Differences in Negative T Waves Between Takotsubo Cardiomyopathy and Reperfused Anterior Acute Myocardial Infarction

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Background: In both takotsubo cardiomyopathy (TC) and reperfused anterior acute myocardial infarction (AMI), negative T waves commonly appear on the ECG in the subacute phase. This study aimed to clarify the ECG differences between these diseases.

Methods and Results: We compared the ECGs with the greatest amplitude of negative T wave from 34 patients with TC and 237 patients with a first reperfused anterior AMI who were admitted within 6h of symptom onset and who had no abnormal Q-waves on discharge ECG. Time from symptom onset to recording the ECG did not differ between TC and anterior AMI (2.4±1.5 vs. 2.1±2.0 days, P=0.48). TC was associated with a greater maximal amplitude of negative T wave (1.00±0.44 vs. 0.79±0.46mV, P=0.044), and a greater number of leads with negative T waves (9.5±1.0 vs. 6.0±2.1, P<0.001). Negative T waves were consistently observed in leads –aVR and V4–6, whereas negative T waves were rare in lead V1 in TC. Negative T waves in lead –aVR (ie, positive T waves in lead aVR) and no negative T waves in lead V1 identified TC with 94% sensitivity and 95% specificity, representing the highest diagnostic accuracy.

Conclusions: During the subacute phase, deeper negative T waves were more frequently and broadly distributed, particularly around leads facing the apical region, in TC than in reperfused anterior AMI. (Circ J 2012; 76: 462–468)

Key Words: Acute myocardial infarction; Electrocardiogram; Takotsubo cardiomyopathy
from an acute atherothrombotic event with rapid and complete lysis of thrombus in the LAD coronary artery. In this study, we assessed the electrocardiographic differences, especially negative T waves, between TC and reperfused anterior AMI in the subacute phase. Such differences may further provide important clues to our understanding of the pathophysiologic mechanisms of these 2 diseases and facilitate differential diagnosis. In TC, transient abnormal Q-waves often appear in the acute phase and usually disappear promptly, followed by the reappearance of R waves.3,11 Our study group therefore included patients with reperfused anterior AMI, particularly those with no abnormal Q-waves on discharge ECG, whose characteristics may be very similar to those of patients with TC.

**Table 1. Baseline Characteristics of the Study Subjects**

<table>
<thead>
<tr>
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<th>TC (n=34)</th>
<th>Anterior AMI (n=237)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>70±11</td>
<td>61±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>29 (85%)</td>
<td>49 (21%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (9%)</td>
<td>57 (24%)</td>
<td>0.048</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (44%)</td>
<td>99 (42%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>5 (15%)</td>
<td>77 (33%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (12%)</td>
<td>148 (62%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Killip class &gt;2 on admission</td>
<td>4 (12%)</td>
<td>7 (3%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Initial LVEF (%)</td>
<td>41±9</td>
<td>52±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak creatine kinase (IU/L)</td>
<td>384±398</td>
<td>1,505±921</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak creatine kinase-MB (IU/L)</td>
<td>36±18</td>
<td>131±102</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean value±SD or number of patients (%).
TC, takotsubo cardiomyopathy; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction.

**Methods**

**Patients**

Clinical features and electrocardiographic findings were retrospectively compared between 34 consecutive patients with TC and 237 consecutive patients with anterior AMI who were admitted to hospital within 6 h of symptom onset. Patients with cardiogenic shock and conditions precluding the evaluation of ST-segment changes on ECG (ie, complete left or right bundle branch block, left ventricular hypertrophy, ventricular pacing, atrial fibrillation or flutter, electrolyte abnormalities, metabolic disease, or treatment with drugs potentially affecting ECG) were excluded from this study. All patients gave informed consent and the study protocol was approved by the institution’s ethics committee.

**TC Group**

Patients who had an acute cardiac event associated with symptoms suggesting TC, such as dyspnea, chest pain/discomfort, or palpitations, were studied.2-4,11,12,13 All patients underwent coronary angiography (CAG) during hospitalization. Emergency CAG was performed in 26 patients (76%) and emergency left ventriculography in 24 (71%). TC was diagnosed according to the following criteria, which incorporated the proposed Mayo criteria for the clinical diagnosis of TC (1–4),3 as well as an additional previously proposed criterion (5):11 (1) transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments with regional wall motion abnormalities extending beyond a single epicardial vascular distribution; (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (ST-segment elevation or T wave inversion); (4) absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, myocarditis, and hypertrophic cardiomyopathy; and (5) the prompt normalization of systolic function after presentation. All patients had ST-segment elevation >0.1 mV in at least 2 contiguous precordial leads on admission ECG.

**Anterior AMI Group**

The diagnosis of anterior AMI was based on typical chest pain and a rise in serum creatine kinase-MB level in accordance with the universal definition of MI,19 as well as precordial ST-segment elevation >0.1 mV in at least 2 contiguous precordial leads on admission ECG. All patients underwent CAG immediately after admission, and the presence of obstruction, severe stenosis, or intracoronary thrombus in the LAD coronary artery was documented. The allocation of reperfusion therapy was left to the discretion of the physician in charge, and successful reperfusion, defined as a Thrombolysis In Myocardial Infarction (TIMI)20 grade 3, was obtained by fibrinolysis in 54 patients and by percutaneous coronary intervention in 183. Emergency left ventriculography was performed in 192 patients (81%). All patients had no history of previous MI and no abnormal Q-waves in leads V2-V5 on discharge ECG.19

**ECG Evaluation**

A 12-lead ECG was recorded on admission and at 3-h intervals during the first 24 h, at 6-h intervals for the next 2 days, and then daily until discharge at a paper speed of 25 mm/s and an amplification of 10 mm/mV. ECGs with negative T waves of greatest amplitude after admission were evaluated. All ECGs were examined by a single cardiologist who was blinded to all other clinical data. ST-segment deviation was measured manually to the nearest 0.5 mm, 80 ms after the J point. ST-segment deviation was considered present if deviation was >0.05 mV in limb leads and >0.1 mV in precordial leads.21 Negative T waves were considered present if the depth was ≥0.1 mV.11,22 In this study, the anatomically contiguous Cabrera sequence (III, aVF, II, –aVR, I, and aV1) was used to display the limb leads in accordance with current international recommendations for the clinical interpretation of ECG.23,24 QT interval was defined as the interval from the beginning of the QRS complex to the end of the T wave. If U waves were present, QT interval was measured to the nadir of the curve between T and U waves. QT interval was corrected for heart rate by Bazett’s formula.25
Blood samples for measurement of creatine kinase levels were obtained on admission and at 3-h intervals during the first 24 h, at 6-h intervals for the next 2 days, and then daily until discharge.

Statistical Analysis
Continuous data are expressed as means±SD, and categorical data are expressed as percentages. Two-tailed unpaired t-test or the Mann-Whitney U statistical test was used to compare continuous variables. Chi-square analysis was used to compare categorical variables. Differences were considered statistically significant at P<0.05.

Results
Study Group
The baseline characteristics of the subjects are shown in

Cardiac Enzyme Study
Blood samples for measurement of creatine kinase levels were obtained on admission and at 3-h intervals during the first 24 h, at 6-h intervals for the next 2 days, and then daily until discharge.

Table 2. Electrocardiographic Findings of the Study Subjects

<table>
<thead>
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<th>TC (n=34)</th>
<th>Anterior AMI (n=237)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (ms)</td>
<td>772±149</td>
<td>788±142</td>
<td>0.62</td>
</tr>
<tr>
<td>Abnormal Q-wave</td>
<td>10 (29%)</td>
<td>59 (25%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Maximal ST-segment elevation (mV)</td>
<td>0.17±0.19</td>
<td>0.22±0.12</td>
<td>0.037</td>
</tr>
<tr>
<td>No. of leads with ST-segment elevation</td>
<td>2.3±2.6</td>
<td>2.8±2.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Maximal QTc interval (ms)</td>
<td>642±93</td>
<td>586±81</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximal amplitude of negative T waves (mV)</td>
<td>1.00±0.44</td>
<td>0.79±0.46</td>
<td>0.044</td>
</tr>
<tr>
<td>No. of leads with negative T wave</td>
<td>9.5±1.0</td>
<td>6.0±2.1</td>
<td>&lt;0.001</td>
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</table>

Data are mean value±SD or number of patients (%).
AMI, acute myocardial infarction; TC, takotsubo cardiomyopathy.

Figure 1. Prevalence of negative T waves in patients with takotsubo cardiomyopathy (TC) and those with anterior acute myocardial infarction (AMI). In the limb leads, the prevalence of negative T waves gradually decreased from leads aVF to III in patients with anterior AMI. In contrast, a high prevalence of negative T waves centered around lead –aVR in TC. In the precordial leads, negative T waves were distributed primarily around leads V2–4 in patients with anterior AMI, but appeared in leads V4–6 in all patients with TC. *P<0.05, **P<0.01 vs. anterior AMI.
Table 1. Patients with TC were older, more likely to be female, and had lower rates of diabetes mellitus, hyperlipidemia, and smoking, a higher rate of Killip class ≥2 on admission, and a longer time from symptom onset to admission than did patients with anterior AMI (TC vs. anterior AMI: 3.3±2.4 vs. 2.2±2.0 h, P<0.001). Among 237 patients with anterior AMI, 35 (15%) had multivessel disease. The initial left ventricular ejection fraction, which was evaluated on right anterior oblique views of left ventriculograms, was significantly lower in patients with TC; however, peak creatine kinase and creatine kinase-MB levels were significantly lower in patients with TC.

Table 3. Predictive Value of Electrocardiographic Variables for the Diagnosis of Takotsubo Cardiomyopathy

<table>
<thead>
<tr>
<th>Presence of positive T waves in lead aV₅ (=Presence of negative T waves in lead –aV₅)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Predictive accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of positive T waves in lead aV₅ and absence of negative T waves in lead V₁</td>
<td>94%</td>
<td>95%</td>
<td>71%</td>
<td>99%</td>
<td>94%</td>
</tr>
</tbody>
</table>

**P<0.01 vs. presence of positive T waves in lead aV₅ and absence of negative T waves in lead V₁.**

PPV, positive predictive value; NPV, negative predictive value.

Figure 2. Representative ECGs of takotsubo cardiomyopathy (TC) and anterior acute myocardial infarction (AMI). **Left** (anterior AMI): negative T waves were observed in leads I, aV₅, and V₁–V₆. **Right** (TC): negative T waves were observed in leads I, II, aV₅, aV₆, and V₂–V₆. Positive T waves were observed in leads aV₅ and V₁. The calibration indicates 1.0mV.

Table 1. Patients with TC were older, more likely to be female, and had lower rates of diabetes mellitus, hyperlipidemia, and smoking, a higher rate of Killip class ≥2 on admission, and a longer time from symptom onset to admission than did patients with anterior AMI (TC vs. anterior AMI: 3.3±2.4 vs. 2.2±2.0 h, P<0.001). Among 237 patients with anterior AMI, 35 (15%) had multivessel disease. The initial left ventricular ejection fraction, which was evaluated on right anterior oblique views of left ventriculograms, was significantly lower in patients with TC; however, peak creatine kinase and creatine kinase-MB levels were significantly lower in patients with TC.

ECG Findings

Time from symptom onset to recording ECGs with the greatest amplitude of negative T waves did not differ significantly between the TC and anterior AMI groups (2.4±1.5 vs. 2.1±2.0 days, P=0.48). Electrocardiographic findings are presented in Table 2. RR intervals and the frequencies of abnormal Q-waves did not differ significantly between TC and anterior AMI. TC was associated with a smaller maximal ST-segment elevation and a longer maximal QTc interval. TC was also associated with a greater maximal amplitude of negative T waves and a greater number of leads with negative T waves. The prevalence of negative T waves is shown in Figure 1.
Negative T waves were consistently observed in leads –aVR and V1–6, whereas negative T waves were rare in lead V1 in TC. As compared with anterior AMI, TC was more frequently associated with negative T waves in leads III, aVF, II, –aVR, I, and V5–6, but was less frequently associated with negative T waves in leads aVL and V1, especially lead V1. The combination of the presence of negative T waves in lead –aVR (ie, positive T waves in lead aVR) and the absence of negative T waves in lead V1 was observed in 94% of the patients with TC, as compared with only 5% of those with anterior AMI (P<0.001). The combination of these 2 findings provided the highest ability to differentiate TC from anterior AMI, as compared with other electrocardiographic findings. Table 3 shows the sensitivity, specificity, positive and negative predictive values, and predictive accuracy of ECG findings for the diagnosis of TC. For other continuous electrocardiographic variables not shown in the Table, no cut-off points were found to discriminate between TC and anterior AMI. Figure 2 shows representative ECGs for a patient from each group.

**Discussion**

This study showed that negative T waves progressively developed in association with QT prolongation in both TC and reperfused anterior AMI during the subacute phase and were especially prominent in the former. In TC, deeper negative T waves were more frequently and broadly distributed, particularly around leads facing the apical region, suggesting differences in the underlying pathologic characteristics of the myocardium between the 2 diseases. TC might be associated with more extensive and more viable, but sympathetically denervated myocardium. The presence of negative T waves in lead –aVR (ie, positive T waves in lead aVR) combined with the absence of negative T waves in lead V1 strongly suggested TC.

TC has been increasingly reported worldwide, and the need to include it in the differential diagnosis of anterior AMI has received considerable attention.1-5,8,10,11 The most common ECG changes associated with TC are ST-segment elevation and negative T waves.1,3,10-12 Previous studies have reported that negative T waves already appear on initial ECGs in many patients with TC.1,12 One might misdiagnose such patients as reperfused anterior AMI and consider starting antplatelet and anticoagulant therapy and performing CAG to decide whether coronary revascularization is required. In patients with TC, however, such treatment at presentation and subsequently is not only unnecessary, but also may increase the risk of bleeding because TC is often associated with acute events such as intracranial bleeding, head trauma, gastric ulcer, or surgery.1,2 In addition, most TC patients are elderly women,1,2,4,6,14 contributing to the risk of bleeding. Electrocardiographic criteria that can be used to differentiate TC from reperfused anterior AMI in the subacute phase are essential for selecting the most appropriate treatment strategy. To clarify the electrocardiographic differences between these 2 diseases in this phase, we studied homogeneous groups of patients. Previous studies have reported highly variable electrocardiographic findings in patients with TC.11,12 In those studies, the elapsed time from symptom onset to recording ECG varied widely, potentially contributing to the heterogeneity of electrocardiographic findings. Mitsuma et al9 reported that serial electrocardiographic changes of TC may reflect its clinical phase; perhaps ST-segment elevation is present in all patients early in the course of TC, and negative T waves appear subsequently. Therefore, our study included only TC patients who were admitted within 6 h of symptom onset and who had acute ST-segment elevation on admission ECG.

In this setting, negative T waves in TC initially deepened with greatest amplitude approximately 2 days after symptom onset, consistent with previous reports.1,3,10 Similar electrocardiographic changes were also observed in reperfused anterior AMI, but were especially prominent in TC. In patients with reperfused anterior AMI, the development of negative T waves in the subacute phase has been attributed to viable but sympathetically denervated myocardium, because sympathetic denervation delays repolarization.26-28 Our findings suggest that TC is associated with more extensive and more viable, but sympathetically denervated myocardium. Peak creatine kinase and creatine kinase-MB levels were significantly lower in patients with TC than in those with reperfused anterior AMI, despite left ventricular dysfunction in the acute phase. These findings also suggested that TC is associated with a greater mass of stunned myocardium.

To our knowledge, only the study reported by Kurisu et al19 scrutinized differences in negative T waves between TC and reperfused AMI. They compared electrocardiographic changes over time between 16 patients with TC and 15 patients with reperfused anterior AMI and a peak creatine kinase level <1,000 U/L. However, changes in the negative T waves in the subacute phase were similar in both groups. Their study included only a small number of patients and assessed electrocardiographic changes in only leads V3–5 among all 12 leads. Moreover, they did not examine differences in the numbers or distributions of leads with negative T waves. We believe that our study is the first to show that TC is associated with deeper negative T waves and more leads with negative T waves, as well as a different distribution of negative T waves compared with reperfused AMI, particularly non-Q-wave AMI. Generally, after ischemia and infarction, T waves often become inverted in leads with previous ST-segment elevation.23 In patients with reperfused anterior AMI, negative T waves were distributed primarily around leads V2–4, facing the anterior region. The extent of negative T waves in reperfused anterior AMI may be influenced by the extent of myocardial ischemic damage. In contrast, in patients with TC, negative T waves were more frequently and broadly distributed, as compared with reperfused anterior AMI. In the limb leads, the high prevalence of negative T waves was centered around lead –aVL. Lead –aVL (+30°) bridges the gap between lead I (0°) and lead II (60°).23,24 In other words, lead –aVR faces the apical region. The frequency of negative T waves was high even in lead II and did not differ significantly from that in lead –aVL, which had a frequency of 100%. As compared with lead II, lead –aVL may more closely reflect the status of wall motion abnormalities centered around the apical region in patients with TC. In anterior AMI, the perfusion territory of the LAD coronary artery usually does not extend to these regions and so the prevalence of negative T waves in lead –aVR is relatively low. In contrast, the extent of negative T waves in TC is very broad, including anterior, lateral, and inferior regions, as well as the apical region, which is beyond the perfusion territory of any single coronary artery. On the other hand, negative T waves less frequently appeared in leads aVL and V1 and were particularly rare in lead V1. These electrocardiographic findings are probably ascribed to the fact that wall motion abnormalities in TC rarely extend to the regions faced by these leads.1,20 Lead aVL faces the upper lat-
eral region, and lead V1 faces the right ventricular anterior region, as well as the right paraseptal region.\textsuperscript{29,31} Moreover, less negative T waves in lead V1 may be attributed to another reason. TC, but not anterior AMI, is usually associated with wall motion abnormalities in the postero lateral region,\textsuperscript{1,32} resulting in negative T waves in this region. This finding is reflected in the appearance of positive T waves in the opposing lead V1.\textsuperscript{28,29,31} We have previously shown that during the acute phase, TC is characterized by the presence of ST-segment elevation in lead –aVR and the absence of ST-segment elevation in lead V1.\textsuperscript{6} During the subacute phase, it is plausible that these findings were reflected in the presence of negative T waves in lead –aVR and the absence of negative T waves in lead V1. The underlying reasons remain speculative, but in the present study these electrocardiographic findings most accurately predicted TC.

Study Limitations
This study was retrospective and performed at a single center. Furthermore, we studied a relatively small number of patients who met strict inclusion criteria to ensure a homogeneous group of subjects. Consequently, our findings may not be able to be extrapolated to a general group of patients with TC and anterior AMI. Finally, caution is required because we retrospectively studied only ECGs with negative T waves of the greatest amplitude to assess the value of electrocardiographic findings for discriminating between TC and reperfused anterior AMI. Further studies of larger number of patients are needed to confirm our findings.

Conclusions
The development of negative T waves differed between TC and reperfused anterior AMI in the subacute phase. This observation may provide important clues to understanding the differences in underlying electrophysiologic mechanisms between TC and reperfused anterior AMI and facilitate the differential diagnosis of these 2 diseases.

References

