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Review

New Insights Into the Use of the 12-Lead Electrocardiogram for Diagnosing Acute Myocardial Infarction in the Emergency Department

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ABSTRACT

The 12-lead electrocardiogram (ECG) remains the most immediately accessible and widely used initial diagnostic tool for guiding management in patients with suspected myocardial infarction (MI). Although the development of high-sensitivity cardiac troponin assays has improved the rule-in and rule-out and risk stratification of acute MI without ST elevation, the immediate management of the subset of acute MI with acute coronary occlusion depends on integrating clinical presentation and ECG findings. Careful interpretation of the ECG might yield subtle features suggestive of ischemia that might facilitate more rapid triage of patients with subtle acute coronary occlusion or, conversely, in identification of ST-elevation MI mimics (pseudo ST-elevation MI patterns). Our goal in this review article is to consider recent advances in the use of the ECG to diagnose coronary occlusion MIs, including the application of rules that allow MI to be diagnosed on the basis of atypical ECG manifestations. Such rules include the modified Sgarbossa criteria allowing identification of acute MI in left

RÉSUMÉ

L'électrocardiogramme (ECG) à 12 dérivations demeure l'un des outils de diagnostic des plus accessibles et des plus utilisés pour orienter vers une prise en charge les patients qui montrent une suspicion d'infarctus du myocarde (IM). Bien que l'élaboration de dosages de la troponine cardiaque de haute sensibilité ait amélioré l'exclusion et la confirmation du diagnostic d'infarctus aigu du myocarde (IAM) et la stratification du risque d'IAM sans sus-décalage du segment ST, la prise en charge immédiate de l'IAM associé à une occlusion aiguë d'une artère coronaire dépend de l'intégration du tableau clinique et des résultats de l'ECG. L'interprétation rigoureuse de l'ECG pourrait aboutir à des caractéristiques subtiles évocatrices d'une ischémie qui favoriseraient le triage rapide des patients ayant une subtile occlusion aiguë d'une artère coronaire ou, à l'inverse, à la détection d'une simulation d'IM avec sus-décalage du segment ST (formes de pseudo-infarctus du myocarde avec sus-décalage du segment ST). Dans le présent article, notre objectif est de tenir compte des récentes

The 12-lead electrocardiogram (ECG) remains the first, most rapid, widely available, noninvasive, and cost-effective diagnostic test for patients with suspected acute coronary syndrome (ACS). It should be recorded within 10 minutes of presentation to the emergency department (ED).[1] Its interpretation, as with any diagnostic test, must always be performed in the context of the patient's clinical presentation and the pretest probability for acute myocardial infarction (AMI). AMI is neatly divided into ST-elevation (STE) myocardial infarction (STEMI) and non-STEMI (NSTEMI). The physiologic substrate for STEMI is acute thrombotic occlusion (ATO), with the risk of irreversible myocardial loss if not immediately treated. ATO is defined in studies referenced below by **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) flow grade of 0, 0/1, or 0-2, or by very high percent acute stenosis. As we will see, such high-risk physiology is frequently diagnosed as NSTEMI (ie, AMI without diagnostic STE), such that the division between the two is not so dichotomous.

Although the diagnosis of STEMI relies primarily on the ECG, the diagnosis of NSTEMI relies primarily on troponin[2] because a significant proportion of patients with AMI present with a "negative" ECG; Welch et al., using

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bundle branch block or ventricular pacing, the 3- and 4-variable formula to differentiate normal ST elevation (formerly called early repolarization) from subtle ECG signs of left anterior descending coronary artery occlusion, the differentiation of ST elevation of left ventricular aneurysm from that of acute anterior MI, and the use of lead aVL in the recognition of inferior MI. Improved use of the ECG is essential to improving the diagnosis and appropriate early management of acute coronary occlusion MIs, which will lead to improved outcomes for patients who present with acute coronary syndrome.

avancées dans l'utilisation de l'ECG pour diagnostiquer les IM associés à l'occlusion d'une artère coronaire, y compris l'application des règles qui permettent le diagnostic de l'IM sur la base de manifestations atypiques à l'ECG. Parmi ces règles, on note les critères de Sgarbossa modifiés qui permettent la détection de l'IAM en présence d'un bloc de branche gauche ou de stimulation ventriculaire, la formule à 3 et à 4 variables pour différencier le sus-décalage normal du segment ST (anciennement appelé la repolarisation précoce) des signes subtiles à l'ECG d'une occlusion de la branche descendante antérieure de l'artère coronaire gauche, la différenciation du sus-décalage du segment ST de l'anévrisme ventriculaire gauche de celui de l'IAM de la paroi antérieure et l'utilisation de la dérivation aVL pour détecter l'IM de la paroi inférieure. Une meilleure utilisation de l'ECG est essentielle à l'optimalisation du diagnostic et de la prise en charge précoce adéquate des IM associés à l'occlusion aiguë d'une artère coronaire, et se traduira par de meilleurs résultats cliniques chez les patients qui sont atteints d'un syndrome coronarien aigu.

registry data, reported that, of myocardial infarction (MI) diagnosed according to creatine kinase MB (CK-MB) fraction (not angiography or troponin), 8% were completely normal and 35% were "nonspecific" (a frequently used synonym for "nondiagnostic"; ie, without diagnostic STE, ST depression [STD], or T-wave inversion).[3] Only 57% had diagnostic STE, STD, or T-wave inversion. All interpretations were as recorded by the treating physician. This highlights a widespread problem with the literature: studies rarely report detailed data on ECG findings and it is thus difficult to know if "nondiagnostic" ECGs might be subtly diagnostic to a more expert clinician. Accordingly, there is a marked paucity of literature describing methods to scrutinize apparently nondiagnostic ECGs to find subtle features of ischemia, and especially of ATO, that might help to identify ACS patients who might benefit from expedited care.

The ECGs of many patients with ACS do not manifest any sign of ischemia, much less of overt STEMI, especially on the initial ECG. Although some of these ECGs are normal, some have STD or T-wave inversion diagnostic of ischemia but not of ATO, and a significant proportion have nonspecific ST/T abnormalities that might or might not be due to ischemia but are not diagnostic. Also, many have confounding preexisting abnormalities (eg, left bundle branch block [LBBB], left ventricular (LV) hypertrophy [LVH]). This heterogeneous group has been interpreted simply as NSTEMI, although it has been long recognized that certain features of these ECGs suggested significant prognostic information.[4] In particular, widespread and profound STD (> 2 mm in 2 consecutive leads) is associated with very high mortality,[5] and T-wave inversion is low risk if it is during pain, in contrast to T-wave inversion after pain resolution, which is high risk post-ischemic T-wave inversion (see an example 12-lead ECG in Supplemental Fig. S1A and B). A review from 2006 cautioned against considering emergent reperfusion therapy for any ECG pattern except for clear STEMI and the "STEMI-equivalent" of isolated STD in V_1-V_3, consistent with an isolated posterolateral (or "posterior") MI (see 12-lead ECG in Supplemental Fig. S2A and B).[6]

Over the past decade, ECG patterns that warrant emergent reperfusion, despite not fulfilling standard STEMI criteria, have been described. Rokos et al. outlined the evidence for many STEMI equivalents in addition to isolated posterior AMI: LBBB that met Sgarbossa criteria, de Winter pattern, and hyperacute T waves, as well as the so-called "left main (LM) coronary occlusion" pattern (diffuse STD with STE in aVR).[7] Some later reviews also addressed the evidence for these STEMI equivalents and for a variety of other abnormalities that merit emergent reperfusion, including discussions of de Winter T waves, Wellens T waves, isolated posterior STEMI, and hyperacute T waves (see Fig. 1A for de Winter T waves).[10-12]

Aside from the previously mentioned patterns, previous reviews document the deficiencies of the ECG, the risk and prognosis of various ECG findings in patients with ACS, and the correlations of infarct location or infarct artery with various locations of STE or STD.[10,11] However, they offer few techniques for identifying, among the many otherwise "nonspecific"-appearing ECGs, signs of ACS that require emergent reperfusion therapy, or for differentiating them from nonischemic STE/STD.

It is important to note that, in the review by Nikus et al., the dichotomous classification of MI into STEMI vs NSTEMI was questioned, because MI is a dynamic process in which the exact same patient's ECGs might have very different patterns depending only on the time at which they are recorded; if there happens to be a diagnostic STE during the recording, it will be STEMI, but if recorded before evolution of, or after resolution of, the STE, it will be called an NSTEMI.[11] This group also recommended classifying hyperacute T waves ("tall and symmetric") and Wellens syndrome (T-wave inversion, with preservation of R waves, in leads V_2-V_4 after resolution of chest pain) as STEMI because both are on the spectrum of ATO: hyperacute T waves represent ATO either immediately after occlusion, or are a residual finding immediately after spontaneous reperfusion (autolysis); Wellens T waves are high-risk postischemic T-wave inversions also seen after spontaneous reperfusion of ATO, in which there is active thrombus and risk of reocclusion.

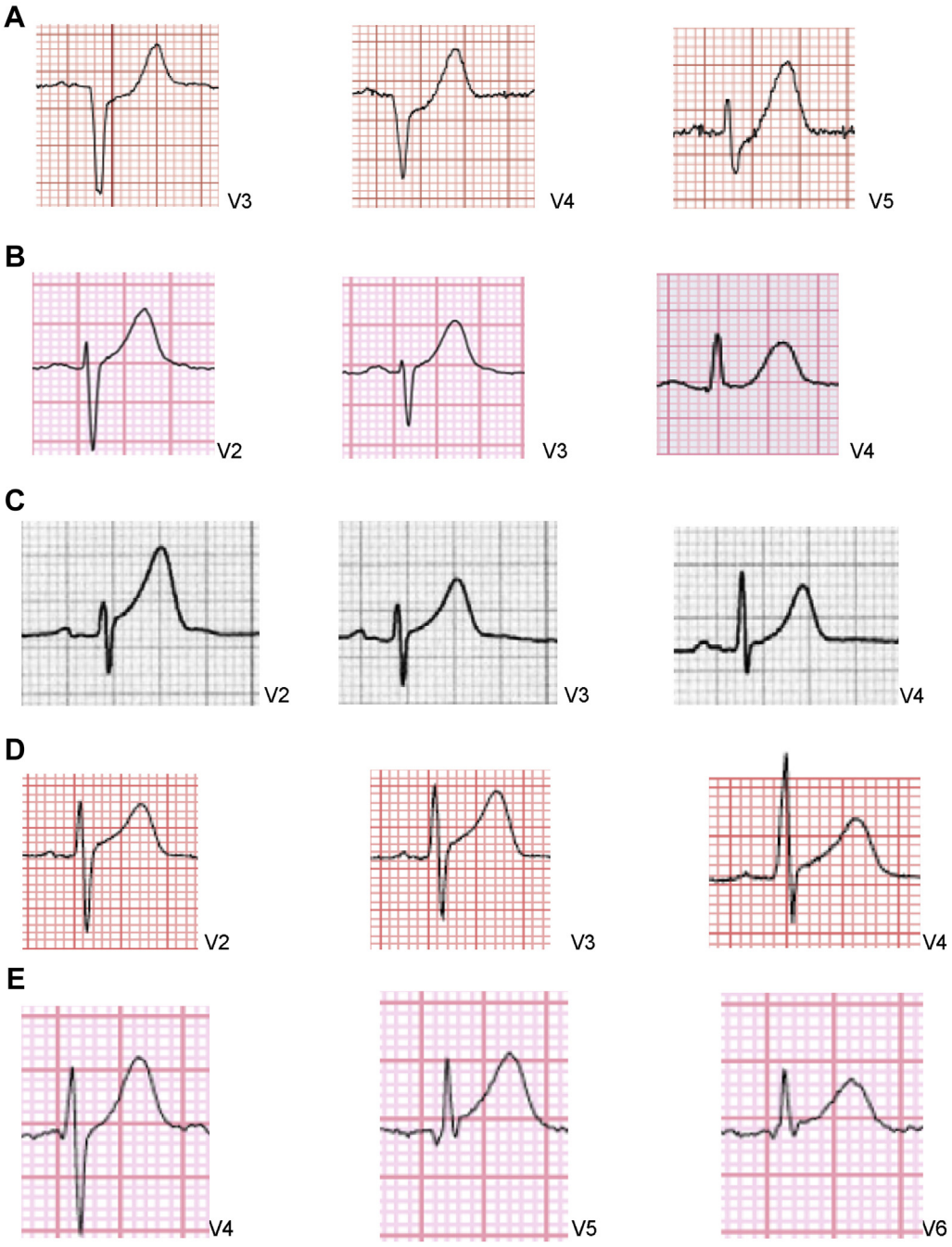

Figure 1. Hyperacute T waves and/or subtle ST-elevation (STE) in the anterior and lateral locations. (**A**) (V_3-V_5) de Winter T waves of left anterior descending artery (LAD) occlusion. These are usually seen in V_2-V_4. See Supplemental Figure S7 for a full 12-lead electrocardiogram (ECG) of another case. (**B**) (V_2-V_4) Hyperacute T waves of LAD occlusion. The full 12-lead ECG is shown in Supplemental Figure S1. This LAD occlusion was predicted by the 3- and 4-variable formulas. Low R-wave voltage in V_4 and low QRS voltage in V_2 makes this very unlikely to be normal STE. (**C**) (V_2-V_4) Hyperacute T waves and subtle STE of LAD occlusion: predicted by the 3- and 4-variable formulas. Low R-wave voltage in V_4 and low QRS voltage in V_2 makes this very unlikely to be normal STE. (**D**) (V_2-V_4) Subtle STE in a case of acute LAD occlusion. This is predicted by the 3- as well as 4-variable formula. Low R-wave voltage in V_4 and low QRS voltage in V_2 make this very unlikely to be normal STE. (**E**) (V_4-V_6) Subtle lateral hyperacute T waves due to occlusion of the first diagonal off the LAD. In a normal ECG, T waves in V_4-V_6 should not be nearly as tall is the R wave. Panels **A**, **D**, and **E** reprinted from Dr Stephen W. Smith's blog, courtesy of Dr Stephen W. Smith. Panel **B** reproduced from Driver et al.[8] with permission from Elsevier. Panel **C** reproduced from Smith et al.[9] with permission from Elsevier.

Contemporary Diagnostic Evaluation of Patients With Suspected AMI Using the 12-Lead ECG

Recently, there has been much focus on the use of contemporary and high-sensitivity cardiac troponin (cTn) measurements to expedite the risk stratification of patients with suspected MI.[13] However, in clinical practice the turnaround time for cTn measurements is often longer than the 60-minute recommended interval.[14] Moreover, nearly half of STEMI

patients, especially those who are early presenters, have an initial troponin level below the 99th percentile upper reference limit.[15,16] All patients with ATO are at risk for significant myocardial loss, whether the ECG actually meets STEMI criteria or not, and those who do not meet STEMI criteria are thus more difficult to identify. However, nuanced evaluation of the 12-lead ECG, which remains the most rapid and readily available diagnostic tool for immediate risk stratification and triaging, might identify a significant proportion of these patients. Troponin "rule-in" strategies (using serial change in high sensitivity troponin at 0-1, 0-2, and 0-3 hours) help to more rapidly identify patients with AMI[13]; more study is needed to determine if they more rapidly identify those with ATO.

If the initial ECG is not diagnostic but the patient remains symptomatic and there is high clinical suspicion for ACS, serial ECGs should be obtained over 15- to 30-minute intervals during the first hour.[1] Fesmire et al. reported that continuous 12-lead ST monitoring over 1 hour improved the sensitivity of the ECG for STEMI and ACS, respectively, from 55% and 28% on the initial 12-lead ECG to 68% and 34%.[17] Similarly, Welch et al. reported that 20% of initially normal or nondiagnostic ECGs later showed "frank" STE.[3]

The first decision in patients with suspected MI should be to identify those with definite acute STEMI for whom clinical practice guidelines recommend the immediate use of antiplatelet as well as anticoagulant therapies, as well as emergent coronary angiography with possible revascularization, if indicated (or fibrinolytic therapy if angiography is unavailable).[18] The Third Universal Definition of MI consensus defines STE as new STE at the J-point in 2 contiguous leads with the following cut points, measured at the J-point, relative to the PQ junction: $\geq$ 0.1 mV in all leads other than leads V_2-V_3 where a cut point of $\geq$ 0.2 mV in men 40 years of age or older; $\geq$ 0.25 mV in men younger than 40 years or $\geq$ 0.15 mV in women.[19] Notably, the study that originated the sex-specific criteria used a cohort from the 1980s and thus the diagnosis of AMI was according to CK-MB; the criteria yielded a sensitivity of only 47% and specificity of 98.5%, compared with the sensitivity of 41.5% and specificity of 96.0% using the original American College of Cardiology/European Society of Cardiology criteria.[20] Had troponin been used for diagnosis of AMI, the sensitivity would have been much lower. These criteria were never validated.

Acute Coronary Occlusion Without Definitive STE: Subtle STEMIs

Despite guidelines recommending the use of these STE cutoffs, older literature shows that standard voltage thresholds are not sensitive for ATO and establish the need for more nuanced ways of recognizing subtle STEMI on the ECG. Schmitt et al. examined a cohort of 418 patients (including 102 with standard and extended ECG leads) with angiographically confirmed diagnosis of thrombotically occluded infarct-related vessel that was subsequently revascularized during the invasive procedure. Sensitivity of conventional leads (I-aVF $\geq$ 1 mm and V_1-V_6 $\geq$ 2 mm) was 85% and 75% for the left anterior descending coronary artery (LAD) and right coronary artery, respectively, and only 50% for the left circumflex artery.[21] Similarly, in a cardiac magnetic resonance imaging study involving 116 patients, the sensitivity of the American College of Cardiology/European Society of Cardiology STEMI criteria was only 50% (95% confidence interval [CI], 37%-63%) with a specificity of 97% and positive predictive value of 94%.[22]

The ECG in many ATO does not meet STEMI criteria. Rokos et al. coined the term "semi-STEMI" (< 1 mm of STE) in a post-hoc analysis of Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI); however, the study greatly underestimated the incidence of semi-STEMI at ~5% because HORIZONS-AMI was a study of STEMI patients, with methods requiring at least 0.1 mV of STE.[23]

In order to find the true incidence of semi-STEMIs, one must use NSTEMI cohorts, because many ATOs are diagnosed only after cTn measurements return with elevated values, followed by a delayed angiogram.

In a 2017 meta-analysis of 7 studies of 40,777 consecutive patients with first NSTEMI, Khan et al. reported that 10,415 (25.5%) had a "totally occluded" infarct artery.[24] All 3 arteries were involved and there was no difference in time to angiography between those with, and those without, ATO, implying that these patients were not prospectively identified using ECG, troponin levels, or clinical factors; moreover, their adjusted mortality risk compared with those with an open artery was higher, short-term (relative risk, 1.67; 95% CI, 1.31-2.13) as well as long-term (relative risk, 1.42; 95% CI, 1.08-1.86). There are other supporting articles described in the next 4 paragraphs that were not included in the meta-analysis.

In a post hoc analysis of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction-38 Substudy, Pride et al. examined a subset of MI patients who presented without STE but with STD in leads V_1-V_4 and reported that one-third of them had an occluded artery with a TIMI flow grade of 0 or 1.[25]

Similarly, in a prospective registry of 447 patients with persistent ischemic symptoms not responding to nitrates with any STE who underwent urgent coronary angiography, Marti et al. reported that 18% of patients had subtle STEMI, defined by STE of 0.1 to 1 mm. ATO was defined as TIMI flow grade 0/1; 91% underwent percutaneous coronary intervention (PCI).[26] Thirteen percent of ECGs in patients with LAD ATO had $\leq$ 1 mm of STE; even more would have failed to meet the current guideline criteria for V_2 and V_3.[24] Subtle STE was not associated with better outcomes than diagnostic STE.

From et al. reported that approximately one-third of patients without STE have a critical culprit lesion on angiography (defined as either a 100% ATO or $\geq$ 90% stenosis with less than TIMI-3 flow). More than 20% of cases with LAD or right coronary artery ATO, and 57% of left circumflex artery lesions, did not meet STEMI criteria.[27]

In an older article by Koyoma et al.[28] in which 404 patients with suspected AMI were taken for immediate angiography, among 125 NSTEMI, 63% had coronary flow limitation and 47% had TIMI-0 flow. TIMI flow was < 3 ($\leq$ 2) in 28 of 43 patients with STD $\geq$ 1 mm, 4 of 5 with STD < 1 mm, 24 of 42 with minimal STE < 1 mm, 15 of 23 with T-wave inversion, 3 of 6 with peaked T-wave, and 4 of 6 with no ST deviation.

One objection to the notion that patients with subtle ATO require emergent angiography and PCI is the misconception that randomized trials of immediate vs next-day

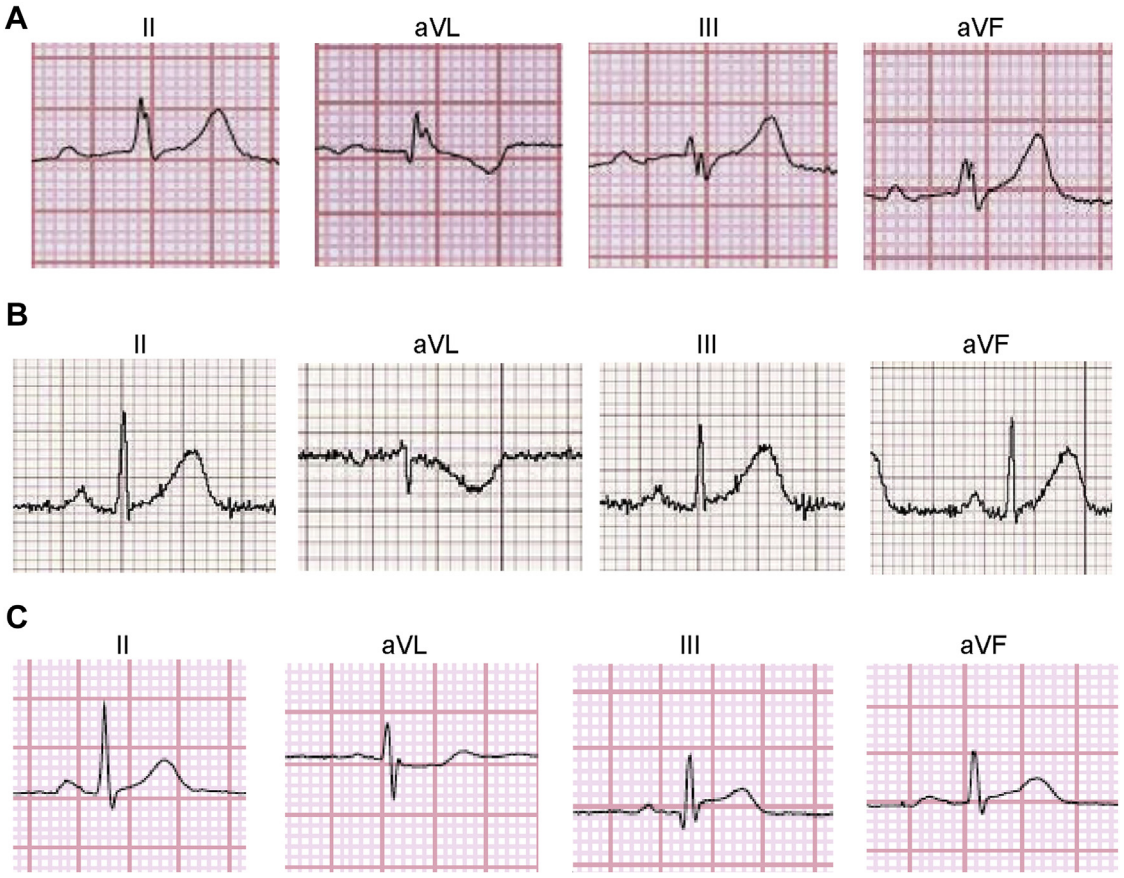

Figure 2. Inferior myocardial infarction. (**A**) (II, aVL, III, aVF) Subtle inferior hyperacute T waves with reciprocally hyperacute inverted T wave in aVL, due to right coronary artery (RCA) occlusion, case 1. The T waves are not large by themselves, but very large in proportion to the QRS. The inverted T wave in aVL is likewise very large compared with the QRS. (**B**) (II, aVL, III, aVF) Subtle inferior hyperacute T waves with reciprocally hyperacute inverted T wave in aVL due to acute RCA occlusion, case 2. (**C**) (II, aVL, III, aVF) Subtle inferior ST-elevation with reciprocal ST depression in aVL due to RCA occlusion. Any ST depression in aVL makes any ST-elevation in lead II very likely to be due to inferior myocardial infarction. Reprinted from Dr Stephen W. Smith's blog, courtesy of Dr Stephen W. Smith.

invasive treatment of NSTEMI do not show benefit for the group managed emergently. This misconception was furthered by the **Tim**ing of Intervention in **A**cute **C**oronary **S**yndrome (TIMACS) trial,[29] which reported no difference in outcome for patients with a **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) score < 140. However, the "early" intervention group had a mean time to angiography of 16 hours, which is not emergent. Furthermore, although it is not stated in the methods, patients with persistent refractory angina were excluded (personal communication from SR Mehta, April 16, 2014). Indeed, the European Society of Cardiology guidelines state that patients with ACS who have very high-risk criteria, which includes "recurrent or ongoing chest pain refractory to medical treatment," should undergo < 2-hour angiography, and they add "regardless of ECG or biomarker findings." They state (correctly) that such patients "have been generally excluded from RCTs."[30] Likewise, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend an immediate invasive strategy for refractory angina.[31] Although no randomized trial has evaluated the subgroup with subtle STE, this is likely a group for which immediate invasive therapy is particularly beneficial.

More recently, the Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients (RIDDLE-NSTEMI) Study randomized 323 NSTEMI patients (patients with refractory ischemia were excluded) to immediate (1.4 hours) vs delayed (61 hours) intervention and reported that the immediate intervention group had a much lower rate of new acute MI or recurrent ischemia.[32] No detailed ECG analysis was done.

Importantly, emergency physicians and cardiologists alike have difficulty in distinguishing ATO from its absence on the ECG; this has been confirmed in multiple studies, with accuracy no better than 75%, and with very poor inter-rater reliability.[33-35] Older studies suggest that a skilled subjective interpretation is superior to any millimetre criteria.[36] Accordingly, contemporary computer algorithms are insensitive (65%) for STEMI, and only approximately 90% specific.[37,38] Thus, it would be useful to have more nuanced ways of identifying subtle ATO on the ECG.

Hyperacute T Waves

STE might be preceded by (or if immediately after reperfusion and resolution of chest pain, followed by) large "hyperacute" T waves (Figs. 1 and 2), which might thus be a

subtle finding of early ATO. The 2004 STEMI guidelines, which have not been revised in this respect, imply that hyperacute T waves are an indication for reperfusion therapy.[39] They are now considered a STEMI equivalent.[7,11] Except to be described as tall and symmetric,[11] hyperacute T waves are not well defined in the literature, and depend on recognition more than on criteria. Smith et al. showed that, among patients with ischemic symptoms and at least 1 mm STE in leads V_2-V_4, there is no difference in T-wave voltage among subtle LAD ATO vs normal STE ("normal-variant STE" or "early repolarization"); rather, the former are much larger only in proportion to the corresponding R wave. Thus, the mean ratio ($\pm$ SD) of T-wave amplitude in V_2-V_4 to R-wave amplitude in V_2-V_4 was 0.7 ($\pm$ 0.4) for normal-variant and 3.1 ($\pm$ 4.3) for "subtle" LAD ATO, with a mean difference of 2.5 (95% CI, 1.8-3.2).[9] In other words, large T waves might be normal in V_2-V_4, but only when there is high R-wave amplitude (see these 10 examples of inferior hyperacute T waves: https://hqmeded-ecg.blogspot.com/2016/05/10-cases-of-inferior-hyperacute-t-waves.html. Here are 10 examples of anterior hyperacute T waves: http://hqmeded-ecg.blogspot.com/2016/04/ten-10-examples-of-hyperacute-t-waves.html. Here are 10 examples of lateral hyperacute T waves: https://hqmeded-ecg.blogspot.com/2017/04/ten-cases-of-hyperacute-t-waves-in-v4-v6.html).

Mimickers of STEMI

There are many conditions with STE that might mimic STEMI and thus affect the specificity of STE.[40] In fact, most STE of at least 1 mm in patients with undifferentiated chest pain result from other conditions, such as normal STE (also known as early repolarization), LVH, acute pericarditis, Takotsubo cardiomyopathy, and LBBB, among others. These ECG patterns might result in false positive cardiac catheterization laboratory activations. Larson et al. examined the false positive rate among 1335 patients with suspected STEMI undergoing coronary angiography and reported that 14% of patients did not have a culprit artery; etiologies of false positive activations were due to conditions such as early repolarization, pericarditis, and LVH, among others.[41]

For this reason, it is essential for clinicians triaging patients with suspected STEMI to understand the nuances in ECG diagnosis to maximize the identification of patients with ATO that benefit from emergent coronary angiography and possible PCI, while also limiting false activations.

Ischemic STE Might Mimic Normal STE, and *Vice Versa*

More importantly, ECGs with STE that is in fact due to ischemia might mimic nonischemic STE. Table 1 lists 8 rules for recognizing ATO in the absence of classic STEMI, or in differentiating ischemic STE from STE due to a STEMI mimic. All are also described in this and the next 4 paragraphs, as well as the following 5 sections. The modified Sgarbossa criteria, in which 2 variants are listed, are applied to LBBB, and appear to be applicable to ECGs with right ventricular pacing. "Terminal QRS distortion" is used to differentiate subtle LAD occlusion from normal-variant STE in right precordial leads; it is not seen in normal-variant STE, and thus is a very specific indicator of LAD occlusion. The 3- and 4-variable formulae are used to differentiate subtle LAD occlusion from normal-variant STE in V_2-V_4; they should only be used when the STE is not obviously due to LAD occlusion, and characteristics of an obvious LAD occlusion are listed. Anterior LV aneurysm morphology (persistent STE after previous MI) is a common false positive, and a rule for differentiating it from acute STEMI is summarized; it is most applicable when there are well-formed Q waves, usually QS waves, in V1-V_4. Finally, in patients with a normal QRS and any amount of STE in inferior leads, look for any STD in lead aVL as a specific indicator of inferior MI.

It is particularly important to recognize that normal STE, also called "normal variant STE" and also formerly referred to as "early repolarization," may mimic inferior, lateral, or anterior STEMI; the latter has normal STE in leads V_2-V_4. Most normal ECGs have at least 1 mm of STE (at the J-point, relative to the PQ junction) in right precordial leads, and might have up to several millimetres.[47,48] Because many acute LAD ATO manifest $\leq$ 2 mm, and even $\leq$ 1 mm, of STE,[26] it is clear that there is significant overlap between normal STE and LAD ATO. Furthermore, 40% of anterior STEMI have upward concavity in all of leads V_2-V_6 and half have no inferior reciprocal STD.[49,50] Thus, the differentiation between the two entities can be very difficult. One feature that clearly rules out normal STE is terminal QRS distortion, defined as absence of both an S wave and a J wave in either of leads V_2 or V_3; it was found in 0 of 171 cases with normal STE in V_2-V_4 (Fig. 3).[44]

How can we recognize subtle LAD ATO when it appears to be normal STE? Smith et al. compared 171 normal STE in V_2-V_4 with 143 "subtle" acute LAD. Subtle was defined as no precordial Q waves, no STE $>$ 5 mm, no STD (either in precordial or in limb leads [particularly in II, III, or aVF]), no straight or convex ST segment in V_2-V_6, and no terminal QRS distortion.[9] They reported that ECGs with normal STE have higher R-wave amplitude and a shorter Bazett-corrected QT (QTc-B). A formula that differentiates the 2 entities was derived and validated in separate cohorts: using the QTc-B, STE at 60 ms after the J-point in lead V_3 (STE60V3), and the R-wave amplitude in V_4 (RAV4), if the formula $1.196 \times \text{STE60V3} + 0.059 \times \text{QTc-B} - 0.326 \times \text{RAV4}$ has a value $>$ 23.4, vs $\leq$ 23.4, the ECG represents LAD ATO with a sensitivity, specificity, and accuracy of 86%, 91%, and 88%, respectively, with positive and negative likelihood ratios of 9.2 and 0.10 (Fig. 4).

These likelihood ratios compared very favourably with standard STEMI "criteria," which had a positive and negative likelihood ratio of 1.5 and 0.6, respectively. There is a free iPhone app called "SubtleSTEMI," which helps assess ECGs in which the differential diagnosis is normal STE vs subtle LAD ATO. There is an Android app called "ECG SMITH." The calculator is also on www.mdcalc.com.

Patients whose ECGs had high (or low) total QRS voltage in lead V_2 (QRSV2) had false positive (or false negative) results. Therefore, the formula was refined and, in multivariate analysis, a high total QRS voltage in V_2 correlated with normal STE and a low voltage with subtle LAD ATO. If the derived, but not yet validated, 4-variable formula: $(0.052 \times \text{QTc} - 0.151 \times \text{QRSV2} - 0.268 \times \text{RAV4} + 1.062 \times \text{STE60V3})$ is $\geq$ 18.2, then LAD ATO is very likely, with 88.8% sensitivity and 94.7% specificity and an area under the curve of 0.9686.[8]

Table 1. Proposed rules for identifying acute coronary occlusion

Rule name	Population	Rule	Sensitivity for occlusion	Specificity
Modified Sgarbossa-1[42]	LBBB	Any 1 of these 3 criteria, in $\geq$ 1 lead: 1. Concordant STE at least 1 mm 2. Concordant STD V_1-V_3 at least 1 mm 3. Excessively discordant STE as defined by ST/S ratio $>$ 25%	80%	99%
		3. Excessively discordant STE as defined by ST/S ratio $>$ 20%	84%	94%
Modified Sgarbossa-2[42]	LBBB	Any single lead with excessively discordant STD or STE defined by $>$ 30% of preceding S or R wave	64%	98%
Modified Sgarbossa for paced rhythm[43]	Right ventricular pacing	Any 1 of these 3 criteria, in $\geq$ 1 lead: 1. Concordant STE of at least 1 mm 2. Concordant STD V_1-V_6 of at least 1 mm 3. Excessively discordant STE defined by ST/S ratio $>$ 25% in any lead	67%	99%
Terminal QRS distortion[44]	Differentiating normal STE from ischemic STE due to LAD occlusion	Absence of S wave and J wave in either of V_2 or V_3	20%	100% (95% CI, 97.8-100)
3-Variable formula to differentiate normal STE from subtle LAD occlusion[9]	Differentiation of normal precordial STE from LAD occlusion. Exclude (obvious LAD occlusion): • STE of $\geq$ 5 mm • Single convex ST segment in V_2-V_6 • Any STD, inferior or anterior • Terminal QRS distortion, as above • Any Q waves in V_2-V_4	• Corrected QT interval, measured using computer • STE60V3 • RAV4; see Figure 1A-C for methods of measurement Formula: 1.196 $\times$ STE60V3 + 0.059 $\times$ QTc-B $-$ 0.326 $\times$ RAV4 Most accurate cut point: if the value is $>$ 23.4, vs $\leq$ 23.4, ECG represents LAD occlusion, AUC = 0.9538	86%	91%
		Cut point of 22.0 (any value $>$ 22 should prompt close evaluation)	96%	81%
4-Variable formula[8]	Same as 3-variable, not validated	Same as 3-variable, but adds total QRSV2 Formula: 0.052 $\times$ QTc $-$ 0.151 $\times$ QRSV2 $-$ 0.268 $\times$ RAV4 + 1.062 $\times$ STE60V3 Most accurate cut point is $\geq$ 18.2; if $>$ 18.2, then LAD occlusion is very likely; AUC = 0.9686	89%	95%
Anterior left ventricular aneurysm, or persistent STE after old anterior MI[45]	STE in V_1-V_4 that could be either acute STEMI or old MI with persistent STE. Q waves, usually QS waves, present in V_1-V_4	If there is a singe lead among V_1-V_4 with a T amplitude to total QRS amplitude ratio of $>$ 0.36, the ECG represents acute STEMI False negative results occur with prolonged chest pain (subacute MI)	92%	69%
ST depression in aVL[46]	ECGs with any STE in II, III, aVF, possible inferior acute MI	Exclude patients with LVH, LBBB, delta wave, paced rhythm With any amount of STD in aVL, any STE in inferior leads is MI until proven otherwise. Cannot differentiate old MI with persistent STE from acute MI	99%	100% (95% CI, 91-100)

AUC, area under the curve; CI, confidence interval; ECG, electrocardiogram; LAD, left anterior descending artery; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; MI, myocardial infarction; QRSV2, QRS voltage in lead V_2; RAV4, R-wave amplitude in V_4; STD, ST depression; STE, ST-elevation; STEMI, ST elevation myocardial infarction; STE60V3, ST elevation at 60 ms after the J-point in lead V_3.

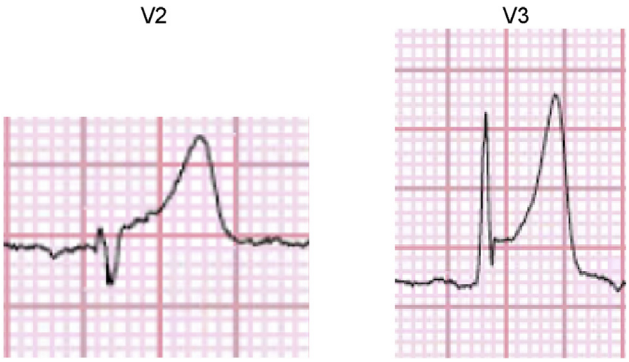

Figure 3. Anterior myocardial infarction with terminal QRS distortion. Terminal QRS distortion due to left anterior descending artery occlusion in a 29-year-old man. Terminal QRS distortion = absence of an S wave as well as a J wave in either of V_2 or V_3 (see lead V_3). Reprinted from Dr Stephen W. Smith's blog, courtesy of Dr Stephen W. Smith.

As with all dichotomous rules, for both formulas there are still false positive and negative results, and the closer the value is to the cutoff, the less reliable the result. In the author's opinion, the rule is best used to identify unsuspected ATO and not to dismiss a worrisome ECG as normal (See Fig. 1B-E for subtle STE of LAD occlusion and Fig. 5 for normal STE in V_2-V_4, and a 12-lead example in Supplemental Figs. S3, and S4; for 12 cases of the use of the 3- and 4-variable formula, see: http://hqmeded-ecg.blogspot.com/2017/11/12-cases-of-use-of-3-and-4-variable.html).

LV Aneurysm

LV aneurysm morphology, or "persistent STE after previous MI" is a common cause of false-positive activation that frequently challenges clinicians. Because acute STEMI as well as LV aneurysm might have Q waves, the primary difference is the size of the T waves, which are larger in acute STEMI. A rule was derived and validated that uses T-wave amplitude to make the distinction between the two.[45,51] If, in a patient with suspicion of ACS, there is STE and well formed Q waves, especially QS waves, in leads V_1-V_4, then the likely differential diagnosis is acute anterior STEMI vs anterior LV aneurysm morphology. If there is a single lead among V_1-V_4, which has a T/QRS amplitude ratio > 0.36, then the diagnosis of acute STEMI is likely with a sensitivity, specificity, and accuracy of 91.5%, 69%, and 89.3%, respectively. False negative results occurred with subacute STEMI (symptoms lasting > 6 hours) because T-wave size diminishes, and Q waves develop, as an infarct progresses. Inferior LV aneurysm remains difficult to distinguish from acute inferior STEMI.

Pericarditis, Inferior Normal STE, and Subtle Inferior Myocardial Infarction

STE of AMI might also be dismissed as pericarditis, especially inferior, lateral, or inferolateral STEMI. As stated previously, normal STE (or "early repolarization") in inferior and lateral leads might also be confused with ischemic STE. Among 426 patients with inferior MI who had a normal QRS, Bischof et al. reported that 99% of ischemic inferior STEs had at least some reciprocal STD in lead aVL, even when the inferior STE (17% of cases) was subtle (< 1 mm), and even when there was STE in V_5 and V_6.[46] In contrast, in pericarditis there was no STD in any lead except aVR. Thus, in patients with ischemic symptoms and a normal QRS, any STD in aVL, especially accompanied by T-wave inversion, should lead to high suspicion of inferior MI (see example in Supplemental Fig. S5). It should be emphasized that ECGs with an abnormal QRS, especially limb lead LVH, LBBB, Wolf-Parkinson-White, known inferior LV aneurysm, or paced rhythm, often have reciprocal STD at baseline, without ischemia, in lead aVL and elsewhere. In contrast, ECGs of

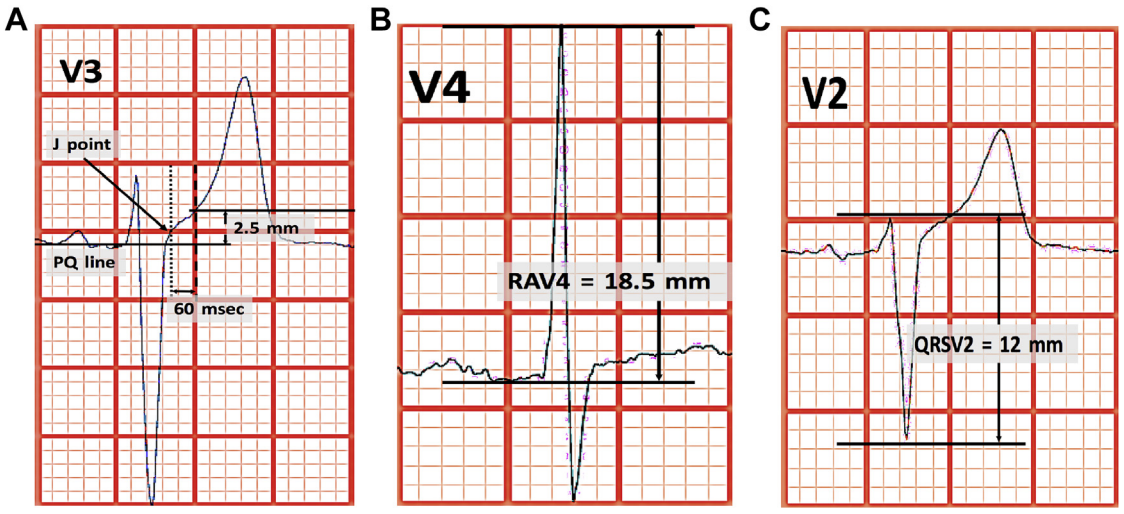

Figure 4. Measurements of variables for the 3- and 4- variable formulas for differentiating normal ST-elevation from subtle left anterior descending artery occlusion. (**A**) Shows the method of measurement of the ST segment at 60 ms after the J point in lead V_3 (STE60V3). The **horizontal line** is drawn from the PQ junction to the right. The J-point is located at the tip of the **long thin arrow**. A **vertical dotted line** is drawn down to the **horizontal line**. Another **thicker vertical dotted line** is drawn 60 ms after this line. The intersection of this **second vertical line** with the tracing is located (intersection of **thick dotted line** and the **second horizontal line** which is 2.5 mm above the **first horizontal line**). Thus, STE60V3 = 2.5 mm (0.25 mV). (**B**) Shows the method of measurement of R-wave amplitude in lead V_4 (RAV4). (**C**) Shows the method of measurement of voltage in lead V_2 (QRSV2).

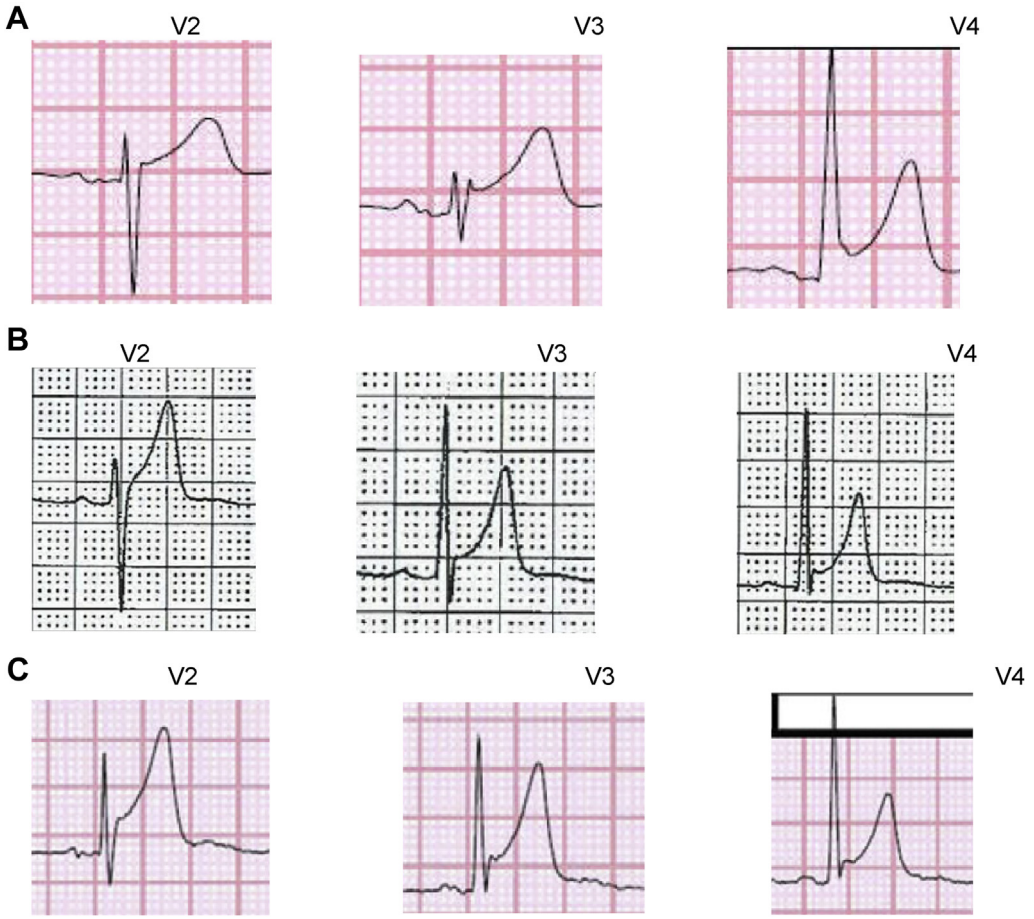

Figure 5. Early repolarization. (**A**) (V_2-V_4) Early Repolarization in V_2-V_4 (normal ST-elevation), case 1. (**B**) (V_2-V_4) Early repolarization in V_2-V_4 (normal ST-elevation), case 2. (**C**) (V_2-V_4) Early repolarization in V_2-V_4 (normal ST-elevation), case 3. Notice there is ST-elevation in V_2 and V_3 meeting criteria for anterior ST-elevation myocardial infarction. There is no terminal QRS distortion (S waves in V_2 as well as V_3). However, because of high R-wave voltage (19 mm in V_4) and short QTc (371 ms), the 3-variable formula value is very low at 19.88 (< 23.4). The 4-variable value is 16.83 (< 18.2). Notice the absence of S wave in V_4 is okay for normal ST-elevation. In V_2, there is an S wave: it barely goes below the PQ junction. Panel **C** reproduced from Smith et al.[9] with permission from Elsevier.

patients with myocarditis often manifest reciprocal STE that might be impossible to distinguish from STEMI without an angiogram.[52] Likewise, normal inferior STE should never be assumed if there is any STD in lead aVL (Fig. 2).

LBBB

LBBB has long been recognized as an impediment to the ECG diagnosis of STEMI. "Appropriate discordance" means that the nonischemic ST segment should be in the opposite direction of most of the QRS. Concordance is when the ST segment is in the same direction as the QRS and 1 mm is very specific for ATO. Furthermore, in "normal" LBBB without acute MI, leads V_1-V_4 have a negative S wave with appropriately discordant STE, and distinguishing this baseline STE from ischemic STE has historically been problematic.

Sgarbossa et al. developed 3 criteria for diagnosis of STEMI in LBBB, in which outcomes were on the basis of CK-MB, not angiography.[53] The Sgarbossa criteria are: (1) 1 mm of concordant STE in any single lead (5 points); (2) 1 mm of concordant STD in 1 of leads V_1-V_3 (3 points); and (3) excessively discordant STE of 5 mm in any lead (2 points). In this point-weighted system, 3 points were required for the diagnosis.[53] The third criterion is important for distinguishing normally discordant STE from excessively discordant STE and is especially important in leads V_1-V_4 for the diagnosis of mid-LAD ATO (proximal LAD occlusion is likely to also manifest concordant STE in lateral leads I and/or aVL due to its effect on the first diagonal artery); however, it did not receive 3 points because it was not specific enough, and this is because 8% of baseline high-voltage LBBBs have at least 5 mm of STE in V_1-V_4. Thus, the Sgarbossa point-based criteria were overall very specific but very insensitive.[53] Smith et al. used an angiographic outcome (not troponin or CK-MB) to study the ECG in LBBB. Their Smith-modified Sgarbossa criteria transform the third criterion into a proportional criterion, such that if the ST/S ratio is $\geq$ 25% in just 1 lead (with at least 1 mm STE), with STE measured at the J-point relative to the PQ junction, then ATO is diagnosed (see Fig. 6 for measurements and 12-lead example in Supplemental Fig. S6).[54] Along with the other 2 criteria, the Smith-modified Sgarbossa criteria are more sensitive as well as more accurate than the original criteria. In the validation study, the sensitivity, specificity, and accuracy of Smith-modified

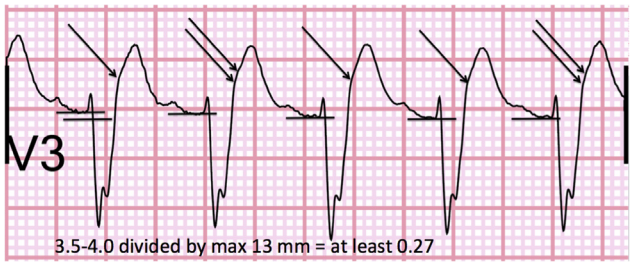

Figure 6. Measuring ST-elevation at the J-point in left bundle branch block to calculate the third criterion of the Smith-modified Sgarbossa criteria, the ST/S ratio. Measurement of the ST/S ratio in lead V_3 in left bundle branch block. The **arrows** point to possible J-points, at either 3.5 or 4.0 mm above the PQ junction. The S wave is at most 13 mm, so the ST/S ratio is, at a minimum 3.5/13 = 0.27 and is thus excessively proportionally discordant. This was a left anterior descending artery occlusion. See Supplemental Figure S4 for a full 12-lead electrocardiogram. Reprinted from Dr Stephen W. Smith's blog, courtesy of Dr Stephen W. Smith.

Sgarbossa criteria for ATO were 80%, 99%, and 95%, vs 49%, 100%, and 91% for the weighted original criteria, and 56%, 94%, and 87% for the unweighted original criteria, respectively.[42] If the ST/S ratio cutoff is $\geq$ 20%, those values were 84%, 94%, and 91%, respectively (Fig. 6). A second rule that was derived and validated is simpler and has 98% specificity, but only 64% sensitivity: any single lead with excessive proportionally discordant STE or STD $\geq$ 30% of the preceding R or S wave was diagnostic of ATO.[42]

Ventricular Paced Rhythm

Similarly, AMI or even ATO in the setting of right ventricular paced rhythm is thought by many to not be diagnosable on the ECG. The ongoing **P**aced **E**lectrocardiogram **R**equiring **F**ast **E**mergent **C**oronary **T**herapy (PERFECT) study (NCT02765477) will examine the sensitivity and specificity of the Smith-modified Sgarbossa criteria for the diagnosis of ATO in patients with a ventricular paced rhythm and potential ischemic symptoms.[55] Preliminary data are very encouraging; among 15 ATO and 79 control participants, the criteria had 67% sensitivity and 99% specificity for ATO.[43]

LVH

LVH might result in secondary repolarization that mimics STEMI. Armstrong et al. analyzed the ACTIVATE-SF database; a registry of consecutive ED STEMI cases, and concluded that an ST/S ratio of $\geq$ 25% is an appropriate cut point for diagnosing STEMI.[56] However, the study did not assess ECGs with very high right precordial S-wave voltages, which are precisely the ECGs that are difficult. Any ST/S ratio > 15% in the setting of high S-wave voltage in V_1-V_3 is suspicious for new anterior STE: 15% of a 30-mm S wave is 4.5 mm, whereas a 25% rule would require 7.5 mm of STE. Unfortunately, convex morphology might be baseline and is not specific for AMI. STD in V_5 and V_6, with reciprocal STE in aVR, occurs frequently in LVH and might mimic ACS.[57]

Takotsubo Cardiomyopathy

Takotsubo might manifest T-wave inversion, but also STE that mimics STEMI. Although earlier work had suggested that ECG criteria might distinguish this STE from anterior STEMI,[58] recent literature does not support this result.[59,60] Although the specificity of various combinations of ECG elements for Takotsubo might be > 95%, the positive predictive value might be as low as 67% because of the low prevalence of Takotsubo. Many anterior STEMI, especially due to wraparound LAD to the inferior wall, have similar ECG findings and also apical ballooning.[61] Therefore, coronary angiography is often essential to rule out ATO, even when the STE pattern as well as cardiac ultrasound suggest Takotsubo.

Lead aVR in ACS[62]

Many experts consider the ECG pattern of STE in aVR, with diffuse STD elsewhere (referred to herein as the "aVR STE pattern"), to be representative of LM ATO.[7] The 2013 ACC/AHA STEMI guidelines consider this a "STEMI equivalent," in which thrombolytic therapy is not contraindicated (evidence level B, no specific class of recommendation).[18] However, these conclusions are on the basis of studies in which LM lesions were not true subtotal or complete occlusion (ie, TIMI 0/1 flow).[62,63] The interventional community defines occlusive LM disease as > 50% according to fractional flow reserve, or $\geq$ 75% stenosis,[64] but urgent or emergent intervention on lesions not meeting these thresholds is only imperative if it is a thrombotic lesion and the patient has refractory ischemic symptoms (ie, not resolved by nitrates, antiplatelet, and antithrombotic therapies; see 3 examples in Supplemental Fig. S7).

Although nearly half of patients with $\geq$ 1 mm STE in aVR due to ACS will require coronary artery bypass surgery for revascularization,[62] the infarct artery is often not the LM, but rather the LAD or severe 3-vessel disease. More importantly, such ECG findings are frequently due to nonocclusive etiologies (eg, baseline LVH, demand ischemia secondary to respiratory failure, aortic stenosis, hemorrhagic shock). Knotts et al. reported that only 23% of patients with the aVR STE pattern had any LM disease (fewer if defined as $\geq$ 50% stenosis). Only 28% of patients had ACS of any vessel, and, of those patients, the LM was the culprit in just 49% (14% of all cases).[57] It was a baseline finding in 62% of patients, usually due to LVH.

Thus, a number of expert reviews emphasize the low specificity of the aVR STE pattern, preferring to label it as circumferential subendocardial ischemia; in this syndrome, STE in aVR is reciprocal STE, reciprocal to an STD vector toward leads II and V_5.[10,12,62]

The aVR STE pattern is also not sensitive for LM ATO. However, anterior STEMI with combined new right bundle branch block and left anterior fascicular block is highly suggestive of LM ATO (see example 12-lead ECG in Supplemental Fig. S8).[65,66]

It should be re-emphasized that true LM ATO (ie, TIMI flow 0) is rare in the ED, because most either die before arrival or are recognized clinically because of cardiogenic shock. Thus, reported specificities of STE in aVR for LM ATO result in very low positive predictive values. Of those who do get to the ED, many present with clear STE.[62,65,66]

The ACC/AHA states that thrombolytics are not contraindicated for diffuse STD "associated with" STE in aVR. Because of the poor specificity of this pattern for LM ATO, we suggest that thrombolytics should only be considered for those with profound STD that is clearly due to ACS, is refractory to all other medical management, and only when PCI is completely unavailable.

Lead aVR in STEMI

Some patients whose ECGs already meet conventional STEMI criteria might also have STE in lead aVR. This finding does not alter the need to pursue emergent reperfusion, although it might suggest a poorer prognosis.[62,67] In a patient with otherwise diagnostic STE, additional STE in aVR does not represent LM ATO and is not helpful in diagnosing the infarct-related artery or the site of occlusion.[68] Less than 3% of anterior STEMI has LM ATO, and most are recognized clinically because of cardiogenic shock.[69,70]

de Winter T Waves

de Winter T waves, as a STEMI equivalent, has been thorougly reviewed.[7,10] We only note that some authors have conflated this rare finding with that of the more common pattern of diffuse STD seen with circumferential endocardial ischemia (see example in Supplemental Fig. S9).[12]

Future Directions in the ECG in ACS

Novel features, some of which might affect reperfusion strategies, continue to be identified in the ECGs of patients with ACS or with symptoms compatible with ACS. As noted previously, the ECG of patients with a ventricular pacemaker might show ischemic changes, and currently is being studied. Similarly, a fragmented QRS is a poor prognostic feature in ACS, suggesting a higher risk of complications and death.[71] Likewise, a prominent J wave suggests a higher risk of ventricular arrhythmias and death during a STEMI.[72]

The standard 12-lead ECG still fails to adequately interrogate the "electrocardiographically silent" lateral and posterior regions of the left ventricle. Body surface mapping (BSM) uses up to 256 leads arrayed over the anterior and posterior torso and allows for broader coverage and higher resolution of ischemic signals. BSM might provide far higher sensitivity in identifying acute coronary occlusion, particularly of the circumflex.[73] Just as with the standard 12-lead, electrical activity measured using BSM at the skin surface does not strictly correlate with that at the myocardial level. The "inverse problem" of reconstructing myocardial electrical signals from those of the surface electrodes is still in initial stages, but might provide more comprehensive assessment of ischemia than the standard 12-lead.[74]

Although computer interpretation is nearly ubiquitous on ECG machines, the benefit (or harm) is unclear, especially with nonexpert clinicians.[75] Even cardiologists who over-read large numbers of ECGs in their own practice disagree about the utility of computer interpretation.[76] Better understanding of the interplay between the clinician and that interpretation is needed.[77] Currently, computer interpretation software uses rule-based algorithms, but artificial intelligence using machine-learning deep neural networks, combined with large databases of ECGs (ie, "big data"), has the potential to revolutionize ECG interpretation in the future (S.W. Smith et al, unpublished data, 2017).

Conclusion

See Table 1 for a summary of rules. The ECGs of many patients with acute coronary occlusion do not meet STE criteria for STEMI, and thus consistently have delayed PCI with worse outcomes. ACS patients with refractory symptoms benefit from emergent angiography. Many of these patients have hyperacute T waves or subtle STE. Others with high-risk ACS have STD only. Recent literature provides insight into identifying these ECGs, and in differentiating them from STEMI mimics, and in diagnosing STEMI in the setting of LBBB and paced rhythm, so that appropriate emergent PCI might be undertaken. Finally, some patients with acute coronary occlusion might have no ECG evidence of ischemia, and emergent angiography, if undertaken, must be on the basis of clinical, biomarker, or echocardiographic findings.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2017.11.011.