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CORRESPONDENCE

Research Correspondence

Simple and Accurate Electrocardiographic Criteria to Differentiate Takotsubo Cardiomyopathy From Anterior Acute Myocardial Infarction

To the Editor: Because clinical features of Takotsubo cardiomyopathy (TC) mimic those of anterior acute myocardial infarction (AMI) (1), the differential diagnosis is important in selecting the appropriate treatment strategy, especially in the acute phase. This study assessed the value of the electrocardiogram (ECG) for discriminating TC from anterior AMI. We retrospectively compared admission ECGs of 33 patients with TC with those of 342 patients with a first anterior AMI who had ST-segment elevation of >1.0 mm in at least 2 contiguous precordial leads. All patients were admitted within 6 h of symptom onset. Patients with left or right bundle branch block, left ventricular hypertrophy, or atrial fibrillation were excluded. All patients with TC fulfilled the Mayo Clinic diagnosis criteria for TC (2); emergency coronary angiography was performed in 25 patients (76%) and emergency left ventriculography in 23 (70%). The diagnosis of anterior AMI was based on typical chest pain lasting for at least 30 min and a typical increase in serum creatine kinase levels to more than twice the upper limit of normal, as well as precordial ST-segment elevation on the admission ECG, as described previously. All patients with anterior AMI underwent emergency coronary angiography, and the presence of obstruction, severe stenosis, or intracoronary thrombus in the left anterior descending coronary artery was documented.

Twelve-lead ECGs were recorded on admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. ST-segment deviation from the baseline PR segment was measured 80 ms after the J point and was considered present if deviation was >0.5 mm in limb leads and >1.0 mm in precordial leads. The anatomically contiguous Cabrera sequence (III, aVF, II, −aVR, I, and aVL) was used to display the limb leads, as recommended in current international clinical interpretation for electrocardiography (3). The QTc interval was calculated using Bazett's formula. We also analyzed the following admission electrocardiographic findings, previously shown to be associated with TC (4): absence of reciprocal changes (defined as ST-segment depression in at least 2 inferior leads) and absence of abnormal Q waves. Comparisons of continuous variables were analyzed with a *t* test. Categorical variables were compared by the chi-square test.

Patients with TC were older (age 70 ± 11 years vs. 61 ± 11 years, $p < 0.001$), were more likely to be women (85% vs. 15%, $p < 0.001$), and had a longer time from symptom onset to admission (3.4 ± 2.0 h vs. 2.7 ± 1.8 h, $p = 0.03$) than did those with anterior AMI. TC was associated with a shorter R-R interval (657 ± 116 ms vs. 791 ± 164 ms, $p < 0.001$), a lower maximal ST-segment elevation (4.5 ± 4.9 mm vs. 7.0 ± 3.0 mm, $p < 0.001$), and a greater number of leads with ST-segment elevation (7.5 ± 2.1 vs. 6.3 ± 2.0, $p = 0.001$), compared with anterior AMI. TC was more frequently associated with ST-segment elevation in leads III, aVF, II, −aVR, and I, especially lead −aVR, and was less frequently associated with ST-segment elevation in leads aVL and V_1 to V_4, especially lead V_1 (Fig. 1A). TC was also more frequently associated with the absence of abnormal Q waves (42% vs. 26%, $p = 0.048$), absence of reciprocal changes (94% vs. 51%, $p < 0.001$), and a longer maximal QTc interval (567 ± 81 ms vs. 489 ± 61 ms, $p < 0.001$). The absence of abnormal Q waves, absence of reciprocal changes, presence of ST-segment elevation in lead −aVR (i.e., ST-segment depression in lead aVR), and absence of ST-segment elevation in lead V_1 identified TC with sensitivities of 42%, 94%, 97%, and 94%, specificities of 74%, 49%, 75%, and 71%, and predictive accuracies of 71%, 53%, 77%, and 73%, respectively. The combination of the presence of ST-segment depression in lead aVR and the absence of ST-segment elevation in lead V_1 identified TC with 91% sensitivity, 96% specificity, and 95% predictive accuracy, which was superior to any other electrocardiographic findings (Fig. 1B).

Time to presentation may determine electrocardiographic presentation. To clarify electrocardiographic characteristics of TC, we studied only patients who were admitted within 6 h of symptom onset. Moreover, most previous studies assessing electrocardiographic findings of TC have paid little attention to limb leads. We therefore evaluated the frequencies of ST-segment elevation in all 12 leads (treating lead aVR as lead −aVR). Compared with anterior AMI, TC was associated with less ST-segment elevation and more frequent absence of abnormal Q waves, suggesting less myocardial damage. Nevertheless, in TC, ST-segment elevation was more extensive, involving not only the anterior region. Most patients with anterior AMI had ST-segment elevation in leads V_1 to V_4, indicating ischemia of the anteroseptal region. The extent of ST-segment elevation in anterior AMI may reflect the extent of area at risk. In TC, ST-segment elevation most frequently occurred in lead −aVR. The display of lead aVR (−150°) is inverted because lead −aVR (+30°) bridges the gap between lead I (0°) and lead II (60°). Lead −aVR faces the apical and inferolateral regions, which none of the standard 12 leads face directly. In anterior AMI, the perfusion territory of the left anterior descending coronary artery usually does not extend to these regions; therefore, the prevalence of ST-segment elevation in lead −aVR is low. Interestingly, diffuse ST-segment elevation (most prominently in lead −aVR) in TC is thought to reflect the extensive distribution of wall-motion abnormalities centered around the apex, extending beyond the perfusion territory of any single coronary artery. On the other hand, ST-segment elevation was rare in lead V_1, which may

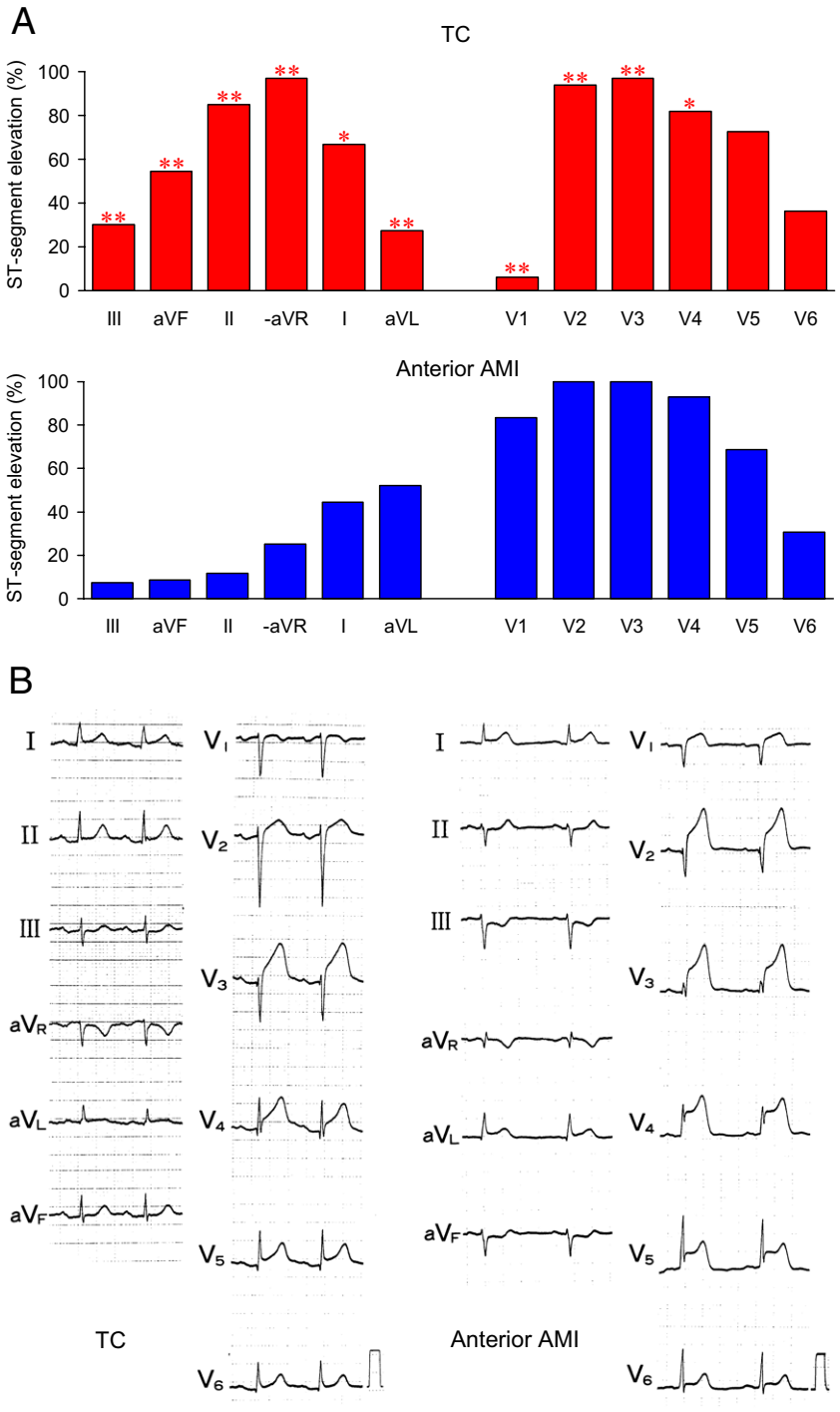

Figure 1 **Comparisons of Admission Electrocardiographic Findings Between TC and Anterior AMI**

The prevalence of ST-segment elevation **(A)** and representative electrocardiograms **(B)** of Takotsubo cardiomyopathy (TC) and anterior acute myocardial infarction (AMI). *$p < 0.05$, **$p < 0.01$ versus anterior AMI.

face the right ventricular anterior region as well as the right paraseptal region. The most likely reason for less ST-segment elevation in lead V_1 in TC is that wall-motion abnormalities in TC rarely extend to the region faced by lead V_1; moreover, less ST-segment elevation may result from the electrical force induced by ST-segment elevation in the posterolateral region (3). One can speculate that TC, but not anterior AMI, is usually associated with ST-segment elevation in the posterolateral region.

We conclude that the ST-segment shift in leads aVR and V_1 can help to differentiate TC from anterior AMI in patients who are

admitted within 6 h of symptom onset. Further studies in larger numbers of patients are needed to verify our results.

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Letter to the Editor

High-Dose Statin, Not So IDEAL?

Tikkanen et al. (1) present an interesting post-hoc analysis of the IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering) study with a novel statistical method using all vascular rather than just the first cardiovascular events recorded, and they propose highly significant p values in support of using top-dose atorvastatin (80 mg/day) versus "standard" dose simvastatin (20 mg/day or uptitrated). The authors propose that such a statistical approach is of value because of the health economic importance of subsequent events, and that their results "suggest that clinicians should not hesitate to prescribe high-dose statin therapy for patients experiencing multiple recurrent cardiovascular events."

The background: The IDEAL study was an apparently well-run, open-label drug comparison trial in all post-myocardial infarct (MI) patients, of whom about 40% had already experienced revascularization and an 8.3% mortality rate (±0.1% between groups) during the mean 4.8 years of follow-up. The lack of mortality benefit is in line with atorvastatin's well-known inability to lower mortality, with the notable findings of the TNT (Treating to New Targets) trial and the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial that ended with numerically more deaths on top-dose atorvastatin than on low-dose and placebo, respectively (2,3).

Since mortality is not reduced, we have to ask about the nature of events prevented. The authors report that the first, second, and third events recorded were 46%, 51%, and 43% on the basis of decisions to hospitalize or to revascularize, whereas nonfatal MIs represented only 18%, 15%, and 15%, respectively. The ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study found angina reduced by 41%, likely by the nitric oxide/endothelial nitric oxide synthase nitroglycerin mimicking action that all statins share (4,5). The amount of angina experienced is a factor potentially affecting the medical decisions and the number of MIs recorded in a trial.

Thus, we have to be careful including these softer end points, and since the authors bring up health economics, we should be aware that at the current (Vermont) retail prices of $5 per pill for "high dose-statin" (Lipitor 80 mg and Crestor 20 mg), it would cost, as an example, from $560,000 to $1,160,000—slightly less in men, more in women—to prevent either a revascularization, stroke, or MI on the basis of the results of the recent JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) primary prevention study (rosuvastatin 20 mg vs. placebo) (6). Even at the current Vermont price for generic lovastatin ($0.78 for 20 mg), such costs, likely even in secondary prevention, may be many times those of an angioplasty, a hospitalization for angina, or the cost of a (not clearly defined nor quantified by Tikkanen et al. [1]) peripheral vascular disease event.

These drug costs call into question the benefit of statins, including high-dose statin, regarding health economic benefits. Therefore, could the authors comment on the health economic effects of their expanded end point analysis, and provide numbers needed to treat for individual end points, with confidence intervals?

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