ST-Segment Elevation Resolution in Lead aVR
— A Strong Predictor of Adverse Outcomes in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome —

Masami Kosuge, MD; Toshiaki Ebina, MD; Kiyoshi Hibi, MD; Mitsuaki Endo, MD; Naohiro Komura, MD; Katsutaka Hashiba, MD; Masayoshi Kiyokuni, MD; Naoki Nakayama, MD; Satoshi Umemura, MD; Kazuo Kimura, MD

Background The impact of ST-segment elevation resolution in lead aVR on outcomes in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) is unclear.

Methods and Results Electrocardiograms (ECGs) were recorded on admission and 6 h later in 367 patients with NSTE-ACS. ST-segment deviation ≥0.5 mm was considered significant: 92 patients had ST-segment elevation in lead aVR on admission ECG (ST\(_{aVR}\)), and 275 did not. Among patients with ST\(_{aVR}\), 50 had ST resolution, defined as a reduction >50% in the degree of ST-segment elevation in lead aVR from admission to 6 h later, and 42 did not. ST\(_{aVR}\) without ST resolution was associated with older age, greater ST-segment depression in other leads on admission and 6 h later, higher rates of positive troponin T, left main and/or 3-vessel coronary disease, and adverse events such as death, (re)infarction, or urgent revascularization within 30 days after admission. Multivariate analysis showed that ST\(_{aVR}\) without ST resolution was the strongest independent predictor of death or (re)infarction within 30 days after admission (hazard ratio 5.62, \(p=0.018\)).

Conclusions ST\(_{aVR}\) without ST resolution is a strong predictor of 30-day adverse outcomes and correlates with the extent and severity of coronary artery disease in patients with NSTE-ACS. (Circ J 2008; 72: 1047–1053)

Key Words: Acute coronary syndrome; Electrocardiogram; Prognosis; ST-segment

Patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) are heterogeneous with regard to both the underlying pathophysiology and future risk of cardiac events. Early risk stratification is crucial for appropriate management of this condition and for deciding whether high-risk patients should receive more potent invasive therapies. The electrocardiogram (ECG) is the most easily accessible and widely used diagnostic tool for risk stratification. It is also inexpensive and non-invasive. Many studies have shown that ST-segment depression on the admission ECG is a powerful predictor of poor outcomes in patients with NSTE-ACS. More recently, several biomarkers of myocardial damage (troponin), inflammation (C-reactive protein, CRP), and hemodynamic stress (brain natriuretic peptide, N-terminal pro-brain natriuretic peptide) have also been linked to the risk of subsequent cardiac events. However, a recent large study of 7,800 patients with NSTE-ACS enrolled in the GUSTO-IV (Global Utilization of Strategies to Open Occluded Arteries-IV ACS) trial highlighted the striking prognostic value of ST-segment depression on admission, even in the context of these expanded biomarker profiles.

Lead aVR, a frequently ignored lead, has not been considered in most previous studies assessing the prognostic role of ECG in patients with NSTE-ACS. However, several studies have found that ST-segment elevation in lead aVR on the admission ECG (ST\(_{aVR}\)) offers better prognostic information than ST-segment depression in leads other than aVR in patients with NSTE-ACS. ST\(_{aVR}\) has been shown to be superior to ST-segment depression in other leads for predicting the risk of death in patients with non-ST-segment elevation acute myocardial infarction. We have also previously shown that ST\(_{aVR}\) is more strongly associated with left main and/or 3-vessel coronary disease and subsequent adverse events than ST-segment depression in other leads in patients with NSTE-ACS. However, the prognostic impact of ST-segment elevation resolution in lead aVR has yet to be investigated, so the present study was designed to investigate the relation of ST-segment elevation resolution in lead aVR to angiographic findings and to 30-day outcomes in patients with NSTE-ACS.

Methods

Patients

We retrospectively studied 367 consecutive patients (mean age 67±10 years, range 38–94; 252 men, 115 women) who fulfilled the following criteria: (1) typical chest discomfort attributed to cardiac ischemia, lasting at least 5 min and occurring within 48 h before hospital admission and in-
volving an unstable pattern of pain, consisting of rest pain, new onset, severe or frequent angina, or accelerating angina; (2) no conditions precluding the evaluation of ST-segment changes on the ECG (left or right bundle branch block, left ventricular hypertrophy, digitalis glycoside therapy, or ventricular pacing); (3) fully assessable ECGs on admission and 6 h after admission; and (4) fully assessable angiographic data during hospitalization. Patients with nonischemic or atypical symptoms, persistent new ST-segment elevation in leads other than aVR, or a recent history (<6 months) of ischemic attacks were excluded. Aspirin, intravenous heparin, and nitrates were administered to most patients. Other clinically indicated medications were used at the discretion of the treating physician. The physicians obtained informed consent from each patient, and the study was approved by the hospital ethics committee.

ECG Analysis

Standard 12-lead ECGs were recorded on admission and 6 h after admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. All ECGs were examined by a single cardiologist who was unaware of all other clinical data. ST-segment shifts were measured 80 ms after the J point for ST-segment depression and 20 ms after this point for ST-segment elevation, using the preceding TP segment as baseline. ST-segment deviation was considered present if deviation was ≥0.5 mm in any lead.

Biomarker Analysis

Blood samples for measurement of plasma CRP levels were taken on admission. High-sensitivity CRP levels were measured by latex CRP Mono tests in a Behring BN II Nephelometer (Behring Diagnostics, Tokyo, Japan) using standard 12-lead ECGs were recorded on admission and 6 h after admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. All ECGs were examined by a single cardiologist who was unaware of all other clinical data. ST-segment shifts were measured 80 ms after the J point for ST-segment depression and 20 ms after this point for ST-segment elevation, using the preceding TP segment as baseline. ST-segment deviation was considered present if deviation was ≥0.5 mm in any lead.

<table>
<thead>
<tr>
<th>Table 1 Baseline Characteristics</th>
<th>STaVR (–) (n=275)</th>
<th>STaVR (+) (n=50)</th>
<th>Resolution (–) (n=42)</th>
<th>Resolution (+) (n=50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±11</td>
<td>69±8</td>
<td>72±10</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>192 (70%)</td>
<td>37 (74%)</td>
<td>23 (55%)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>56 (20%)</td>
<td>13 (26%)</td>
<td>12 (29%)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Prior PCI</td>
<td>53 (19%)</td>
<td>10 (20%)</td>
<td>7 (17%)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Prior CABG</td>
<td>13 (5%)</td>
<td>6 (12%)</td>
<td>3 (7%)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>84 (31%)</td>
<td>17 (34%)</td>
<td>20 (48%)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>173 (63%)</td>
<td>38 (76%)</td>
<td>28 (67%)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>142 (52%)</td>
<td>23 (46%)</td>
<td>23 (55%)</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean value±SD or number (% of patients).

*STaVR, ST-segment elevation in lead aVR on admission electrocardiograms (ECG); Resolution, reduction >50% in the degree of ST-segment elevation in lead aVR from admission to 6 h later; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HMG CoA, hydroxymethylglutaryl-coenzyme A reductase inhibitor; CRP, C-reactive protein; CK-MB, creatine kinase MB isoenzyme.*
polystyrene microbeads coated with monoclonal mouse antibodies. In addition, a qualitative assay for cardiac-specific troponin T (Roche Diagnostics, Tokyo, Japan; detection limit, 0.1 ng/ml of cardiac-specific troponin T) was simultaneously performed. A troponin T level ≥0.1 ng/ml was defined as positive. The test was repeated at 8–12 h in patients who were negative for troponin T within 6 h after the onset of symptoms. Levels of creatine kinase MB isoenzyme (CK-MB) were determined on admission, at 3-h intervals during the first 24 h, and in any patient with suspected reinfarction.

**Angiographic Analysis**

All patients underwent cardiac catheterization at a median of 3 days after admission. All coronary angiograms were evaluated by a single cardiologist who was unaware of all other clinical data. Stenosis ≥50% in the diameter of the left main coronary artery or ≥75% in 1 or more of the major epicardial vessels or their main branches was considered asclinically significant.

**Clinical Data Collection**

All patients were followed up for 30 days after admission to hospital. Major adverse events were defined as death, myocardial (re)infarction, or urgent revascularization within 30 days after admission. Myocardial (re)infarction was diagnosed on the basis of either enzyme or ECG evidence. Enzyme evidence of re-infarction was defined as a re-elevation of the CK-MB level to higher than the upper limit of normal if the previous level was in the normal range, or as 50% above the previous level if the previous level was higher than the upper limit of normal.

**Statistical Analysis**

Continuous data are expressed as means±SD, and categorical data are expressed as percentages. Analysis of variance was used to calculate p-values for continuous variables. Chi-square analysis was used to compare categorical variables. Differences were considered statistically significant at p<0.05. Event-free curves were generated by the Kaplan-Meier method and compared by the log-rank test. We used Cox proportional-hazards regression analysis to calculate adjusted hazard ratios and 95% confidence intervals for major predictors of adverse events (defined as death, myocardial (re)infarction, or urgent revascularization within 30 days after admission) among the variables associated (p≤0.20) with these endpoints on univariate analysis. Data were analyzed using SAS version 8.2 (SAS Institute, Cary, NC, USA) and SPSS version 12.0 (SPSS Inc, Chicago, IL, USA).

**Results**

In total, 92 patients had ST abdominal aVR, and 275 did not. Among the patients with ST abdominal aVR, 50 had ST resolution, defined as a reduction >50% in the degree of ST-segment elevation in lead aVR from admission to 6 h later, and 42 did not.

**Patients’ Characteristics**

The baseline clinical characteristics of the patients, according to ST-segment status in lead aVR, are shown in Table 1. Patients who had ST abdominal aVR without ST resolution were older and had higher rates of using ß-blockers and nitrates before admission and intravenous nicorandil in hospital, Killip class ≥2 on admission, and positive troponin T, as well as a higher level of CK-MB on admission. Heart rate on admission was higher in patients with ST abdominal aVR. There was a trend toward a lower rate of men, a higher rate of diabetes mellitus, and a higher level of high-sensitivity CRP on admission in patients who had ST abdominal aVR without ST resolution, but the differences did not reach statistical significance. There were no significant differences in prior myocardial infarction, prior revascularization, hypertension, symptom onset ≤6 h, or systolic blood pressure on admission among the 3 groups. Coronary artery bypass surgery was more frequently performed during hospitalization in patients who had ST abdominal aVR without ST resolution.

**ECG Findings**

The ECG findings according to ST-segment status in lead aVR are shown in Table 2. On the admission ECG, all patients with ST abdominal aVR had ST-segment depression in leads...
other than aVR. The sum of ST-segment depression was higher in patients who had ST\(^a_{\text{aVR}}\), especially those without ST resolution. On ECG recorded at 6h after admission, all patients who had ST\(^a_{\text{aVR}}\) without ST resolution had ST-segment depression in leads other than aVR. The sum of ST-segment depression 6h later was higher in patients with ST\(^a_{\text{aVR}}\), especially those without ST resolution. Among patients with ST\(^a_{\text{aVR}}\), those without ST resolution had a greater magnitude of ST-segment elevation in lead aVR on admission and 6h later than did patients with ST resolution.

**Angiographic Findings and Cardiac Procedures During Hospitalization**

The angiographic findings of the patients according to the ST-segment status in lead aVR are shown in Table 2.

**Table 3 Adverse Events Within 30 Days After Admission**

<table>
<thead>
<tr>
<th>30-day outcome</th>
<th>ST(^a_{\text{aVR}}) (–) (n=275)</th>
<th>ST(^a_{\text{aVR}}) (+) Resolution (+) (n=50)</th>
<th>ST(^a_{\text{aVR}}) (+) Resolution (–) (n=42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0.048</td>
</tr>
<tr>
<td>Myocardial (re)infarction</td>
<td>2 (1%)</td>
<td>2 (4%)</td>
<td>8 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or (re)infarction</td>
<td>2 (1%)</td>
<td>3 (6%)</td>
<td>9 (21%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>8 (3%)</td>
<td>5 (10%)</td>
<td>6 (14%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Urgent CABG</td>
<td>4 (2%)</td>
<td>3 (6%)</td>
<td>22 (52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent revascularization (PCI or CABG)</td>
<td>12 (4%)</td>
<td>8 (16%)</td>
<td>28 (67%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any of the above</td>
<td>14 (5%)</td>
<td>9 (18%)</td>
<td>30 (71%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are number (%) of patients. Abbreviations as in Table 1.
ST-Segment Elevation Resolution in aVR.

Table 4  Multivariate Predictors of 30-Day Adverse Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Death or (re)infarction</th>
<th>Death, (re)infarction or urgent revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Positive troponin T</td>
<td>4.14</td>
<td>1.17–22.6</td>
</tr>
<tr>
<td>STaVR (–)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>STaVR (+) resolution (+)</td>
<td>2.10</td>
<td>0.52–10.5</td>
</tr>
<tr>
<td>STaVR (+) resolution (–)</td>
<td>5.62</td>
<td>2.10–64.1</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

Discussion

To the best of our knowledge, this is the first study to examine the prognostic value of ST-segment elevation resolution in lead aVR in patients with NSTE-ACS. We found that STaVR without ST resolution (ie, persistent ST-segment elevation in lead aVR) was the strongest predictor of adverse outcomes at 30 days and was closely associated with the extent and severity of underlying coronary artery disease in patients with NSTE-ACS. In contrast, STaVR with ST resolution (ie, transient ST-segment elevation in lead aVR) was not significantly associated with 30-day outcomes. These findings suggest that analysis of the ST-segment changes in lead aVR after admission can facilitate risk stratification in patients with NSTE-ACS.

Possible Mechanisms of ST-Segment Elevation in Lead aVR

Acute coronary syndromes are categorized into ST-segment elevation myocardial infarction and NSTE-ACS. The mechanism underlying ST-segment elevation in lead aVR may differ between these 2 conditions. In ST-segment elevation myocardial infarction, ST-segment elevation in lead aVR may reflect transmural ischemia in the dominant basal septum, often caused by left-main obstruction or obstruction of the proximal left anterior descending coronary artery with involvement of the first septal branch20,21 resulting in a superior orientation of the ST-segment vector15. In NSTE-ACS, ST-segment elevation in lead aVR may reflect global subendocardial ischemia. Lead aVR has the unique position of “looking” into the left ventricular cavity from the right shoulder22. In circumferential ischemia, often associated with left main or 3-vessel disease, accompanied by a sudden dramatic increase in left ventricular end-diastolic pressure and severe extensive ischemia of the subendocardial layer23, the ST-segment vector is directed to the right, resulting in ST-segment elevation in lead aVR. We and other investigators have shown that ST-segment elevation in lead aVR is closely associated with left main and/or 3-vessel disease in patients with NSTE-ACS16–18. In the present study, the frequency of ST-segment elevation in lead aVR on the admission ECG was 25%, as compared with 7–33% in previous studies16–18. The frequency of ST-segment elevation in lead aVR may differ according to disease severity on coronary angiography, which varies depending on the type of study and inclusion criteria for patients.

Persistent ST-Segment Elevation in Lead aVR After Admission

Kaul et al9 showed that the persistence of ST-segment depression beyond 6 h after symptom onset was more associated with a 3-fold higher risk of death or myocardial infarction at 6 months than was the resolution of ST-segment depression within 6 h in patients with NSTE-ACS. This finding suggests that prolonged ST-segment depression correlates with worse outcomes. We have also previously demonstrated that persistent ST-segment depression 6 h after admission is associated with multivessel disease and 30-day adverse events in patients with NSTE-ACS, but did not consider lead aVR in that study23. We subsequently showed that ST-segment elevation in lead aVR on admission is more strongly associated with left main and/or 3-vessel coronary disease and subsequent adverse events than is ST-segment depression in other leads in patients with NSTE-ACS17,18. The present study confirms and extends our previous findings by showing that persistent ST-segment elevation in lead aVR was closely associated with “severe” left main and/or 3-vessel disease and a strikingly higher risk of 30-day adverse events in patients with NSTE-ACS. In patients who had persistent ST-segment elevation in lead aVR, severe and prolonged myocardial ischemia refractory to medical treatment, associated with more severe and unstable coronary artery disease, might have contributed to the lack of ST resolution. Consequently, urgent coronary artery bypass graft surgery was more frequently performed in these patients. Early identification of patients with left main and/or 3-vessel disease who require surgical revascularization is crucial for deciding whether early treatment with clopidogrel should be initiated. Because combined antiplatelet therapy with aspirin and clopidogrel improves outcomes in patients with NSTE-ACS24,25 the addition of clopidogrel to aspirin

Patients with STaVR, especially those without ST resolution, had a higher rates of multivessel disease and left main and/or 3-vessel coronary disease. In particular, the rates of severe left main and/or 3-vessel coronary disease, defined as 75% stenosis of the left main coronary artery and/or 90% stenosis in 2 proximal lesions of the major epicardial vessels, were much higher in patients who had STaVR without ST resolution (Fig 1).

Predictors of 30-Day Outcome

Patients with STaVR without ST resolution had higher rates of death, (re)infarction, or urgent revascularization within 30 days after admission (Table 3, Fig 2). In the multivariate models, STaVR without ST resolution was the strongest predictor of restricted events (death or [re]infarction) and the composite endpoint (death, [re]infarction, or urgent revascularization) at 30 days, followed by positive troponin T (Table 4). The other variables associated with these endpoints on univariate analysis, including age, sex, Killip class, high-sensitivity CRP, CK-MB, the magnitude of ST-segment depression on the admission and 6 h later, and the sum of ST-segment depression on the admission and 6 h later, were not significant predictors of these endpoints. STaVR with ST resolution was also not a significant predictor of these endpoints.
on admission has been recommended. However, such combination therapy can increase the risk of major bleeding in patients undergoing early coronary artery bypass graft surgery within 5 days after the withdrawal of clopidogrel. Therefore, some have recommended that clopidogrel not be given until after angiography to avoid an increased risk of bleeding in patients likely to require immediate surgery. However, this recommendation is not included in the European Society of Cardiology guidelines, because such patients are relatively uncommon and surgery can frequently be deferred for several days. Nonetheless, postponing treatment with clopidogrel may be advantageous in selected patients who require immediate surgery. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of NSTE-ACS recommend early invasive management for high-risk patients; however, a meta-analysis of randomized clinical trials showed no incremental improvement in outcomes when angiography was performed within 24 h. Our results suggest that early coronary angiography can be expedited by postponing clopidogrel in patients with persistent ST-segment elevation in lead aVR who are likely to need immediate surgical revascularization.

ST-Segment Elevation in Lead aVR vs ST-Segment Depression in Other Leads

Several clinical trials have demonstrated the prognostic importance of the magnitude of ST-segment depression in patients with NSTE-ACS. In our study, persistent ST-segment elevation in lead aVR was associated with a greater degree of ST-segment depression on admission and 6 h later. However, multivariate analysis showed that persistent ST-segment elevation in lead aVR per se, apart from the magnitude of ST-segment depression, was related to adverse outcomes. We and other investigators have found that ST-segment elevation in lead aVR on admission offers better prognostic information than ST-segment depression in other leads in patients with NSTE-ACS.

Study Limitations

This study was retrospective, performed at a single center, and included a small number of patients who underwent coronary angiography during hospitalization. Moreover, we examined the prognostic implications of ST-segment elevation in lead aVR only with respect to 30-day outcomes. However, in the GUSTO-IV trial of 7,800 patients with NSTE-ACS, ST-segment depression on admission had a greater prognostic impact on mortality at 30 days than on mortality at 1 year. The prognostic value of ST-segment depression on admission thus appears to be higher for outcomes at 30 days. Furthermore, the rate of either death or (re)infarction was low overall in our study, which may reflect genetic and environmental differences between Japan and other countries or a higher rate of revascularization during hospitalization. Further studies in larger numbers of patients are needed to verify the prognostic impact of ST-segment elevation in lead aVR.

Conclusion

ST-segment elevation in lead aVR 6 h after admission provides very useful information about the need for more aggressive treatment and the extent and severity of underlying coronary artery disease, and can be used to predict outcomes in patients with NSTE-ACS. The predictive power of this simple, readily available, and noninvasive prognostic factor is very strong, facilitating the timely triage of patients to appropriate therapeutic interventions.

References


