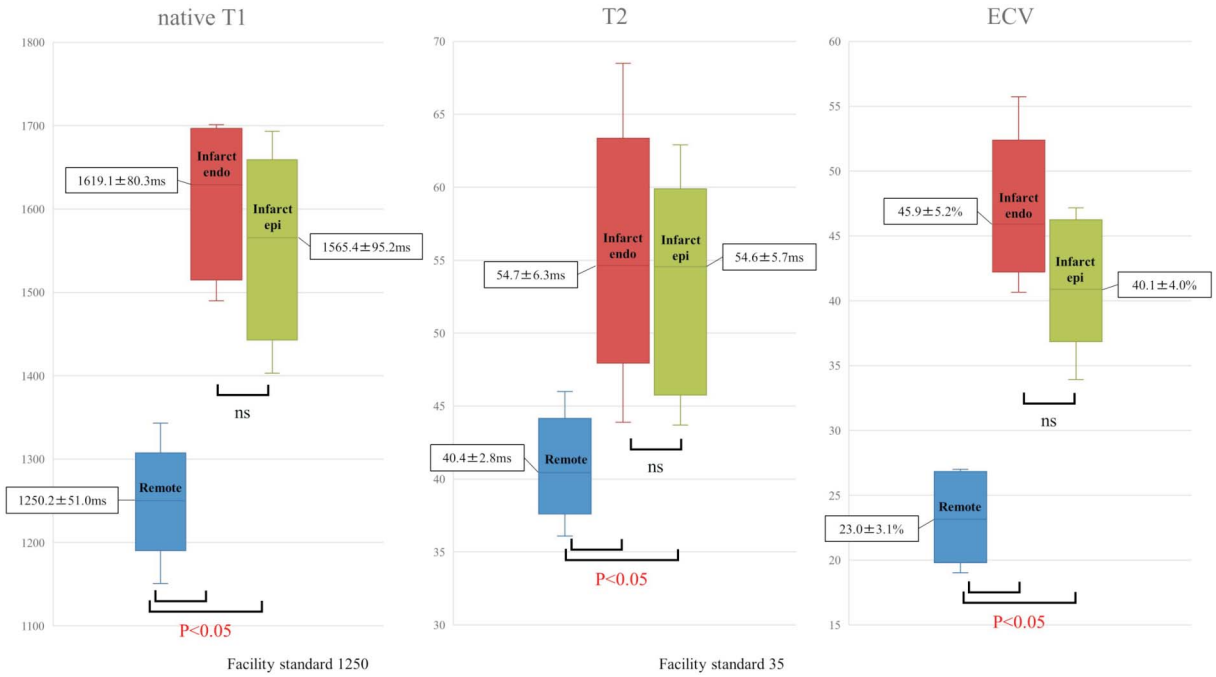

Figure 3. Significantly higher values were observed for native T1 and T2 and ECV of the infarcted-endo and infarcted-epi areas compared to the remote area, with no significant difference between the infarcted-endo and infarcted-epi for these values.

3.4. Follow-up data about wall-motion

We followed up 15 patients with echocardiography on admission and after median 266 days from reperfusion. The improvement in left ventricular local asynergy was observed in 8 cases, but the remaining 7 cases did not improve after reperfusion. Table 2 lists the parameters of the patients who local asynergy improved during the chronic phase and the patients who did not. There was a significantly lower value for epicardial side of native T1 in the improving asynergy patients compared to patients who have not improvement (1457.3 ± 85.2 vs. 1575.6 ± 88.6 ms; $p < 0.05$).

4. Discussion

The main findings of the present study were: 1) T1 mapping, T2 mapping, and LGE could be used to classify and quantify the myocardial injury, and 2) epicardial non-contrast T1 mapping provided clear distinction between the transmural and non-transmural infarction in patients with AMI, and were related to improvement in myocardial wall motion in the chronic phase. These were that enabled

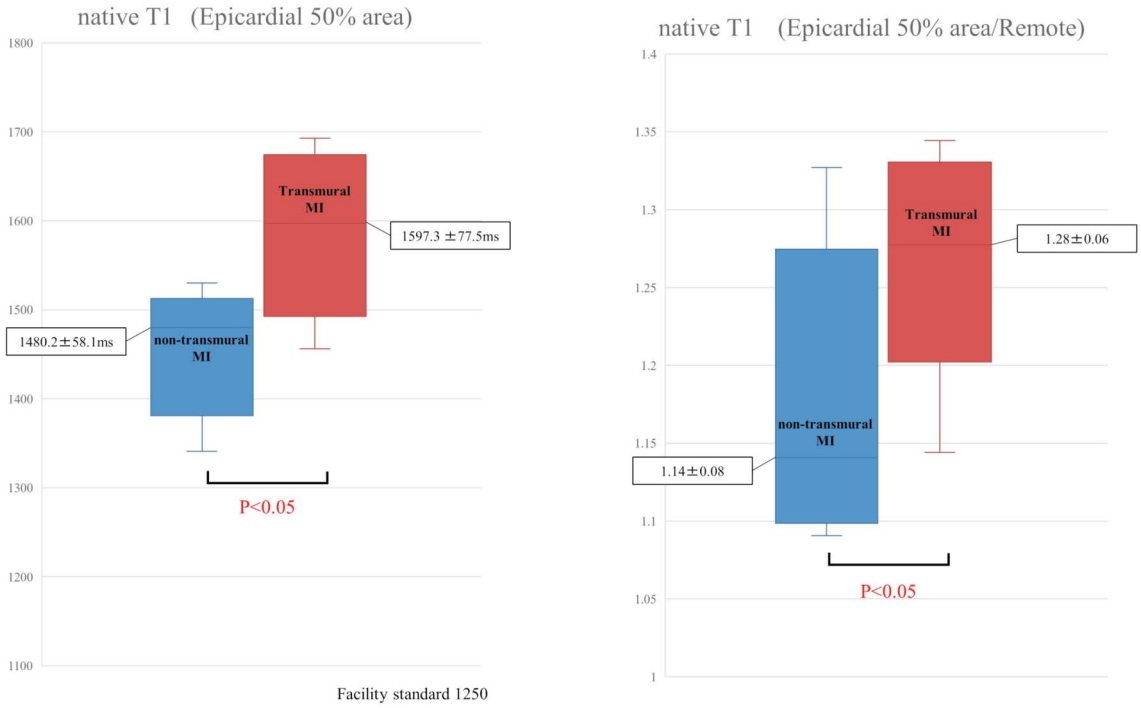

Figure 4. A significantly higher value was observed for native T1 of the transmural infarct compared to that of the non-transmural infarct. The result obtained by dividing the native T1 value of epicardial 50% area by that of the remote area was also significantly higher in the transmural infarct than the non-transmural infarct.

Table 2
Parameters of wall-motion follow-up.

	Improvement of ventricular asynergy (n = 8)	Non-Improvement of ventricular asynergy (n = 7)	p value
Age (years)	66.8 ± 11.4	63.1 ± 12.4	ns
Men, n (%)	4 (50)	6 (86)	ns
Transmural infarction classified by CMR, n (%)	2 (25)	6 (86)	< 0.05
Peak creatine kinase levels (IU/L)	1867 (816–7272)	4416 (1561–8229)	ns
Door to reperfusion time (min)	64 (55–79)	127 (75–196)	< 0.05
Native T1 of epicardial 50% area (ms)	1457.3 ± 85.2	1575.6 ± 88.6	< 0.05

quantification of each myocardium after reperfusion in acute phase using by LGE, T1 mapping, T2 mapping, and revealed epicardial side native T1 value had the possibility of being a useful tool for quantitatively evaluating myocardial viability without contrast mediums.

Native T1 and ECV values were different among the infarcted, salvaged, and remote areas in the non-transmural infarction. However, there were no differences in these parameters between the infarct-endo and infarct-epi areas of the transmural infarction. It was assumed that the native T1 and ECV values were related with the severity of the myocardial injury, suggesting that the severity of myocardial injury could be quantitatively evaluated using native T1 and ECV values.

Our ECV results were consistent with a preclinical study by Arheden et al., in which the ECV of the entire area at risk in reperfused AMI was less than that of the infarcted core, and was greater than the remote myocardium.[10] Regarding ECV in the acute phase after MI, Kidambi et al. reported that ECV of the infarct zone after AMI offered increased accuracy to predict ejection fraction and functional recovery compared to LGE alone.[11] Thus, ECV is a potential prognostic factor of the myocardium after MI.

Additionally, the results from T2 mapping were different from the native T1 and ECV results. However, there was no significant difference between the infarcted and salvaged areas, indicating that the T2 values were not affected by myocardial injury, but were strongly influenced by edematous changes. In the AMI setting, the extracellular space is expanded by edema and inflammation, as well as by the contrast agent entering the intracellular space through the damaged cell membranes. Thus, LGE in the acute phase of MI may undergo changes due to edema, as well as myocardial injury.[12] However, as there was no significant difference between the infarcted and salvaged areas for the T2 value, it is likely that LGE in the acute phase had less influence on edema, but a strong relationship with myocardial injury.

To distinguish between myocardium that can improve wall motion or not, we assumed that the native T1 value of the epicardial side of the myocardium was useful. We also compared the native T1 value of the epicardial 50% area. As expected, the native T1 value of the epicardial 50% area was significantly different between the transmural and non-transmural infarctions. From this result, we considered that the unique T1 value of the epicardial 50% area could be used as a tool for evaluating myocardial survival rate without using contrast media.

These results were based on the concept of "wavefront phenomenon of myocardial death"; the infarcted area extended from the endocardium to the epicardium, when the duration of coronary artery occlusion increased.[13] Therefore, as the myocardial injury occurs from the endocardial side, if the injury is non-transmural, the native T1 value on the epicardial side would not be significantly prolonged. Con-

versely, if the injury is transmural, the native T1 value on the epicardial side would be significantly prolonged. Several uses have been identified via quantifying the myocardium after the onset of MI with MRI and survival evaluation using non-contrast T1 mapping has gained attention. Kali et al. reported that native T1 mappings with 3T could determine the location, size, and transmurality of CMR imaging with high diagnostic accuracy in canine models.[14] Researchers reported that non-contrast T1 mapping evaluated myocardial viability with the same accuracy as LGE in 25 patients with chronic MI.[15] This study also reported that the researchers could substitute LGE for native T1 mapping in the chronic phase after MI; however, it is clinically desirable to predict myocardial function recovery in acute phases.

Erica et al. conducted MRI in the acute phase and evaluated the function of the myocardium to assess whether acute T1 values predicted functional recovery within 6 mo. The researchers determined that there was a significant relationship between the acute T1 values and improvement in function within 6 mo;[7] however, in that study, T1 mapping was positioned as an important complementary technique for LGE and T2WI, as contrast agents were required to identify the MVO regions. In the present study, it was possible to minimize the inclusion of MVO within the measurement range by measuring the native T1 value on the epicardial side because MVO first appeared centrally in the infarcted core, gradually extending toward the epicardium over time.

From the results of this study, there are various advantages for using MRI during the acute phase of AMI. First, myocardial viability evaluation, which had been previously dependent on visual evaluation, can now be done quantitatively, thereby making evaluation more objective. Second, the ability to quantitatively evaluate the salvaged area can be applied to the treatment strategy such as administration beta blockers and may be useful for predict prognosis. Third, with the native T1 value, there is no need to use contrast media, and viability evaluation can be performed in dialysis patients and those who cannot use contrast agent because of the risk of nephrogenic systemic fibrosis. Fourth, those in a poor status after AMI can undergo CMR tests, which precisely map examinations within short periods. Fifth, compared to the LGE test, the burden of examination is reduced because of the short breath hold time.

5. Limitation

There were limitations in this study. First, the present investigation was performed at a single facility, and the number of patients was small. Second, the timing of MRI should have been altered, as the native T1, native T2, and ECV values were thought to change with time after MI. Third, if MVO regions exceeding 50% of the myocardium were identified, the native T1 values on the epicardial side would not accurately reflect myocardial injury. However, these issues may be reconciled if MVO regions could be accurately detected using native T1 values. Fourth, there was an issue with image resolution. In the present study, ROIs were manually determined, and accurate ROI determination was not possible for slices with poor resolution. In addition, we studied one slice of the short-axis with the strongest edema; thus, the entire MI cannot be accurately reflected. Although, the slices were examined, slices which could not set MVO regions because resolution issues were also allowed.

6. Conclusion

In AMI patients, it was possible to quantitatively evaluate the infarcted region using CMR. Additionally, the native T1 value of the epicardial 50% area was useful as an evaluation of myocardial viability without the use of contrast medium. Further studies are needed to clinically utilize these quantitatively evaluated measures and determine whether the epicardial side of native T1 value can be a prognostic factor for MI can be expected.

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