Clinical Implications of Electrocardiograms for Patients With Non-ST-Segment Elevation Acute Coronary Syndromes in the Interventional Era

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In patients with non-ST-segment elevation acute coronary syndromes, early risk stratification is crucial for appropriate management of this condition and for deciding whether early invasive strategies should be adopted. The electrocardiogram (ECG) has been extensively used for risk stratification, and the presence of ST-segment depression is an especially strong predictor of poor outcomes. Furthermore, quantitative analysis of ST-segment depression, ie, the degree and extent of ST-segment depression, and the time from symptom onset to the evaluation of ECG provide important information on prognosis. ST-segment elevation in lead aVR in addition to ST-segment depression in other leads is a very valuable marker of left main and/or 3-vessel disease. This review explores the clinical importance of the ECG in the current interventional era. (*Circ J* 2009; 73: 798–805)

Key Words: Acute coronary syndrome; Diagnosis; Electrocardiogram; Prognosis

Patients with non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) are heterogeneous with regard to both the underlying pathophysiology and the future risk of cardiac events! Early risk stratification is crucial for appropriate management of this condition and for deciding whether early invasive strategies should be adopted? Because of its simplicity, safety, widespread availability and low cost, the electrocardiogram (ECG) has been extensively used for risk stratification. The ECG plays a central role in diagnostic and triage pathways for NSTEMI-ACS and provides important prognostic information in the current interventional era.

Importance of ECG in Risk Stratification

Two treatment strategies have emerged for the early management of NSTEMI-ACS: one strategy is invasive, and the other is conservative. General consensus has been reached that patients at higher risk benefit more from early invasive strategies, increasing the importance of appropriate risk stratification. Recently, biomarkers of myocardial damage (troponin), inflammation (C-reactive protein), hemodynamic stress (brain natriuretic peptide, N-terminal pro-brain natriuretic peptide) and renal function (creatinine) have also been linked to the risk of subsequent cardiac events^{3–5} However, the GUSTO-IV (Global Utilization of Strategies to Open Occluded Arteries-IV ACS) trial of 7,800 patients with NSTEMI-ACS has highlighted the striking prognostic value of ST-segment depression on admission as compared

with independent factors, including expanded biomarker profiles as well as traditional risk factors (**Figure 1**).³ The ECG thus continues to have important roles in prognosis as well as in diagnosis and selection of the optimal treatment strategy in patients with NSTEMI-ACS.

ST-Segment Depression

ST-segment changes are considered the most important electrocardiographic feature during acute myocardial ischemia. In patients with transmural ischemia, ST-segment elevation is present in leads facing the site of ischemia. Therefore, the ischemia-related artery can be predicted on the basis of the leads showing ST-segment elevation during ischemic attacks. Whereas in many patients with non-transmural ischemia, ST-segment depression occurs in leads V4 to V6 leads (mainly in lead V5) independently of the ischemia-related artery, in which underlying mechanism remains unclear. It is thus difficult to predict the ischemia-related artery on the basis of these leads. On exercise thallium myocardial scintigraphy, however, the site of a reversible decrease in blood flow corresponds to the region supplied by the ischemia-related artery, even in patients who have ST-segment depression in leads V4 to V6 (primarily lead V5) during myocardial ischemia.

The presence of acute ischemic changes on the admission ECG has been associated with a higher risk of cardiac events; ST-segment depression is an especially strong predictor of poor outcomes in patients with NSTEMI-ACS.^{3,6–15} The presence of even minimal (0.05 mV) ST-segment depression has been shown to be independently associated with adverse outcomes.⁶ Furthermore, the degree and extent of ST-segment depression, not only its presence or absence, strongly correlate with the severity and outcomes of coronary artery disease.^{3,7,12–14} Increased mortality has been associated with increased cumulative ST-segment depression or an increased number of leads with ST-segment depression on admission in patients with NSTEMI-ACS. A meta-analysis of 12,030 patients with stable coronary artery

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Figure 1. Relative contributions of significant, independent factors to the prediction of 30-day death, 30-day death/myocardial infarction (MI), and 1-year death. ST-segment depression on admission had a very high prognostic value even after considering independent factors such as expanded biomarker profiles in addition to traditional risk factors in 7,800 patients with non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) in the GUSTO-IV trial (Reproduced with permission from *J Am Coll Cardiol* 2006; **48**: 939–947). Creat Cl, creatinine clearance; CRP, C-reactive protein; Curr Smok, current smoker; HR, heart rate; Hx angina, history of angina pectoris; Hx CABG, history of coronary artery bypass graft; Hx CHF, history of congestive heart failure; Hx MI, history of MI; Hx LipidRx, history of hyperlipidemic therapy; Hx PCI, history of percutaneous coronary intervention; Hx strk, history of stroke; NT-proBNP, N-terminal pro-brain natriuretic peptide; ST-sep, ST-segment depression; TnT, troponin T; Wgt, weight.

Table. Differences in Treatment Outcomes at 1 Year: Patients Classified According to Summed ST-Segment Deviation and Total Number of Leads With ST-Segment Deviation

	Noninvasive strategy	Invasive strategy	Adjusted odds ratio* (95%CI)
Endpoint: death/myocardial infarction			
Summed ST-segment deviation			
0–0.25 mV	9.3%	11.8%	1.26 (0.70–2.28)
0.30–0.55 mV	13.3%	6.2%	0.42 (0.23–0.80)
≥0.6 mV	19.4%	9.5%	0.41 (0.24–0.70)
Number of leads with ST-segment deviation			
0–4 leads	9.1%	10.0%	1.13 (0.65–1.97)
5–7 leads	15.7%	8.0%	0.45 (0.25–0.81)
≥8 leads	19.2%	13.5%	0.36 (0.51–1.43)

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*Adjusted for age, gender, previous myocardial infarction, diabetes, hypertension, smoking status, and troponin T.
CI, confidence interval.

disease enrolled in 60 studies demonstrated that the amount of ST-segment depression during exercise stress testing is strongly associated with critical coronary artery disease, such as left main and/or 3-vessel disease (LM/3VD).¹⁶ This finding could be extended to ST-segment changes on admission in patients with NSTEMI-ACS. The increased mortality in patients with higher ST-segment depression might be explained by their increased severity of coronary artery disease, and such patients with higher ischemic burden derive a good deal of benefit, as reflected in decreased mortality and morbidity, from invasive treatment strategies (Table).^{13,14} Quantitative electrocardiographic analysis thus provides important information on prognosis and expected benefits of treatment. In addition, the time from symptom onset to the evaluation of ECG appears to have an important impact on its prognostic value. Kaul et al demonstrated that patients with ST-segment depression for more than 6 h after symptom onset have a higher risk of death or myocardial

infarction at 6 months than those with ST-segment depression within 6 h of symptom onset.¹⁴ It was demonstrated that among NSTEMI-ACS patients with ST-segment depression on the admission ECG, those with persistent ST-segment depression 6 h after admission despite intensive medical treatment have a higher risk of adverse events at 30 days.⁹ Such patients have higher frequencies of multivessel disease, severe stenosis, visible thrombi and complex culprit lesions. Prolonged as well as profound ST-segment depression may be indicative of more severe and/or unstable coronary artery disease. Serial analysis of ECGs can provide additional information that can enhance the accuracy of predicting outcomes in patients with NSTEMI-ACS.

ST-Segment Elevation in Lead aVr

Previous most studies assessing the clinical significance of the admission ECG in patients with NSTEMI-ACS have

Figure 2. Electrocardiogram (ECG) of left main and/or 3-vessel disease (LM/3VD). (A) Representative ECG on admission in patients with LM/3VD (Reproduced with permission from *Am J Cardiol* 2005; 95: 1366–1369) ST-segment depression is found in leads I, II, aVL, aVF, and V4 to V6, whereas ST-segment elevation of 0.15 mV occurs in lead aVR. Coronary angiography showed total occlusion of the right coronary artery (segment 3) and 75% stenosis of the left main trunk, left anterior descending coronary artery (segment 6), and left circumflex coronary artery (segment 11). (B) LM/3VD is associated with extensive ischemia of the endocardial side of the left ventricle (white part of the Figure), resulting in ST-segment depression in most leads, but ST-segment elevation in lead aVR (a so-called “cavity lead”).

focused on ST-segment deviation in leads other than aVR; that is, clinicians have used an “11-lead” ECG, neglecting lead aVR.^{3,6–15} Therefore, the clinical significance of ST-segment deviation in lead aVR in patients with NSTEMI-ACS remains poorly understood.

Several studies have found analysis of lead aVR to be useful for the evaluation of NSTEMI-ACS.^{17–21} Gorgels et al. reported that ST-segment elevation in lead aVR accompanied by ST-segment depression in leads I, II and V4 to V6 during episodes of angina is highly suggestive of LM/3VD in patients with rest angina.¹⁷ Barrabés et al demonstrated that the presence of ST-segment elevation in lead aVR predicts the risk of in-hospital death in patients with a first non-ST-segment elevation acute myocardial infarction.¹⁸ In that study, ST-segment elevation in lead aVR was also related to LM/3VD; however, coronary angiography was performed in only 56% of the subjects within 6 months after infarction.

Early identification of patients with LM/3VD, whose prognosis remains poor, is an important factor in selecting the optimal treatment strategy for patients with NSTEMI-ACS. Because combined antiplatelet therapy with aspirin and clopidogrel improves outcomes in patients with NSTEMI-ACS, current international clinical guidelines for the management of NSTEMI-ACS recommended the early initiation of treatment with this combination of drugs.^{2,22} However, such combined therapy can increase the risk of perioperative bleeding and the need for blood transfusions in patients undergoing immediate coronary artery bypass graft surgery (CABG).²³ Therefore, early (ie, before angiography), accurate, non-invasive identification of patients with LM/3VD is thus a major clinical issue with important therapeutic implications. We examined the predictors of LM/3VD on the admission ECG in patients with NSTEMI-ACS who underwent coronary angiography in the acute phase.¹⁹ ST-segment elevation in lead aVR was found to be highly suggestive of LM/3VD (**Figure 2A**), and the converse was also true, ie, the absence of this finding was rarely associated with LM/3VD.¹⁹ Furthermore, ST-segment elevation in lead aVR on admission has been shown to have higher prognostic value than ST-segment depression in other leads in patients with NSTEMI-ACS both in some single-centers and a multi-center trial.^{18–21} However, Yan et al recently reported that ST-segment elevation in lead aVR was associated with higher unadjusted in-hospital and 6-month mortality, but did not provide better prognostic information than comprehensive risk stratification using the validated GRACE (Global Registry of Acute Coronary Events) risk model.²⁴ This conclusion was based on an analysis of data from 5,064 patients in the GRACE study. The inconsistent prognostic values of ST-segment elevation in lead aVR may be explained by the lower prevalence of ST-segment elevation in lead aVR in the study by Yan et al²⁴ (only 7.3%) than in previous studies (27–33%)^{18–20}; the lower prevalence in the former may have limited the power of the study to explore the relation between ST-segment elevation in lead aVR and outcomes reliably.²⁵ In patients with NSTEMI-ACS, disease severity on coronary angiography, which varies depending on the type of study and inclusion criteria, influences the prognostic implications of ST-segment elevation in lead aVR. Moreover, among patients with NSTEMI-ACS who have ST-segment elevation in lead aVR on the admission ECG, those in whom ST-segment elevation in lead aVR persists 6 h after admission despite intensive medical treatment have a higher risk of adverse events at 30 days than those in whom ST-segment elevation in lead aVR rapidly resolves

Figure 3. (A) Rearrangement of limb leads. Rearrangement of the limb leads in the order of III, aVF, II, I and aVL (ie, in the order that the regions face the heart) facilitates an understanding of their spatial relationship to the heart (Modified reproduced with permission from *Heart* 2000; **83**: 657–660). (B) Prevalence of negative T waves in patients with acute coronary syndrome (ACS) and those with acute pulmonary embolism (APE) (Modified reproduced with permission from *Am J Cardiol* 2007; **99**: 817–821). In the setting of ACS, (1) in the limb leads, negative T waves were rare in the inferior leads, especially in lead III, whereas negative T waves were frequently observed in leads I and aVL, particularly the latter; (2) in the precordial leads, negative T waves were mainly found in leads V3 and V4. The distribution of negative T waves appears to reflect the extent of severe ischemia caused by LAD disease. In the APE setting: (1) in the limb leads, negative T waves frequently appeared in the inferior leads, especially lead III, but were not found in lead I or aVL; (2) in the precordial leads, negative T waves were observed mainly in leads V1 and V2, and gradually decreased from leads V3 to V6. Dilatation of the right ventricle is thought to extend to region(s) facing the lead(s) with negative T waves.

after admission.²⁶ The former have more severe LM/3VD on coronary angiography than the latter.

Possible Mechanism of ST-Segment Elevation in Lead aVR

Lead aVR has a unique position because the positive pole is oriented to the right upper side of the heart.^{27,28} The mechanisms underlying ST-segment elevation in lead aVR might differ between ST-segment elevation and non-ST-segment elevation ACSs. In ST-segment elevation ACS, ST-segment elevation in lead aVR might reflect transmural ischemia in the basal septum, often caused by obstruction of left-main or the proximal left anterior descending coronary artery (LAD) with involvement of the first septal branch, resulting in a superior orientation of the ST-segment vector.^{29,30} In NSTEMI-ACS, lead aVR looks into the left ventricular cavity from the right shoulder (**Figure 2B**). Lead aVR is therefore referred to as a “cavity lead” and ST-segment elevation in this lead might reflect global subendocardial ischemia. When circumferential ischemia, often associated with LM/3VD, is accompanied by severe extensive ischemia of the subendocardial layer, the ST-segment vector is directed to the right shoulder, resulting in ST-segment elevation in lead aVR.³¹

Conventionally, non-ST-segment elevation ACS is defined

without considering ST-segment deviation in lead aVR. However, ST-segment elevation in lead aVR is a very valuable marker in “so-called” non-ST-segment elevation ACS.³²

QRS Duration

Although electrocardiographic assessment of myocardial ischemia is usually based on ST-segment deviation, QRS prolongation has been shown to be more sensitive than ST-segment changes for the detection of myocardial ischemia.³³ Several studies have found that that exercise-induced QRS prolongation is related to the severity and extent of coronary artery disease.³⁴ However, the relation between QRS duration on the admission ECG and the severity and extent of coronary artery disease has not been explored previously in patients with NSTEMI-ACS. We recently reported that not only ST-segment elevation in lead aVR and positive-troponin T on admission but also prolonged QRS duration, ie, maximal QRS duration >90 ms, on the admission ECG (QRS duration was measured from the beginning of the Q wave until the cut-point between the baseline and the perpendicular line starting from the end of the S wave [J point]) were highly suggestive of LM/3VD in patients with NSTEMI-ACS.³⁵ QRS prolongation is most likely to be caused by extensive isch-

Figure 4. Representative electrocardiograms on admission of acute coronary syndrome (ACS) and acute pulmonary embolism (APE) (Reproduced with permission from *Am J Cardiol* 2007; **99**: 817–821). (A) ACS. Negative T waves were seen in leads I, aVL and V1 to V6. Coronary angiography revealed 90% stenosis of the left anterior descending artery (segment 6). (B) APE. Negative T waves were seen in leads III, aVF and V1 to V4. A computed tomographic scan of the chest showed multiple filling defects in the main right and left pulmonary arteries. Lung perfusion scintigraphy revealed filling defects in the right upper, right middle and left upper lung fields.

emia. Experimental studies have reported that myocardial ischemia results in slow conduction velocity in ischemic areas³⁶ Such decreased conduction velocity is apparently a consequence of regional hyperkalemia, caused by leakage of potassium from ischemic cells. This decreased conduction velocity associated with myocardial ischemia is manifested as QRS prolongation on the surface ECG.

Combined Prognostic Utility of ECG and Biomarkers

Greater ST-segment deviation has been shown to be associated with a higher levels of cardiac troponins^{9,13,14} Troponins T and I are recognized as powerful predictors of outcomes in patients with NSTEMI-ACS^{2,3,14} Several studies have found that ST-segment depression in leads other than lead aVR combined with troponin levels on admission is useful for the evaluation of NSTEMI-ACS^{11,14,15} Holmvang et al showed that baseline values of troponins T and I combined with ST-T changes at presentation were useful for predicting death or myocardial infarction at 30 days in patients with unstable coronary artery disease¹⁵ Kaul et al noted that positive troponin T was associated with a higher risk of death or myocardial infarction at 6 months within each ST-segment depression category (no, 0.1 mV, and 0.2 mV ST-segment depression) among patients with NSTEMI-ACS¹⁴ ST-segment depression and troponins are markers of different pathophysiological mechanisms implicated in NSTEMI-

ACS. A combination of these 2 variables may therefore provide higher prognostic accuracy than either variable alone. Furthermore, ST-segment elevation in lead aVR combined with troponin T is an incrementally stronger predictor of adverse outcomes at 90 days as compared with either of these variables alone in patients with NSTEMI-ACS²⁰ These findings emphasize that ECG and biomarkers are complementary for the assessment of risk in patients with NSTEMI-ACS and suggest that both should be employed in prognosis and decision making.

Negative T Waves in NSTEMI-ACS

In patients with NSTEMI-ACS, ST-segment changes are considered the most important ECG feature, but T-wave changes have been shown to be more common than ST-segment changes^{6,37,38} A meta-analysis of 10,150 patients with NSTEMI-ACS demonstrated that women were significantly more likely to have negative T waves³⁸ T-wave changes have had little prognostic value in several large randomized clinical trials⁷ Savonitto et al reported that isolated negative T waves on the admission ECG were associated with less severe coronary disease and a relatively benign prognosis as compared with ST-segment changes among patients with ACS⁸ However, none of these studies used a quantitative approach to T-wave analysis. Holmvang et al noted that negative T waves in ≥ 5 leads at randomization was an independent predictor of death or myocardial infarction at 30

days in patients with NSTEMI-ACS.¹⁵ Jacobsen et al also suggested that patients with ≥ 6 leads showing abnormal T waves with concomitant ST-segment depression had a higher risk of death or myocardial infarction at 1 year when they did not receive early coronary angiography in patients with NSTEMI-ACS.³⁹ Negative T waves can actually be preceded by a transient ST-segment elevation that resolves by the time the ECG is recorded. Therefore, the ischemia-related artery can be predicted on the basis of the distribution of negative T waves. For example, negative T waves in precordial leads are most likely caused by LAD disease.⁴⁰

Electrocardiographic Differential Diagnosis of ACS and Acute Pulmonary Embolism (APE)

Negative T waves in precordial leads also frequently appear in patients with APE.^{41–44} The electrocardiographic manifestations of APE include rhythm and conduction disturbances and changes in P waves, QRS complexes or T waves. These abnormalities have been shown to be highly variable and frequently transient.^{41,42} Of many ECG abnormalities associated with APE, negative T waves are the most common as well as the most persistent change.^{41–44} Symptoms of APE, such as chest pain or dyspnea, are non-specific and are often difficult to differentiate from symptoms of ACS.^{44,45} The majority of preventable deaths associated with APE have been ascribed to missed diagnoses rather than to failure to respond to available therapies.⁴⁵ Elevated cardiac troponin levels are found in high-risk APE as well as in ACS; this variable is therefore of limited value for differential diagnosis.⁴⁶ Echocardiography is useful for discriminating between high-risk APE and ACS.⁴⁷ However, echocardiography has several technical limitations, and fully assessable echocardiographic images are not always obtained.

We examined electrocardiographic differences between patients with APE and ACS who had negative T waves in ≥ 2 contiguous precordial leads (V₁ to V₄).⁴⁸ The distribution of negative T waves obviously differed between APE and ACS, and this difference was useful for differential diagnosis (**Figures 3A,B**). The presence of negative T waves in both leads III and V₁ strongly suggested APE (the sensitivity and specificity of this ECG finding for the diagnosis of APE were 88% and 99%, respectively), thereby allowing APE to be simply but accurately differentiated from ACS (**Figures 4A,B**). The diagnosis of APE relies predominantly on the magnitude of clinical suspicion. This simple ECG criterion may help to correctly diagnose APE.

In the setting of ACS, the presence of negative T waves in lead V₁ may suggest ischemia of the upper paraseptal region, probably due to proximal LAD disease.⁴⁹ When the LAD is proximally occluded, ST-segment depression in inferior leads can be caused by reciprocal changes associated with transmural ischemia in the high anterobasal region.⁵⁰ If an LAD that wraps around the apex and supplies the inferior wall (a so-called “wrapped LAD”) is proximally occluded, ST-segment deviation in inferior leads has been shown to be minimally depressed or isoelectric; consequently, negative T waves in these leads are rarely observed in this situation.^{50,51} In contrast, a distally occluded LAD that wraps around the apex, in which the injury current is directed horizontally and therefore does not influence ST-segment deviation in inferior leads, is thought to be prerequisite for ST-segment elevation in inferior leads.⁵¹ The incidence of ST-segment elevation in inferior leads has been reported to range from only 5% to 16% in anterior acute

myocardial infarction. Consequently, negative T waves in lead III are usually not accompanied by negative T waves in lead V₁ in patients with ACS.

The mechanism responsible for the occurrence of negative T waves after APE is not completely understood, but may involve the development of acute cor pulmonale caused by enlargement of the right ventricle due to rapid right ventricular pressure overload, potentially leading to severe ischemia of the right ventricle.⁴⁴ Negative T waves in leads III, V₁ and V₂ are very common in patients with APE.⁴⁸ Lead III faces the inferior region of the right ventricle, and leads V₁ and V₂ face the anterior region of the right ventricle. With increasing severity of right heart failure and dilation of the right ventricle towards the left, negative T waves are thought to move in a left direction, ie, from lead V₁ to V₆ in the precordial leads and from lead III to aVF to II lead in the limb leads (**Figure 3A**). The number of leads with negative T waves is thus closely associated with the severity of APE, as well as with adverse in-hospital outcomes.⁴³ Patients with severe APE may be more likely to be given a misdiagnosis of ACS caused by the LAD disease, because negative T waves appear most commonly in the precordial leads.

Concluding Remark

ECG wave patterns are influenced by a number of factors, including physique and dimensions of the thorax. ECG diagnosis is challenging in patients with secondary ST-T changes caused by bundle-branch block or cardiac hypertrophy, those with Wolff-Parkinson-White syndrome and those who are receiving ventricular pacing or digitalis. The ECG should be used with a thorough understanding of these drawbacks. Despite the development of improved diagnostic strategies, the ECG remains an essential clinical tool for the evaluation of ACS because it is inexpensive, readily available, and noninvasive.

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