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Review

STEMI: A transitional fossil in MI classification?

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ABSTRACT

An important task in emergency cardiology is distinguishing patients with acute coronary occlusion (ACO), who will benefit from emergent reperfusion therapy, from those without ongoing myocyte loss who can be managed with medical therapy and for whom potentially harmful invasive interventions can be deferred. The electrocardiogram is critical in this process. Although the ST-segment elevation myocardial infarction (STEMI)/non-STEMI paradigm is well-established, with "STEMI" representing ACO, its evidence base is poor, and this can have dire consequences. The universally recommended STEMI criteria do not accurately diagnose ACO; in fact, they miss more than one-fourth of the patients with ACO, and also result in a substantial burden of unnecessary catheterization laboratory activations. We here discuss why we believe it is time to change the current STEMI/non-STEMI paradigm.

"Words, like eyeglasses, blur everything that they do not make clearer".
[Joseph Joubert]

Introduction

Patients with acute coronary occlusion (ACO) or near occlusion, with insufficient collateral circulation, have myocardium that is at imminent risk of infarction (MI) without immediate reperfusion. An important issue in emergency cardiology is the recognition of patients with ACO, and distinguishing them from patients who do not have MI, and also from those who do have MI but who do not have ACO with its ongoing myocyte loss, and for whom potentially harmful invasive interventions can be deferred by management with anti-platelet and anti-thrombotic therapy. The electrocardiogram (ECG) plays a central role in this process.

Before the reperfusion era, the established MI paradigm was Q-wave/non-Q-wave MI dichotomy, as clinicians had little to offer patients while they were completing their MI, except to classify them according to whether their subsequent ECG developed Q-waves, the ominous sign of the irreversible loss of substantial myocardium [1]. The term "Q-wave-MI" implicitly referred to ACO with completed infarction, one which had not undergone reperfusion therapy.

At the end of the last millennium, a major paradigm shift occurred as a result of the large scale randomized-controlled trials of fibrinolytics vs. placebo [2]. The Fibrinolytic Therapy Trialists' (FTT) meta-analysis combined data from 58,600 patients and showed that the mortality rate was significantly lower in those who received fibrinolytics [3]. Subgroup analyses indicated that patients with ST-segment elevation (STE) on the ECG gain a slightly better survival benefit from emergent reperfusion than patients whose ECGs did not have STE. From then on, the term STEMI became synonymous with ACO that necessitates acute reperfusion. After fine-tuning of STE cutoffs, universally agreed STEMI criteria became the current guideline-supported ECG paradigm [4–6].

However, evidence accumulated in the past 20 years indicate that there is room for substantial improvement in the ECG diagnosis of ACO. Here we discuss why we believe it is time to free the underlying pathology of ACO from its current name, which is based on the inadequate and misleading surrogate ECG sign of "ST Elevation," and call for the next major shift in MI classification [7].

STEMI criteria were not designed to diagnose ACO

Patients with ACO are the cohort that is believed to benefit from emergent reperfusion therapy. However, fibrinolytic studies did not investigate the presence or absence of ACO among enrolled patients. Angiography was not employed in these studies at any time; instead, the researchers randomized patients with "suspected MI," most with concerning but undefined ECG findings, to fibrinolytics vs. placebo, with mortality as the outcome measure, but without any confirmation

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of presence or absence of ACO. In this high-risk population, which was explored in the seminal FTT meta-analysis, the mortality rate was significantly lower in those who received fibrinolytics, even without considering any ECG parameter. When the authors compared the effects of fibrinolytics in all patients to the effects in subsets of patients with ST-segment depression (STD), STE, and "normal", they found the that STE, vaguely defined, was the ECG finding most closely associated with the benefit of fibrinolytics, with an improvement in the NNT for short term mortality from 56 to 43, compared to giving fibrinolytics to all patients with suspected AMI. Conversely, the subgroups of STD and "normal" ECG showed a nonsignificant trend to mortality harm [3]. However, four [8–11] of the nine trials did not even use ECG for enrollment, and the remaining five defined their version of STE with varying cutoffs, and without any specified measurement methods. STD was also poorly defined, including as little as 1 mm in as little as one lead, with treatment usually beyond 6 h. Thus, STEMI criteria are neither established as the most accurate markers of ACO, nor as the most accurate markers of benefit of reperfusion criteria.

STEMI cut-offs were not fine-tuned by comparing who had ACO and who did not

To reconcile different STE criteria used in various studies, Menown et al. [12] compared STE in normal subjects and patients with MI. The logistic regression analysis indicated that the best cut-off was ≥2 mm STE in at least one of the anteroseptal leads (V1–4), or ≥1 mm in any of the other leads. This study provided the basis for the first universal definition of MI [13]. However, the diagnosis of MI was done by CK-MB, not ACO on angiography, so these criteria could not differentiate ACO from non-ACO, as the STEMI/non-STEMI dichotomy purports to do. Furthermore, the sensitivity for MI by biomarker positivity was only 56%, with a specificity of 94%. Another non-angiographic study of that era showed that the subjective interpretation of MI on the ECG was far more sensitive and specific than any millimeter criteria [14].

In 2004, Macfarlane et al. [15] hypothesized that age and sex-based cutoffs would improve the utility of STE cutoffs. They used logistic regression techniques to derive revised STEMI criteria. Unfortunately, this study again chose CK-MB positivity for the final outcome; no angiographic outcomes were included. In 2009, AHA/ACCF/HRS [16] used these data and introduced the current "STEMI criteria", which were repeated throughout the future guidelines, as recent 4th universal definition of MI [6]. Unfortunately, despite all efforts to fine-tune STE criteria, the medical community had to accept a low sensitivity for AMI.

Subtleties of ECG interpretation are lost when only STE is emphasized

Several studies have demonstrated that factors other than STE can help to diagnose ACO or to exclude it. Proportionality, which is unfortunately completely absent in the STEMI criteria, is a common factor in most of these studies: proportionality is the idea that any amount of STE or STD, or T-wave size, must be assessed relative the QRS amplitude. The lower the QRS voltage, the more significant is any STE or STD or T-wave size. For example, a logistic regression formula [17,18] and a rule-of-thumb [19] have been found to be very effective in differentiating subtle left anterior descending (LAD) coronary artery occlusion from normal variant STE, and they were very accurate in identifying LAD occlusion in patients with only 1 mm of STE in just 1 of leads V2-V4. These rules use four common variables: STE at 60 milliseconds after the J-point in lead V3, QT interval, R-wave amplitude in V4, and total QRS amplitude in V2 [17–19]. Similarly, Armstrong et al. [20] showed that STE >25% of the QRS amplitude can specifically be used for differentiating STE due to ACO from STE due to left ventricular hypertrophy. Modified Sgarbossa criteria (QRS-STE concordance or STE/S wave amplitude ratio >25% when QRS and STE are discordant) were derived, validated, and shown to accurately diagnose ACO in presence of left bundle branch block [21,22] and ventricular paced rhythm [23]. Similar differentiation rules were also published for left ventricular aneurysm and pericarditis [24–26].

Additional clues should also be taken into account when differentiating STE due to ACO from other causes. It has been shown that normal variant anterior STE is always accompanied by an S-wave or a prominent J-wave notch in both V2 and V3; absence of this feature was called "terminal QRS distortion" and was only seen in LAD-ACO [27]. In patients with inferior STE, whether >1 mm or <1 mm, it has been shown that any STD in derivation aVL accurately identifies the STE due to inferior MI (Fig. 1) [25,26]. Furthermore, additional patterns may exhibit noncontiguous STE or simply not show any STE at all. It has been shown that STE in lead I, aVL and only V2 accompanied by STD in other anterior leads (South African flag sign) can be seen in diagonal occlusions (Fig. 2) [28,29]. STE only in lead III and STD in lead I, V4–6 may indicate inferior MI with multivessel disease (Fig. 3) [30,31]. Hyperacute T-waves [32,33] (Fig. 4) and de Winter pattern [34] are also indicators of probable ACO. Of note, isolated "posterior" MI is another well-known entity that does not present with STE in 12-lead ECG, but this was appropriately addressed in the guidelines (Fig. 5) [4–6,35]. Lastly, other QRS complex and T-wave changes can influence the reperfusion decision. A subacute process with well-developed Q-waves and T-wave negativity or spontaneous reperfusion with terminal T-wave inversion are not accounted in the STEMI/non-STEMI paradigm focusing on only ST-segments [36].

In conclusion, these studies indicate that the ECG has the capability of recognizing ACO with high accuracy beyond mere STE, but that a compilation of ECG tools will inevitably be necessary for diagnosis rather than using a single set of STEMI millimeter criteria which are not at all accurate when universally applied (Table 1). Also, it shows how the discovery of new patterns indicating ACO is possible if we free ourselves from the restriction of STEMI criteria.

STEMI/non-STEMI paradigm fails to identify ACO

Studies show STEMI criteria miss nearly one-third of ACO [35,37–42] with the result that this unfortunate group of patients, labeled as non-STEMI, are deprived of emergent reperfusion therapy, just as they were in the old days of Q-wave/non-Q-wave MI approach. Marti et al. [37] showed that approximately one-fifth of the patients with ACO had equal or less than 1 mm of STE, including 18% of left anterior descending artery occlusions. Schmitt et al. [38], found that 29% of patients with ACO did not meet STEMI criteria. The highest miss rate (50%) was recorded in patients with left circumflex occlusion. A post-hoc analysis of the PARAGON-B trial [39] showed that 27% of the patients with non-STEMI had completely occluded culprit vessels at the time of next day angiography. These patients had larger infarct sizes and higher long-term mortality. Similarly, post-hoc analysis of the TRITON-TIMI-38[35] 26.2% of the patients with non-STEMI completely occluded culprit vessels at the time of angiogram. Khan et al. [40] performed a meta-analysis from seven studies including a total of 40,777 NSTEMIs, 25.5% of which had ACO found on angiography an average of 24 h after presentation. These numbers underestimate ACO in non-STEMI, since a large percentage of total thrombotic occlusions spontaneously reperfuse by next day angiogram; unfortunately, many only autolyze after a substantial loss of myocardium.

These findings are important for two further reasons. First, those non-STEMI with unrecognized ACO had higher short and long-term risk of mortality compared to non-STEMI without ACO. A recent systematic review was in line with these observations; patients with ACO but without STE had a 1.5 times higher relative risk of mortality compared to those without ACO [43]. Second, in these studies, clinical parameters did not compensate for the silence of the ECG. Although guidelines recommend urgent (<2 h) invasive evaluation "regardless of ECG or biomarker findings" in patients with persistent pain, hemodynamic compromise, severe heart failure, and/or arrhythmias in order to

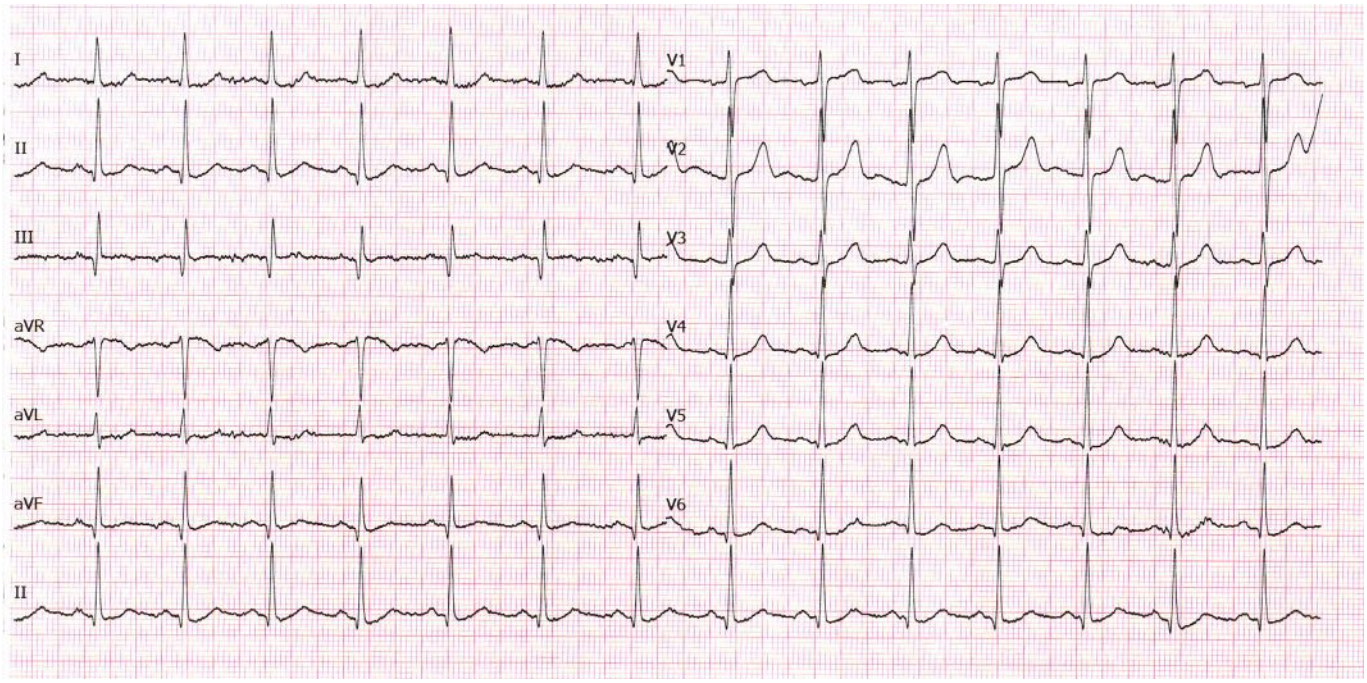

Fig. 1. An inferior OMI not meeting the STEMI criteria. The reciprocal STD in lead aVL is subtle but diagnostic [25,26]. The angiogram revealed an acute circumflex artery occlusion.

identify patients with ACO but without STE [4,5], these guidelines were not acted upon or the physicians were simply unable to identify the patients with ACO among all patients with undifferentiated chest pain, even in the highly observed setting of an RCT. Also, the 4th Universal of MI definition [6] acknowledges other ECG markers of ACO than STE. Nevertheless, the data from the above studies confirm that ACO is routinely missed, in spite of persistent chest pain, and this must be at least partly a result of ECGs that do not meet criteria. Though no study has specifically addressed whether physicians feel compelled to be restricted by the STEMI millimeter criteria, there is a wealth of anecdotal data in addition to the above studies [44].

Last, but not least, when STEMI criteria were prospectively tested for the prediction of ACO [45], a startlingly low sensitivity of 21% for computer algorithm measurement of STEMI criteria, and 49% for cardiologist subjective evaluation, was found. Moreover, physicians across all specialties have poor accuracy and poor interrater reliability for detecting ACO under the current paradigm [46], and cannot even agree on where and how to measure the ST [47].

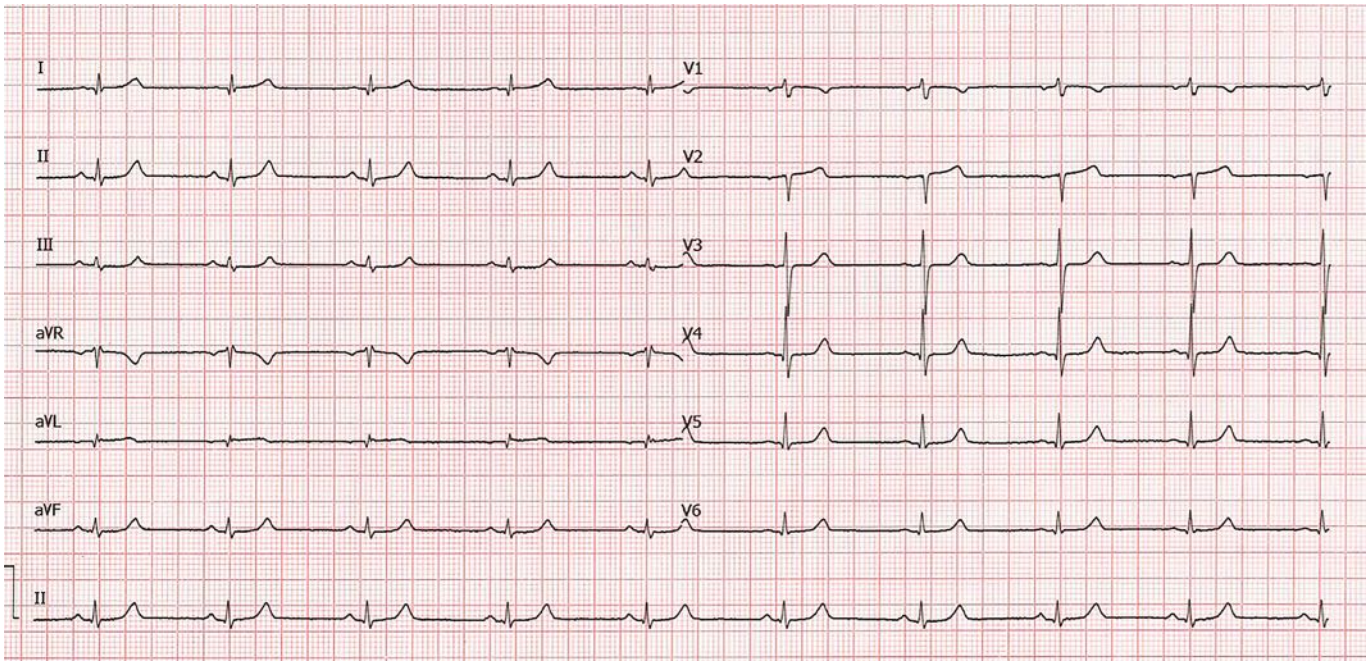

Fig. 2. Mid-anterior infarction due to an acute diagonal artery occlusion (South African flag sign) [28,29] with STE less than 1 mm in lead I and aVL, and non-contiguous STE in anterior leads (lead V_2 registers STE whereas other anterior leads show STD).

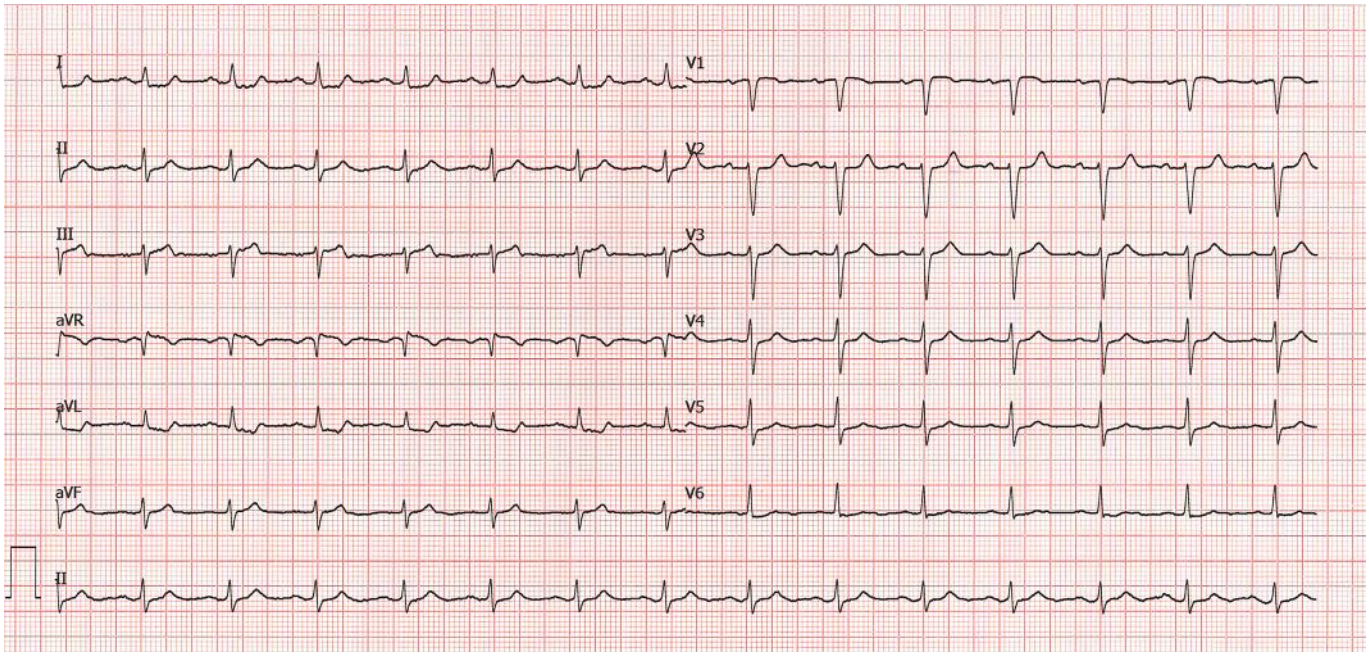

Fig. 3. Aslanger's pattern [31] with STE only in lead III. Angiogram showed multivessel disease with acute right coronary artery occlusion.

A better alternative is available: the OMI/non-OMI paradigm

It is not clear why a disease of a known pathophysiology (ACO) was named with an inaccurate surrogate ECG sign (Q-wave MI/non-Q-wave MI or STEMI/non-STEMI) instead of the pathologic substrate itself (ACO-MI/non-ACO-MI or OMI for short), but this fundamental mistake created important implications for our current practice. As outlined above, ACO can be reliably recognized with the help of many other ECG findings, such as minor STE not fulfilling STEMI criteria [37,48–51], STE disproportionate to preceding QRS [17–19], unusual patterns with contiguous leads showing opposite ST deviations [28,29] and some patterns not showing STE at all [32–34,49,50].

Recently, the DIagnostic accuracy oF electrocardiogram for acute coronary OCClUsion resuLTing in myocardial infarction (DIFOCCULT)

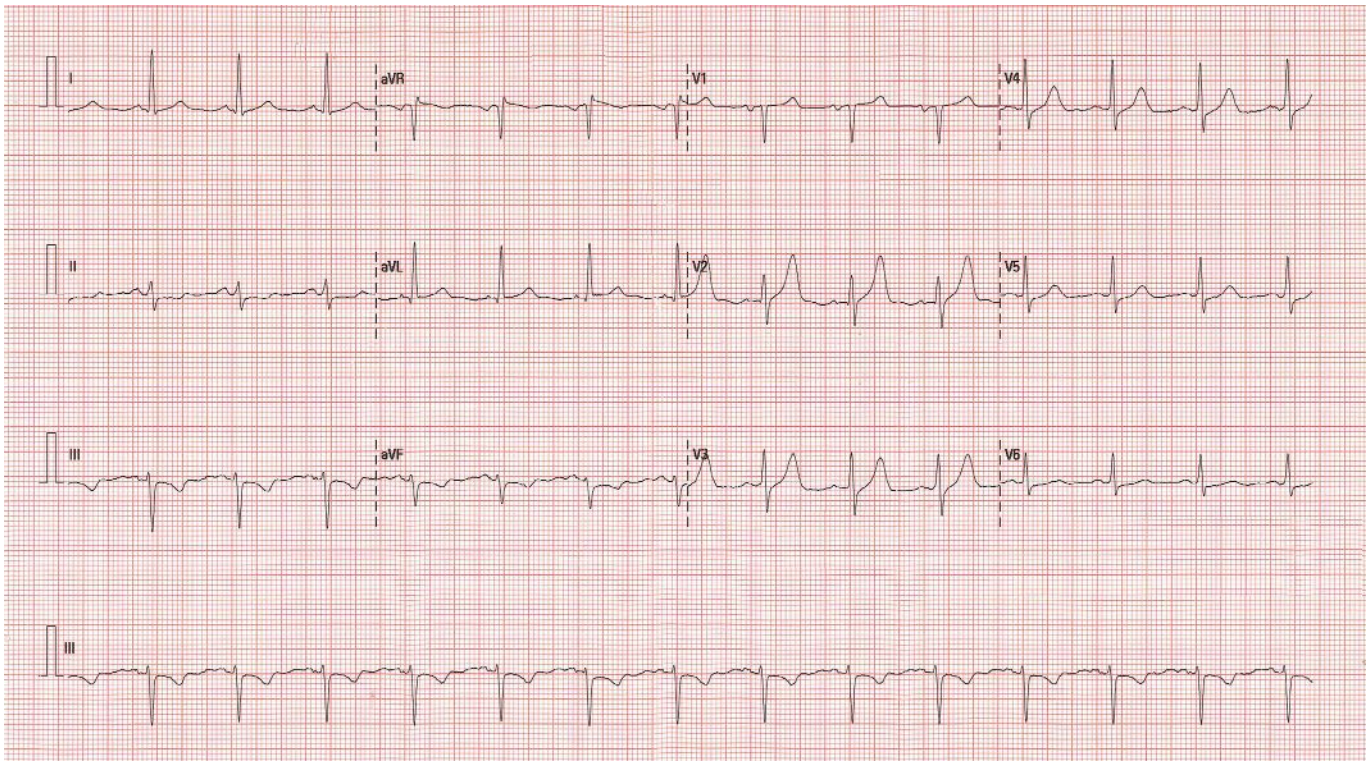

Fig. 4. Another ECG example with ACO but not meeting the current STEMI criteria. Anterior hyperacute T-waves [32,33] and reciprocal inferior STD due to a proximal left anterior descending artery occlusion.

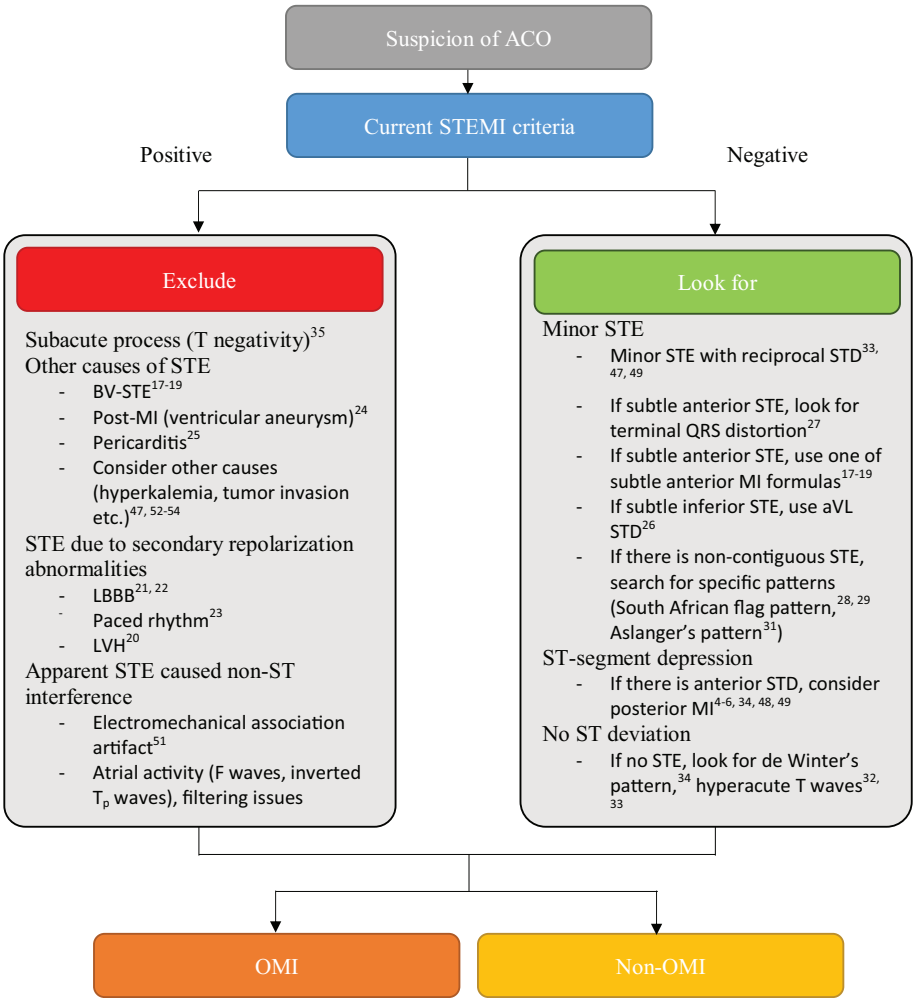

Fig. 5. DIFOCCULT Algorithm. The left-handed side is designed to exclude OMI mimics, and the right-handed side is designed to uncover OMIs that are not fulfilling STEMI criteria. LBBB, left bundle branch block; LVH, left ventricular hypertrophy; MI, myocardial infarction; OMI, occlusion myocardial infarction; STD, ST-segment depression; STE, ST-segment elevation [52–54].

Table 1
A comparison of diagnostic characteristics of various electrocardiographic differentiation criteria.

	Differentiation	Sensitivity	Specificity
Aslanger et al. [19]	BVSTE vs ACO	86	92
Armstrong et al. [20]	LVH vs ACO	64	93
Smith et al. [22]	ACO in LBBB	91	90
Mitchell et al. [23]	ACO in paced rhythm	67	99
Klein et al. [24]	LVA vs ACO	91	81
Bischof et al. [25]	Pericarditis vs ACO	98	100
Hillinger et al. [45] Current STEMI criteria (computer algorithm)	Non-ACO vs ACO	21	99
Hillinger et al. [45] Current STEMI criteria (cardiologist interpretation)	Non-ACO vs ACO	49	98

ACO, acute coronary occlusion; BVSTE, benign variant ST-segment elevation; LBBB, left bundle branch block; LVA, left ventricular aneurysm; LVH, left ventricular hypertrophy; STEMI, ST-segment elevation myocardial infarction.

study [51], compared OMI/non-OMI approach with STEMI/non-STEMI paradigm. This is the largest study specifically designed to challenge 20 years of unquestioned dominance of the STEMI/non-STEMI paradigm. In this study, a set of predefined ECG findings (Fig. 5) in addition to STEMI criteria were used, and the final outcome was a composite ACO endpoint. In accordance with the previous observations, over one-fourth of the patients initially classified as having non-STEMI were re-classified by the ECG reviewers as having OMI. This subgroup had a higher frequency of ACO, myocardial damage, and both in-hospital and long-term mortality compared to the non-OMI group. The OMI/non-OMI approach to the ECG had a superior diagnostic accuracy compared to the STEMI/non-STEMI approach in the prediction of both ACO and long-term mortality. Furthermore, early intervention in patients with OMI-predicting ECGs was associated with lower long-term mortality, whereas early intervention increased long-term mortality in patients with non-OMI-predicting ECGs.

Limitations

The new OMI/non-OMI approach will unavoidably have some limitations. Although the diagnosis of OMI is not limited to ECG, an OMI approach to ECG will probably miss some ACOs, too. Further studies are needed to discover additional patterns indicating ACO.

Furthermore, the OMI/non-OMI requires improved ECG interpretation skills. The complex DIFOCCULT algorithm depicted in Fig. 5 may be intimidating at first glance, but pattern recognition is immediate for an expert, and every physician who deals with patients with suspicion of ACO should strive to attain this level of proficiency. Attaining widespread expertise may be difficult in the clinical practice, and means of improving interpretation skills need to be developed and studied, and prospectively tested with outcome measures in future clinical

trials, but this does not vindicate reducing a complex disease requiring a nuanced approach to a single insufficiently accurate measurement which is chosen simply because more clinicians can supposedly easily apply it. Computer intervention, especially deep convolutional neural networks [55], are certain to be of help in the future, but for the time being it is the clinicians who need to improve their diagnostic skills.

A possible objection to the proposed paradigm shift is that the current guidelines already recommend early catheterization in some non-STEMI patients [56]. However, 'high-risk' criteria defined by the guidelines fail to recognize many OMIs as well as other high-risk acute coronary syndromes, as we discussed above. It should be emphasized that a diagnosis of non-OMI does not necessarily negate the need for emergent catheterization. As the guidelines indicate, 'high-risk' patients, such as those with left main coronary artery critical stenosis, hemodynamic disturbance, dynamic ECG changes (including Wellens' syndrome [57]), ongoing ischemia etc., are still candidates for urgent revascularization under the OMI/non-OMI paradigm.

Another possible objection to the OMI/non-OMI paradigm is whether the newer ECG patterns discussed above have been tested well enough so that the patterns could be introduced in a new universal definition of MI. Although a complete OMI/non-OMI approach needs to be tested in prospective trials, its individual ECG components are reasonably evidence-based as presented in Table 1. Furthermore, it should be bear in mind that the STEMI criteria, the current accepted norm, have never been tested in nor designed for the differentiation of different clinical conditions from MI, as we discussed above. Moreover, it should be considered that the predictive accuracy of any ECG sign is dependent on the pre-test probability. Therefore, every ECG sign, especially the subtle ones, should be interpreted in the clinical context.

Lastly, it should be noted that we even do not have established evidence to support reperfusion therapy for all MIs [51,58]. As in stable coronary artery disease, emergent revascularization may require a critical amount of salvageable myocardium to lead better outcomes, but this hypothetical amount needs to be evaluated in future studies. In the meantime, it is hard to imagine that we would not intend to open an acute coronary thrombotic occlusion which we know to be present.

Conclusion

The STEMI/non-STEMI paradigm is flawed and has been a barrier to progression of our performance in diagnosis of ACO. As it is a complex process of deciding whether the ECG indicates ACO, a set of tools will inescapably be necessary for the diagnosis rather than using a single point measurement of the ST-segment. The new OMI/non-OMI paradigm will not be limited to the ECG; it will also require a more active and prospective use of ultrasound, biomarkers, computed tomography, and even conventional angiography if the ECG is inconclusive and the clinical suspicion is high. However, the ECG still is and probably will be the crucial first-line diagnostic test, and it has the required diagnostic capability for improved diagnosis. Furthermore, researchers should also actively look for possible discovery of new ECG patterns indicating ACO, as the list is continually being expanded. Nevertheless, we believe that it is time for a new paradigm shift from STEMI/non-STEMI to OMI/non-OMI in the acute management of MI.

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