Implications of Using the Cabrera Sequence for Diagnosing Acute Coronary Syndrome
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The 12-lead electrocardiogram (ECG) is the important, initial examination for diagnosing acute coronary syndrome (ACS). In the traditional 12-lead ECG display, the precordial leads are displayed in their anatomically contiguous order, which makes it easy to understand the positional relationships between the precordial leads and the heart, but the limb leads are not. The “Cabrera sequence” displays the limb leads in an anatomically contiguous manner, which facilitates understanding of the positional relations between the limb leads and the heart, resulting in more rapid, easy, and accurate ECG interpretation than the traditional limb leads display. This review explores the clinical advantages of the Cabrera sequence as compared with the traditional limb leads display for the diagnosis of ACS. (Circ J 2016; 80: 1087–1096)

Key Words: Acute coronary syndrome; Cabrera sequence; Electrocardiogram

Acute coronary syndrome (ACS) is an emergency cardiovascular disease with a risk of cardiac events soon after its onset; prompt and precise diagnosis and treatment are essential. Although various diagnostic techniques have been developed, the 12-lead electrocardiogram (ECG) is simple, readily available, noninvasive, and inexpensive, making it the most important initial examination for the diagnosis of ACS. In the traditional 12-lead ECG display, the precordial leads are displayed in their anatomically contiguous order from the right anterior lead (V1) to the left lateral lead (V6), and it is easy to understand the positional relationships between the precordial leads and the heart. However, the limb leads are not displayed in their anatomically contiguous order. For the limb leads to be displayed in an anatomically contiguous manner from the left superior-based to right inferior, the display should be aVL, I, –aVR (ie, the inverse lead of aVR), II, aVF, and III1-3 (Figure 1). In this configuration, lead –aVR (+30°) bridges the gap between lead I (0°) and lead II (+60°) and faces the apical and inferolateral regions. This display, known as the “Cabrera sequence”4-5 was recommended in the 2000 European Society of Cardiology/American College of Cardiology guidelines for universal adoption in 12-lead electrocardiography. Standardization documents endorsed by both the American Heart Association and the American College of Cardiology have also stated that the Cabrera sequence is an appropriate alternative to the traditional limb leads display. The Cabrera sequence facilitates understanding of the positional relationships between the limb leads and the heart. Pahlm et al showed that students who were taught ECG interpretation with the use of the Cabrera sequence calculated the electrical axis more accurately and in less time than those who were taught using the traditional limb leads display. Use of the Cabrera sequence might result in more rapid, easy, and accurate ECG interpretation than the traditional limb leads display. This review explores the clinical advantages of the Cabrera sequence as compared with the traditional limb leads display for the diagnosis of ACS.

ST-Segment-Elevation Acute Myocardial Infarction (AMI)

Reperfusion therapy has become an established treatment for ST-segment elevation AMI, increasing the need for early diagnosis and treatment. In the acute phase of ST-segment elevation AMI, the ECG can provide useful information, such as the infarct location, the culprit site, and the extent of area at risk.

Inferior AMI
Identification of the Culprit Artery
Inferior AMI presenting with ST-segment elevation in leads II, III, and aVF can be caused by occlusion of either the right coronary artery (RCA) or the left circumflex coronary artery (LCX). In inferior AMI, the RCA is most often the culprit artery. Although several ECG criteria have been proposed to identify the culprit artery, comparison of the degree of ST-segment elevation in lead II and with that in lead III is simple but useful for diagnosing the culprit artery; that is, greater ST-segment elevation in lead III than in lead II strongly suggests RCA occlusion. The RCA supplies blood mainly to the right inferior myocardium, whereas the LCX supplies blood to the posterior, posterolateral, or posteroinferior myocardium, and its perfusion territory varies considerably. Consequently, when the RCA is occluded, the spatial vector of the ST-segment will be directed...
more to the right than when the LCX is occluded. This results in greater ST-segment elevation in lead III than in lead II.\textsuperscript{9,11} The Cabrera sequence makes it easy to understand these differences in the direction and degree of inferior ST-segment elevation caused by RCA (Figures 2A, B)\textsuperscript{8} and LCX occlusion (Figure 2C)\textsuperscript{8}, thereby facilitating rapid and easy diagnosis of the culprit artery.

\textbf{Identification of High-Risk Patients With a Larger Area at Risk} During inferior AMI, if the perfusion territory of the culprit artery is large and extends to the apical and inferolateral regions, ST-segment elevation will also be present in lead –aVR in addition to the inferior leads. The Cabrera sequence makes it easy to understand that ST-segment elevation in lead –aVR during inferior AMI reflects a larger area at risk, which facilitates early risk stratification (Figures 2B, C)\textsuperscript{8}. ST-segment elevation in lead –aVR is inverted to become ST-segment depression in the opposing lead aVR in the traditional limb leads display (Figures 2B, C)\textsuperscript{8}. We previously reported that in patients with inferior AMI who underwent successful recanalization within 6h of symptom onset, greater ST-segment depression in lead aVR on the admission ECG was associated with a larger infarct size regardless of the culprit artery (ie, RCA or LCX).\textsuperscript{12} Moreover, ST-segment depression >0.1 mV in lead aVR identified patients with impaired myocardial reperfusion (myocardial blush grade 0/1 after reperfusion) with 92% sensitivity and 67% specificity, which was superior to any other ECG finding\textsuperscript{12} (Figure 2).\textsuperscript{8} Impaired myocardial reperfusion has been shown to be a powerful predictor of poor outcomes, even after successful recanalization.\textsuperscript{13} Our findings suggest that in patients with inferior AMI, greater ST-segment depression in lead aVR (ie, ST-segment elevation in lead –aVR) is useful for identifying high-risk patients most likely to benefit from aggressive therapeutic strategies designed to improve myocardial reperfusion.

\textbf{Anterior AMI} \\
\textbf{Identification of High-Risk Patients With a Larger Area at Risk} Among patients with anterior AMI, the presence of ST-segment elevation in leads I and aVL has been shown to be associated with short-term poorer outcomes,\textsuperscript{14} probably attributed to a larger area at risk with anterolateral wall involvement. If the area at risk is more extensive and extends to the apical and inferolateral regions, ST-segment elevation will also be present in lead –aVR, which is reflected in ST-segment depression in lead aVR. The Cabrera sequence makes it easy to understand that ST-segment elevation in lead –aVR during anterolateral AMI reflects an extensive area at risk (Figure 3).\textsuperscript{15} We previously reported that in patients with anterolateral AMI who underwent successful recanalization within 6h of symptom onset, ST-segment depression in lead aVR on the admission ECG was associated with a large infarct size and left ventricular dysfunction at discharge (Figure 3).\textsuperscript{15} Patients with ST-segment depression in lead aVR had greater ST-segment elevation in the precordial leads, particularly V5 and V6, which face the posterolateral wall adjacent to the apex of the left ventricle (Figure 3)\textsuperscript{15}. ST-segment depression ≥0.05 mV in lead aVR identified patients with a predischarge left ventricular ejection fraction (LVEF) ≤35\% with 90\% sensitivity and 80\% specificity, which was superior to ST-segment elevation in leads V5 and V6. ST-segment depression in lead aVR (ie, ST-segment elevation in lead –aVR) is useful for predicting high-risk patients with anterolateral AMI who have predischarge left ventricular dysfunction despite successful recanalization. Thus, lead –aVR is a valuable lead for early risk stratification of anterolateral AMI as well as inferior AMI.

\textbf{Differential Diagnosis of Anterior AMI and Takotsubo Cardiomyopathy (TC)} 
TC is a recognized novel cardiac syndrome characterized by transient left ventricular dysfunction without obstructive coronary disease, ECG changes (ST-segment elevation, negative T waves, or both), or elevated cardiac enzymes.\textsuperscript{4,16-21} Symptoms of TC, such as chest pain/discomfort or dyspnea, have been shown to be similar to those of AMI. The most
common type of TC is the apical, and in this type of TC, ST-segment elevation occurs mainly in the precordial leads immediately after symptom onset. Thus, the symptoms and ECG findings of TC mimic those of anterior AMI in the acute phase, and differentiation between these diseases can be challenging, but is essential for deciding whether reperfusion therapy is required. A few studies have reported several differences in the ECG findings between TC and anterior AMI, such as the absence of reciprocal ST-segment depression in the inferior leads and the absence of abnormal Q waves. However, other studies have proposed that the ECG findings in TC are heterogeneous; no ECG criterion allowed TC to be reliably differentiated from anterior AMI with enough certainty to preclude the need for cardiac catheterization.

Figure 2. Representative ECGs of inferior acute myocardial infarction. The limb leads are displayed using the traditional display (Left) and the Cabrera sequence (Right). (A) Culprit lesion, proximal RCA (segment 1). Peak creatine kinase level, 1,354 IU/L; myocardial blush grade after reperfusion, 3. (B) Culprit lesion, proximal RCA (segment 1). Peak creatine kinase level, 5,355 IU/L; myocardial blush grade after reperfusion, 0. (C) Culprit lesion, proximal LCX (segment 11). Peak creatine kinase level, 5,026 IU/L; myocardial blush grade after reperfusion, 0. The degree of inferior ST-segment elevation is greatest in lead III, followed by lead aVF, and lowest in lead II in RCA occlusion (A,B), whereas it is similar in leads II, III, and aVF in LCX occlusion (C). These findings are more easily interpreted when the limb leads are displayed using the Cabrera sequence than the traditional display. ST-segment depression in lead aVR in the traditional display is inverted to become ST-segment elevation in lead –aVR in the Cabrera sequence. LCX, left circumflex artery; RCA, right coronary artery. (Reproduced with partial modifications from Kosuge M, et al.)

Thus, the symptoms and ECG findings of TC mimic those of anterior AMI in the acute phase, and differentiation between these diseases can be challenging, but is essential for deciding whether reperfusion therapy is required. A few studies have reported several differences in the ECG findings between TC and anterior AMI, such as the absence of reciprocal ST-segment depression in the inferior leads and the absence of abnormal Q waves. However, other studies have proposed that the ECG findings in TC are heterogeneous; no ECG criterion allowed TC to be reliably differentiated from anterior AMI with enough certainty to preclude the need for cardiac catheterization. However, the time elapsed from symptom onset to recording ECG varied widely among previous studies assessing the ECG
Figure 3. Representative ECGs of anterolateral acute myocardial infarction. The limb leads are displayed using the traditional display (Left) and the Cabrera sequence (Right).

(A) Culprit lesion, proximal LAD (segment 6). Predischarge LVEF, 49%.

(B) Culprit lesion, proximal LAD (segment 6). Predischarge LVEF, 44%.

(C) Culprit lesion, proximal LAD (segment 6). Predischarge LVEF, 35%. The extent of ST-segment elevation in the limb leads is greatest in (C), followed by (B), and is smallest in (A). These findings are more easily interpreted when the limb leads are displayed using Cabrera sequence than the traditional display. Note that the extent of ST-segment elevation in the limb leads is associated with left ventricular function at discharge. LAD, left anterior descending; LVEF, left ventricular ejection fraction. (Reproduced with partial modifications from Kosuge M, et al.15)
Diagnostic Value of Cabrera Sequence

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 V1, which may face the right ventricular anterior region as well as the right paraseptal region. The most likely reason for less ST-segment elevation in lead V1 in TC is that wall-motion abnormalities in TC less frequently extend to the region faced by lead V1; moreover, less ST-segment elevation may result from the electrical force induced by ST-segment elevation in the posterolateral region. One can speculate that TC, but not anterior AMI, is usually associated with ST-segment elevation in the posterolateral region. Another reason for less ST-segment elevation in lead V1 in TC might be related to sex. Most patients with TC are elderly women, whereas the majority of patients with AMI are men. In healthy individuals, the magnitude of ST-segment elevation in lead V1 is generally smaller in females than in young and middle-aged males.

Non-ST-Segment Elevation ACS (NSTE-ACS)

Patients with NSTE-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. The 12-lead ECG plays a central role in the diagnostic and triage pathways for NSTE-ACS and provides important prognostic information. Acute ischemic ECG changes at presentation have been shown to be associated with a higher risk of cardiac events; in

Figure 4. Prevalence of ST-segment elevation in takotsubo cardiomyopathy (TC) and anterior acute myocardial infarction (AMI). The Cabrera sequence is used to display the limb leads. In the limb leads, ST-segment elevation is distributed primarily around lead –aVR in TC. In anterior AMI, the prevalence of ST-segment elevation gradually decreased from leads aVL to III. In the precordial leads, high rates of ST-segment elevation were found in leads V2–4 in TC as well as in anterior AMI, but the prevalence of ST-segment elevation in lead V1 is markedly lower in TC than in anterior AMI (*P<0.05, **P<0.01 vs. anterior AMI). (Reproduced with permission from Kosuge M, et al.27)
Figure 5. Representative ECGs in (A) takotsubo cardiomyopathy (TC) and (B) anterior acute myocardial infarction (AMI). The limb leads are displayed using the traditional display (Left) and the Cabrera sequence (Right). In TC, ST-segment elevation more broadly distributes as compared with that in anterior AMI. The Cabrera sequence makes it easy to understand such differences in the distribution of ST-segment elevation between TC and anterior AMI. (Reproduced with partial modification from Kosuge M, et al.27)
Diagnostic Value of Cabrera Sequence

We studied the differences in negative T waves among ACS caused by LAD disease, APE, and TC in patients who were admitted within 48 h of symptom onset. The numbers and maximal amplitudes of negative T waves were greatest in patients with TC, followed by those with ACS, and were lowest in patients with APE. In our study, the Cabrera sequence was used to display the limb leads (Figures 6 and 7). The distribution of negative T waves obviously differed among these 3 diseases, and such differences were useful for differential diagnosis. Negative T waves in both leads III and V1 identified APE with 90% sensitivity and 97% specificity. Negative T waves in lead –aVR (ie, positive T waves in the opposing lead aVR in the traditional limb leads display) and no negative T waves in lead V1 identified TC with 95% sensitivity and 97% specificity. These values represented the highest diagnostic accuracies. The reasons why negative T waves are differently distributed among ACS, APE, and TC are uncertain, but may reflect differences in underlying electrophysiologic mechanisms of the 3 diseases.

Negative T Waves in ACS

As shown in Figure 6 and Figure 7A, patients with ACS caused by LAD disease, negative T waves in the precordial leads are distributed primarily around leads V2–4 facing the anterior region of the left ventricle. In the limb leads, negative T waves are common in lead aVL facing the lateral region of the left ventricle. The extent of negative T waves is thought to reflect the perfusion territory of the LAD.

Negative T Waves in APE

As shown in Figure 6 and Figure 7B, negative T waves are the most common, persistent ECG change in patients with APE. It has been suggested that severe ischemia of the right ventricle may result from an acute right ventricular
Figure 7. Representative ECGs of acute coronary syndrome (ACS), acute pulmonary embolism (APE), and takotsubo cardiomyopathy (TC) showing the limb leads using the traditional display (Left) and the Cabrera sequence (Right). (A) ACS caused by LAD disease. Negative T waves are observed in leads I, aVL, and V1–6. (B) APE showing negative T waves in leads II, III, aVF, and V1–5. (C) TC showing positive T waves in lead aVR in the traditional display inverted to become negative T waves in lead –aVR in the Cabrera sequence. Negative T waves were broadly distributed in all leads except for leads III and V1. The Cabrera sequence makes it easy to understand the differences in the distribution of negative T waves among these 3 diseases.
pressure overload, impaired coronary blood flow, and hypoxia caused by APE, possibly leading to negative T waves.29 In our study, negative T waves in leads III, V1, and V2 were very common in patients with APE. 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 resulting from limited pericardial expansion, negative T waves are thought to move towards the left (ie, from leads III to aVR to II in the limb leads and from leads V1 to V6 in the precordial leads). Negative T waves are rare in leads –aVR, V5, and V6, and are not found in leads I and aVL. These findings are probably ascribed to the fact that dilation of the right ventricle in APE rarely extends to the regions faced by these leads.

Negative T Waves in TC
As shown in Figure 6A and Figure 7C, in TC the negative T waves commonly appear after the resolution of initial ST-segment elevation;18 therefore, the distribution of subsequent negative T waves might be similar to that of acute ST-segment elevation. As mentioned before, during the acute phase, TC is characterized by ST-segment elevation in lead –aVR (ie, ST-segment depression in lead aVR) and no ST-segment elevation in lead V1.27 During the subacute phase, it is plausible that these findings are reflected in negative T waves in lead –aVR (ie, positive T waves in lead aVR) and no negative T waves in lead V1.41 The development of negative T waves after reperfusion of AMI has been attributed to viable but sympathetically denervated myocardium, because sympathetic denervation delays repolarization.28 We have previously shown that negative T waves progressively develop in both TC and reperfused anterior AMI during the subacute phase and are especially prominent in the former, suggesting that TC might be associated with more viable but sympathetically denervated myocardium.41

Conclusions
The Cabrera sequence is not widely used in clinical practice. The conservative nature of the cardiology community in addition to the large number of existing ECGs recorded with the traditional limb leads display may explain the non-adoption of the Cabrera sequence.2 However, this review indicates that the Cabrera sequence is clinically advantageous as compared with the traditional limb leads display because it provides a more rapid, easy, and accurate ECG interpretation not only for the diagnosis of ACS but also its differential diagnosis. Today’s technology makes it possible to easily change the mode of limb leads display to the Cabrera sequence on the electrocardiographic recorder. We hope that our findings will contribute to the use of the Cabrera sequence in clinical practice.

Disclosures
The authors declare no conflicts of interest.

References


