Prevalence and Signal Characteristics of Late Gadolinium Enhancement on Contrast-Enhanced Magnetic Resonance Imaging in Patients With Takotsubo Cardiomyopathy

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Background: To determine the prevalence and signal intensity (SI) characteristics of late gadolinium enhancement (LGE) on magnetic resonance imaging (MRI) in takotsubo cardiomyopathy (TC).

Methods and Results: Cine, black-blood T2-weighted and LGE MR images were acquired in 23 patients with TC within 72 h of onset. Wall motion abnormality (WMA), edema and LGE were evaluated with a 16-segment model. The SI characteristics of LGE were analyzed using SI distribution in remote normal segments as reference. Follow-up MRI was performed 3 months later. Retrospective analysis of LGE MRI was also performed in 10 patients with acute myocardial infarction (AMI) to compare the SI characteristics between TC and AMI. In acute phase, WMA and edema were observed in 236 (64%) and 205 (56%) of 368 segments. LGE was observed in 10 (2.7%) of 368 segments and in 5 (22%) of 23 patients. All LGE lesions in TC exhibited transmural enhancement. The contrast-to-noise ratio (CNR) in TC was significantly lower than that of AMI (3.1±0.3 standard deviations (SD) vs. 6.1±1.2 SD, P<0.01), and CNR value of 4 was useful for distinguishing TC from AMI. Both LGE and WMA disappeared within 12 months.

Conclusions: Grey myocardial signal on LGE MRI may be observed in patients with TC. However, the extent of LGE is substantially less than that of WMA and edema, and disappears within 12 months. (Circ J 2012; 76: 914–921)

Key Words: Cardiac magnetic resonance; Late gadolinium enhancement; Myocardial edema; Takotsubo cardiomyopathy; Wall motion

Takotsubo cardiomyopathy (TC) is a cardiovascular event characterized by acute chest pain with ST-segment elevation and/or T-wave inversion, absence of substantial coronary arterial narrowing on angiography, and reversible systolic dysfunction with abnormal wall motion of the mid and distal left ventricle.1-3 Cardiac magnetic resonance imaging (MRI) has emerged as a non-invasive imaging modality that permits assessment of myocardial infarction and edema, as well as left ventricular (LV) function.4,4 In most of the previous studies that have evaluated MRI findings of TC,7-12 the absence of late gadolinium enhancement (LGE) was considered to be an important finding to differentiate TC from acute myocardial infarction (AMI) in patients with acute chest pain. Recently, several reports indicated that TC may exhibit LGE in the acute phase.13-16 In a recent multicenter study evaluating TC patients in Europe and the United States, LGE was detected in 9% of TC patients, by using a threshold of 3 standard deviations (SD) above the mean of remote normal myocardium to define the presence of LGE.17 However, the signal intensity (SI) characteristics of LGE in TC were not well defined in comparison with AMI in those previous studies. In addition, limited data are currently available regarding the prevalence of LGE in TC patients in Japan. Accordingly, the purpose of our study was to determine the SI characteristics of LGE in patients with TC in comparison with AMI, and to evaluate the relationship between the presence of LGE and recovery of wall motion abnormality (WMA).

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Methods

Patients With TC

All examinations were approved by the institution’s board of medical ethics and clinical investigation and all subjects gave written informed consent. We enrolled 28 consecutive patients...
CMR in Takotsubo Cardiomyopathy

(22 women; 70±10 years) with TC from April 2006 to December 2008. Diagnostic criteria of the subjects were (1) cardiac symptoms, usually consisting of anterior chest pain, (2) transient akinesia or dyskinesia of the LV apical and mid-ventricular segments, extending beyond a single epicardial vascular distribution demonstrated by echocardiography and catheter left ventriculography, (3) absence of obstructive coronary disease or angiographic evidence of plaque rupture on catheter coronary angiography, (4) dynamic ST-segment elevation or T-wave inversion suggestive of AMI, (5) absence of pheochromocytoma, and (6) absence of myocarditis or typical ischemic LGE on cardiac MRI. Exclusion criteria were clinical instability, severe arrhythmia, previous history of MI, and general contraindications to MRI such as claustrophobia, pacemakers or implantable defibrillator devices. Of the 28 patients who met these diagnostic criteria, none was excluded because of the exclusion criteria. All cardiac MRI protocols, including cine MRI, black-blood T2-weighted (T2W) MRI and LGE MRI, were completed in 23 patients within 72 h of the onset of symptoms; 4 patients did not undergo T2W MRI, and 1 patient did not undergo LGE MRI because of an inability to repeat breath-holding during image acquisition. Consequently, these 5 patients were not included in the data analysis of this study. Follow-up cardiac MRI was performed in all of the 23 patients.

Laboratory and Electrocardiography Measurements

Upon admission, and every 8h until a peak level was confirmed, the measurements of creatine kinase (CK) and CK-MB were performed in all patients following standard procedures. Serum concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T (TnT) were measured in 15 of 23 patients (65%). An ECG was performed daily during the acute phase, and heart rate, ST-segment deviation, T-wave inversion, and corrected QT interval (QTc) were determined.

MR Image Acquisitions

The patient was placed supine in a clinical 1.5-T MR imager (Achieva, Philips Medical Systems, Best, The Netherlands) with 5-channel cardiac coils around the chest. All MR images were electrocardiographically gated and obtained during repeated breath-holds. Surface-coil intensity correction was performed for cine MRI, T2W MRI and LGE MRI. Cine MR images were acquired with a steady-state free-precession sequence with the following parameters: repetition time of 3.2 ms, echo time of 1.6 ms, flip angle of 55°, matrix of 190×190, field of view of 350 mm, section thickness of 10 mm and SENSE factor of 2. After acquiring cine MRI images on the 2- and 4-chamber long-axis projections, we obtained short-axis cine MR images that encompassed the LV from base to apex. For the assessment of myocardial edema, T2W breath-hold black-blood triple-inversion fast spin echo images were obtained with the following parameters: repetition time of 3.2 ms, echo time of 1.6 ms, flip angle of 55°, matrix of 190×190, field of view of 350 mm, section thickness of 10 mm and SENSE factor of 2. After acquiring cine MRI images on the 2- and 4-chamber long-axis projections, we obtained short-axis cine MR images that encompassed the LV from base to apex. For the assessment of myocardial edema, T2W breath-hold black-blood triple-inversion fast spin echo images were obtained with the following parameters: repetition time of 3.2 ms, echo time of 1.6 ms, flip angle of 55°, matrix of 240×164, field of view of 380 mm and slice thickness of 8 mm. T2W images were acquired on short-axis imaging planes (4 slices), vertical long-axis plane (1 slice) and horizontal long-axis plane (1 slice). LGE MRI was acquired 10 min after intravenous administration of 0.15 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering AG, Berlin, Germany). A segmented inversion-recovery 3D gradient-echo sequence was used with the following parameters: repetition time of 3.9 ms, echo time of 1.2 ms, flip angle of 15°, acquisition matrix of

<table>
<thead>
<tr>
<th>Table 1. Percentage of Pixels Exhibiting SI Greater Than Mean+2 SD of the SI in Remote Normal Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects (n=20), 320 segments</td>
</tr>
<tr>
<td>0%</td>
</tr>
<tr>
<td>82</td>
</tr>
<tr>
<td>TC patients (n=23), 368 segments</td>
</tr>
<tr>
<td>76</td>
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</table>

SI, signal intensity; SD, standard deviation; TC, takotsubo cardiomyopathy.
Table 2. Patient Characteristics Including Electrocardiographic Findings and Cardiac Enzymes

<table>
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<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Risk factors</th>
<th>Precipitating stress</th>
<th>ECG ST elevation</th>
<th>Peak CK (IU/L) normal&lt;180</th>
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<td>Quarrel</td>
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<td>42</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>F</td>
<td>HTN</td>
<td>Accident involving family member</td>
<td>I, II, III, aV, aV</td>
<td>189</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
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<td>Unknown</td>
<td>I, II, III, aV, aV</td>
<td>330</td>
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</tr>
<tr>
<td>4</td>
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<td>Quarrel</td>
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<td>F</td>
<td>HTN</td>
<td>Ileus, Dehydration</td>
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<td>46</td>
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<tr>
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<td>Quarrel</td>
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<tr>
<td>7</td>
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<td>M</td>
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<td>Distress</td>
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<tr>
<td>8</td>
<td>67</td>
<td>F</td>
<td>None</td>
<td>Aspiration</td>
<td>I, aV, aV, V, aV, V</td>
<td>134</td>
<td>21</td>
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<td>9</td>
<td>77</td>
<td>F</td>
<td>HTN, Dyslipidemia</td>
<td>Bleeding, Anemia</td>
<td>II, III, aV, V, aV</td>
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<td>16</td>
</tr>
<tr>
<td>10</td>
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<td>F</td>
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<td>Bleeding, Anemia</td>
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<td>143</td>
<td>22</td>
</tr>
<tr>
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<td>None</td>
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<tr>
<td>12</td>
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<td>Anemia</td>
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<td>280</td>
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</tr>
<tr>
<td>14</td>
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<td>M</td>
<td>NTN, smoking</td>
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<tr>
<td>15</td>
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<td>F</td>
<td>DM</td>
<td>Quarrel</td>
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<tr>
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<td>HTN, Dyslipidemia</td>
<td>Quarrel</td>
<td>V, aV, V, aV, aV</td>
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<tr>
<td>17</td>
<td>41</td>
<td>F</td>
<td>None</td>
<td>Accident</td>
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<td>26</td>
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<td>20</td>
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<tr>
<td>19</td>
<td>77</td>
<td>F</td>
<td>HTN, Dyslipidemia</td>
<td>Quarrel</td>
<td>II, III, aV, V, aV</td>
<td>252</td>
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<tr>
<td>20</td>
<td>74</td>
<td>M</td>
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<td>Accident involving family member</td>
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<tr>
<td>21</td>
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<td>None</td>
<td>Quarrel</td>
<td>–</td>
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<tr>
<td>22</td>
<td>84</td>
<td>F</td>
<td>None</td>
<td>Quarrel</td>
<td>II, III, aV, V, aV</td>
<td>184</td>
<td>14</td>
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<tr>
<td>23</td>
<td>81</td>
<td>F</td>
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<td>Unknown</td>
<td>V, aV, aV, V, aV</td>
<td>96</td>
<td>10</td>
</tr>
</tbody>
</table>

HTN, hypertension; DM, diabetes mellitus; CK, creatine kinase.

224×157, reconstruction matrix of 512×512, a field of view of 380 mm and section thickness of 10 mm and SENSE factor of 2. The inversion time was adjusted to minimize the signal from normal myocardium in each patient, by using a look-locker sequence to find a null point of normal myocardium. A typical inversion time for LGE MRI ranged from 230 to 270 ms. Vertical long-axis images, horizontal long-axis images and short-axis images of the LV from base to apex were acquired during repeated breath-holds.

MR Image Analysis

MR images were transferred to an image analysis workstation (Virtual Place Advance, Aze, Tokyo, Japan). LV ejection fraction, volumes and mass were determined from cine MRI on consecutive short-axis images by manually tracing the endocardial and epicardial borders at end-systole and end-diastole. Further visual and semiquantitative analysis used the 16 segments of the American Heart Association model for the assessment of LV regional WMA, myocardial edema and LGE. Regional wall motion was determined on cine MRI and was considered as abnormal if wall thickening (end-systolic thickness – end-diastolic thickness) was less than 2 mm. The presence or absence of myocardial edema on T2W MRI was determined by the consensus of 3 experienced readers (2 cardiologists and 1 radiologist) who were blinded to the patient’s identity. For the assessment of myocardial edema on T2W MRI, the ratio of the mean SI of myocardium compared with that of the skeletal muscle was used and edema was considered to be present if the ratio was more than 2.0. Bright signal on T2W MRI because of slow chamber blood was excluded from analysis by referencing cine MR images acquired on the same slice location.

Presence or Absence of LGE

Myocardial segments that exhibited abnormal SI on LGE MRI in patients with TC were determined as follows. To minimize subjective interpretation regarding the presence or absence of LGE, we firstly determined the normal range of myocardial SI in 20 control subjects (16 women, 68±7 years) who had normal cine, T2W and LGE MR images, as well as normal ECG and normal coronary arteries on angiography, and in 23 TC patients. In the control subjects, the mean and SD of the SI were measured in 16 LV myocardial segments. In patients with TC, remote normal myocardium was defined as visually normal myocardium without LGE in an area free of artifact. The mean and SD of the SI were determined as follows. To minimize subjective interpretation regarding the presence or absence of LGE, we firstly determined the normal range of myocardial SI in 20 control subjects (16 women, 68±7 years) who had normal cine, T2W and LGE MR images, as well as normal ECG and normal coronary arteries on angiography, and in 23 TC patients. In the control subjects, the mean and SD of the SI were measured in 16 LV myocardial segments. In patients with TC, remote normal myocardium was defined as visually normal myocardium without LGE in an area free of artifact. However, it should be noted that because of...
statistical variation of SI in each pixel, a certain percentage of pixels in each myocardial segment may exhibit SI greater than the threshold of a mean+2 SD, even in a normal segment. The percentage of myocardial pixels exhibiting SI greater than mean+2 SD was calculated in each of 16 segments as follows, using an image analysis function provided in the workstation that can determine number of the pixels above a given threshold value in the region of interest:

Percentage of enhanced pixels = (number of pixels with SI >mean+2 SD of remote myocardium/total number of pixels in each segment)×100.

Table 1 demonstrates the percentage of the pixels that exhibited SI greater than mean+2 SD of the SI in remote normal myocardium. By using a threshold value of 15%, all myocardial segments in normal control subjects were categorized as normal. Based on this result, we used the threshold value of 15% to define the segments with positive LGE in patients with TC.

For the objective assessment of SI characteristics of LGE in TC patients, we retrospectively evaluated LGE images in 10 patients with AMI (6 women, 74 ±12 years) who underwent contrast-enhanced MRI within 5 days after onset. These 10 patients had typical chest pain, characteristic abnormal findings on ECG and an increased level of CK-MB fraction enzyme (>9 μg/L). The culprit artery was the left anterior descending artery in 4, the right coronary artery in 4, and the left circumflex artery in 2 patients. LGE MR images in 10 AMI patients were acquired using the same acquisition protocol and gadolinium dose as used for the patients with TC. Visual assessment of LGE MRI in the 10 AMI patients revealed 18 segments of infarction, including 3 subendocardial infarctions.

To determine the characteristics of LGE in patients with TC in comparison with those with AMI, the contrast-to-noise ratio (CNR) of LGE lesion was calculated in both groups of patients as follows:26

\[ \text{CNR} = \frac{(\text{SI}_{\text{enhanced region}} - \text{SI}_{\text{remote}})}{\text{SD}_{\text{remote}}}. \]

### Statistical Analysis

Values are presented as mean±SD. Statistical analysis was performed using commercially available software (SPSS 11.0, Chicago, IL, USA). The Mann-Whitney U test was used to examine statistically significant differences between continuous values in different groups. A P-value <0.05 was considered to be significant.

### Results

The clinical findings of the 23 TC patients who completed the MRI protocol are listed in Table 2. The mean age was 72±10 years, 18 patients (78%) were female, and 14 patients (61%) had no cardiac risk factors. Precipitating factors included emotional stress in 14 cases (61%) and physical stress in 7 cases (30%). The remaining 2 patients (9%) had no identifiable triggering event. In 20 patients (87%), ST-segment elevations of at least 1 mm were observed in the anterior leads on admission, and the other 3 patients (13%) had diffuse T-wave inversion. The QTc was prolonged in all patients, the maximal prolongation (570 ms; range, 464–651) typically occurring at 24–72 h. The maximum CK varied from 88 to 400 U/L (normal value, 180 U/L), and for CK-MB from 9 to 46 U/L (normal value, 17 U/L), and decreased to normal levels within 3 days.
Figure 2. Cine MRI, T2-weighted (T2W) MRI and late gadolinium enhancement (LGE) MRI in a 69-year-old patient with takotsubo cardiomyopathy (TC) in (A) the acute phase and (B) the chronic phase. Apical ballooning and myocardial edema are observed on T2W MRI in the acute state (red arrows), (+) slow flow artifact. LGE MRI reveals slightly increased myocardial signal intensity in the inferior wall (yellow arrows). Myocardial edema, LGE and wall motion abnormality disappeared after 3 months. MRI, magnetic resonance imaging.
Left ventriculography showed akinesia in the anterolateral, apical, diaphragmatic and septal areas, as well as a hypercontractile base in all patients. Treatment varied according to the discretion of the attending physician. Discharge medications included, but were not limited to, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (7 of 23 patients), β-blockers (4 of 23 patients), and warfarin (5 of 23 patients).

The characteristic MRI findings in the acute phase are listed in Table 3. In the acute phase, all patients demonstrated Wall Motion Abnormalities (WMA) from the mid-ventricular to apical regions in the LV. WMA was observed in 236 (64%) of 368 segments. Myocardial edema on T2W MRI was observed in 205 (56%) of 368 segments, and in 22 (96%) of 23 patients. LGE was observed in 10 (2.7%) of 368 segments and in 5 (22%) of 23 patients. All instances of LGE were observed in the area exhibiting both WMA and edema, and it had a transmural distribution (Figure 2A). The CNR of segments with LGE in patients with TC was 3.1±0.3, significantly lower than that of the infarct segments in patients with AMI (6.1±1.2, P<0.01) (Figure 3). CNR of 4 seems to be a meaningful and optimal value for the differentiation of TC and AMI with a sensitivity of 100% (10/10 segments) and specificity of 94% (17/18 segments).

At 3 months after symptom onset, no edema was observed on T2W MRI in any of the patients. Of the 10 segments showing LGE in the acute phase, LGE had disappeared in 5 segments in 2 patients (Figure 2B). All segments showing no LGE revealed complete recovery of WMA. However, residual WMA was observed in the remaining 5 segments with LGE in 3 patients. Both LGE and WMA had disappeared on follow-up MRI performed at 6 months (2 patients) and 12 months (1 patient) after onset, confirming the diagnosis of TC.

**Discussion**

The results from this study demonstrated that LGE on MRI occurred in approximately 20% of Japanese patients with TC in the acute phase, whereas myocardial edema on T2W MRI was observed in nearly all patients. We also found that the mean CNR of the LGE lesion, determined as an index of increased SI in comparison with normal segments, was significantly lower than that of the infarct segments in patients with AMI (3.1±0.3 vs. 6.1±1.2, P<0.01).

Cardiac MRI is emerging as the imaging method of choice for differentiating TC, embolic infarction and myocarditis, when obstructive coronary artery disease needs to be ruled out in the presence of wall motion anomalies. Previous studies reported that cardiac MRI findings in patients with TC are typically characterized by the absence of myocardial enhancement on LGE MRI, despite severe ventricular dysfunction.7–12 Therefore, the presence of LGE has been generally considered as indicative of embolic infarction or myocarditis, depending on the transmural distribution of enhancement. However, recent studies indicate that LGE may occur in patients with TC. Sharkey et al reported that 1 of 22 TC patients, who had presented in cardiac arrest, exhibited LGE in the acute phase.15

In a report by Rolf et al, myocardial LGE was observed in 5 of 15 patients with TC, indicating that the presence of LGE does not rule out the possibility of TC.16 Eitel et al recently reported that LGE was found in 9% of TC patients in a multicenter study performed in Europe and the United States.17

In the current study, LGE was observed in 5 of 23 TC patients. However, all LGE lesions seen in TC patients were not as bright as those observed in patients with AMI by qualitative assessment. In order to reliably determine the presence of LGE in TC, it is important to define the threshold for differentiating normal myocardium and abnormal myocardium on LGE MRI, and to evaluate the SI characteristics in patients with TC in comparison with MI. In previous studies in patients with MI, abnormal SI was most often defined as >mean+2 SD27–29 by using the mean and SD values in remote normal segments. When evaluating the presence or absence of LGE by using a segment-based analysis, it should be acknowledged that a certain percentage of pixels in normal segments may exhibit SI >mean+2 SD, because the SI values in imaging pixels demonstrate statistical variation. Therefore, we calculated the percentage of pixels showing SI >mean+2 SD in myocardial segments in normal subjects, as well as in patients with TC, by using an image analysis tool that can determine number of the pixels above a given threshold value in the region of interest. We found that myocardial segments can be considered to be abnormal on LGE MRI when the percentage of high-intensity pixels (>mean+2 SD in remote normal segment) exceeded 15%. By using this approach, we could determine the presence or absence of LGE in patients with TC without depending on the arbitrary decisions of observers.

We found that the CNR of LGE lesions in TC was significantly lower than that in patients with AMI. The SI of MI on LGE MRI has been analyzed by several investigators. MI may have spatial heterogeneity, ranging from complete necrosis in the core to an admixture of necrosis and viable myocytes in the border zones.24,30 Yan et al reported that SI thresholds >3 and 2–3 SDs above the remote reference segment represent the core infarct zone and peri-infarct zone, respectively.24 In a recent study by Eitel et al investigating TC patients,17 the thresholds were set at 3 and 5 SD (3 SD represents the cutoff for normal and LGE in TC, and 5 SD represents the cutoff for TC and AMI) above the mean SI of apparently normal myo-
cardium. However, the thresholds used in Eitel’s study were adopted from a previous study in patients with AMI. In our current study, the SI characteristics of LGE lesions were compared between TC and AMI patients. As demonstrated in Figure 3, a CNR value of 4 seems to be meaningful and optimal for differentiating between TC and AMI with a sensitivity of 100% and specificity of 94%.

During follow-up, myocardial LGE persisted at 3 months in 3 patients, whereas myocardial edema on T2W MRI has disappeared by 3 months in all patients. We also found that the segments with LGE at 3 months exhibited residual WMA. This observation is in good agreement with a previous study by Sharkey et al, who reported that approximately 5% of TC patients showed delayed LV ejection fraction normalization up to 12 months. Bellera et al recently reported that LGE was observed in 3 of 17 patients with apical ballooning syndrome on contrast-enhanced MRI performed at 11±9 months, indicating the presence of irreversible myocardial damage in these patients. However, in our current study, all LGE lesions disappeared within 12 months after onset. Although the mechanisms that cause LGE in TC patients have not been determined, pathologic changes in patients with TC reported in several recent studies may explain LGE. In the study by Nef et al, increased interstitial space with cell debris, macrophages, and fibroblasts, without signs of oncotic and apoptotic cell death, was observed in TC. Another recent study by Rolf et al reported increased collagen-I and transient fibrosis in the extracellular space in patients with TC. Such pathologic changes may result in a mild to moderate increase in the distribution volume of extracellular MRI contrast medium, causing a grey signal on LGE MRI. However, histologic confirmation was not obtained in our current study.

Clinical Implications
In patients with TC, WMA usually returns to normal within several weeks. However, we found that approximately 20% of TC patients demonstrated a grey myocardial signal on LGE MRI, which is associated with late recovery of WMA. When LGE is observed in patients with suspected TC, analysis of SI on LGE MRI using a CNR value of 4 will be useful for distinguishing TC and AMI. In addition, a grey myocardial signal in TC usually demonstrates transmural distribution, with the extent of LGE substantially smaller than that of WMA and myocardial edema. Cardiac MRI may reveal other abnormalities in TC, including ventricular thrombi that may not be well visualized by echocardiography.

Study Limitations
Several limitations to this study should be acknowledged. First, the sample size was small. Second, endomyocardial biopsies were not obtained. Third, we used multichannel receiver coils to obtain LGE MRI. Although the CNR on LGE MRI was measured in previous studies using similar approaches to that used by us, it should be noted that accurate calculation of CNR is difficult because the noise in the reconstructed images varies spatially because of coil sensitivity and geometry factors.

In conclusion, we determined the presence and absence of LGE in patients with TC by using a semiquantitative approach that did not depend on subjective interpretation by observers. Grey gadolinium enhancement with transmural distribution was observed in 22% of patients with TC. On LGE MRI, a CNR value of 4 is useful for distinguishing TC from AMI. The presence of LGE in the acute phase may indicate late recovery of WMA, whereas LGE and WMA disappeared in all patients by 12 months. Follow-up cardiac MRI study is useful to confirm the recovery of functional and histological alternations in TC patients.

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Disclosure
None.

References


