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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

Diagnosis of Occlusion Myocardial Infarction in Patients with Left Bundle Branch Block and Paced Rhythms

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Abstract

Purpose of Review A number of criteria have been developed to aid with the diagnosis of occlusion myocardial infarction (OMI) in patients with left bundle branch block (LBBB) and ventricular paced rhythms (VPR). The current guidelines do not provide clear preference for any specific ECG criteria in LBBB and paced rhythm patients.

Recent Findings This review delineates the difficulties of electrocardiographic diagnosis of OMI in both LBBB and VPR patients. We describe the original Sgarbossa and the newer criteria and their diagnostic performances. We highlight the expected changes of newer pacing modalities and how they may interfere with the electrocardiographic diagnosis of OMI.

Summary We recommend utilizing the Cai et al. algorithm, which combines clinical assessment with the Smith Modified Sgarbossa ECG criteria, for both LBBB and right ventricular pacing patients with suspected OMI. There is limited data concerning ECG changes of OMI in patients with the newer pacing modalities, such as biventricular, His-bundle, or left bundle branch pacing.

Keywords Occlusion myocardial infarction · Sgarbossa criteria · Smith-modified Sgarbossa criteria · Right ventricular pacing · ST-elevation myocardial infarction · Left bundle branch block

Introduction

Occlusion myocardial infarction (OMI) due to acute thrombotic occlusion of an epicardial coronary artery requires immediate diagnosis and management. The most widely recognizable and accepted ECG feature of OMI is ST-elevation (STE) meeting criteria specified in the Fourth Universal Definition of Myocardial Infarction (UDMI) [1]. However, not all OMIs manifest STE meeting these criteria, or even any STE at all [2, 3]. Among the many OMIs not captured by the STE criteria are OMI associated with left bundle branch block (LBBB) and Right Ventricular Pacing (RVP).

This review delineates the difficulties of ECG OMI diagnosis in both LBBB and electronically paced patients, summarize common criteria and their diagnostic performance, as well as highlight the expected physiologic changes of newer pacing modalities and how they may or may not interfere with the diagnosis of OMI.

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The diagnosis of OMI in LBBB is difficult because the normal sequence of ventricular depolarization and repolarization is altered by LBBB producing ST-T wave changes that mask or mimic the expected AMI ECG changes [4]. This is clinically relevant because LBBB that is new, vs. old, is by no means a reliable marker of acute OMI. In fact, in patients who present to the emergency department with symptoms of acute coronary syndrome (ACS), those who have new, vs. old, vs. no LBBB have the same incidence of AMI at 7.3%, 5.2% and 6.1% respectively. The Minneapolis Heart Institute studied patients who were referred for primary PCI for suspected OMI and compared those with new LBBB ($n=131$) to all others (old LBBB or no LBBB, $n=3772$). TIMI 0/1 flow was found in 20% of new LBBB patients vs. 48% of others, and compared to controls they were older, more commonly women, had a lower ejection fraction, and more often presented with cardiac arrest or heart failure than those without new LBBB [5]. Patients with new LBBB had fewer culprit arteries than patients without new LBBB (54.2% vs. 86.4%, $p<0.001$) and higher all-cause mortality [5]. Mehta et al. studied patients with symptoms of ACS and new LBBB referred for angiography; < 30% of the patients had cardiac troponin elevation > 99th percentile, and only 54% of the patients underwent emergent coronary angiography [6]. Of these, 22% had a culprit vessel occlusion, while only 11.6% [6] underwent emergent revascularization. Nestelberger et al. confirmed AMI as the diagnosis in 30% of high-risk patients presenting with LBBB and ischemic symptoms, with similar incidence in those with known LBBB vs. those with presumably new LBBB (29% vs 35%, $p=0.42$) [7]. These studies demonstrate that most patients presenting with suspected AMI and new LBBB often receive inappropriate therapy, are found to have diagnoses other than type-1 AMI and have poor outcomes [5, 7, 8].

Diagnosis of OMI in the Setting of LBBB

Sgarbossa Criteria

Sgarbossa analyzed ECGs of 131 North American patients enrolled in the GUSTO-1 trial (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) who had LBBB and AMI, and compared to a control group of equal number of asymptomatic LBBB patients, with chronic, stable coronary disease. They found that requiring at least 3 points from the following criteria components yielded a specificity over 90% for a diagnosis of AMI in the LBBB patients [9]: (1) concordant ST-segment elevation (STE) of ≥ 1 mm in ≥ 1 lead (5 points), (2) concordant ST-segment depression (STD) of ≥ 1 mm in any one of leads V1–V3 (3 points), or (3) excessively discordant STE, defined as ≥ 5 mm in 1 or more leads when the QRS is negative (2 points). As such, 5 mm of discordant STE, by itself, was not considered adequate for the diagnosis of AMI and would require further testing. However, a mid-LAD occlusion would be expected to manifest STE in only V1–V4, the very leads in which excessively discordant STE is the only means of making the diagnosis (Fig. 1). Thus, by Sgarbossa's criteria, a mid-LAD occlusion would probably almost always be missed. Only proximal LAD occlusion, which might cause concordant STE in I and/or aVL, could be diagnosed. The results showed good specificity for all three components tested but low sensitivities (Table 1).

The highest sensitivity and positive likelihood ratio were seen with the concordant STE ≥ 1 mm rule. Several subsequent studies consistently found Sgarbossa criteria to be highly specific but not sensitive (Tables 2 and 3).

There are several limitations to the original Sgarbossa's study. Sgarbossa used any AMI (CK-MB elevation) as an endpoint—a wide population with substantial heterogeneity that is not limited to OMI [1]. However, angiography was not part of the GUSTO-1 trial. The study's cohort size was relatively limited ($n=131$). The control group is also a weakness: asymptomatic patients with stable coronary disease. Currently, there is limited data on the performance of the original Sgarbossa criteria in patients with angiography-adjudicated OMI diagnosis. Smith reported poor sensitivity and good specificity for the original Sgarbossa criteria (Table 2) [10, 11]. Nestelberger et al. [7] found the Sgarbossa criteria to be specific, but not sensitive, for AMI as diagnosed by high sensitivity troponin, but did not use an OMI outcome (Table 3).

Di Marco et al. [12] performed a multicenter study assessing the diagnosis performance of various modified ECG criteria for the diagnosis of OMI. OMI was inappropriately defined as an acutely occluded artery (thrombolysis in myocardial infarction [TIMI] 0) or an acute lesion with TIMI flow 1 associated with a troponin rise and fall above the 99th percentile upper reference limit. They found that a Sgarbossa score ≥ 3 had low sensitivity but high specificity for the diagnosis of OMI (Table 2). Of note, only 1 of 4 patients with a culprit lesion in the left main coronary artery had a Sgarbossa score > 3. Compared to a Sgarbossa score > 3, a score > 2 was associated with relatively improved sensitivity (48%, $p=0.02$) but worse specificity (81%, $p<0.001$) [12].

Modifications to the original Sgarbossa criteria have been tested to improve the criteria accuracy. For example, the Sgarbossa criteria have been studied without a point system (unweighted, meaning that excessively discordant STE does qualify for OMI diagnosis); this reduces specificity (94% vs. 100%) but improves sensitivity (56% vs.

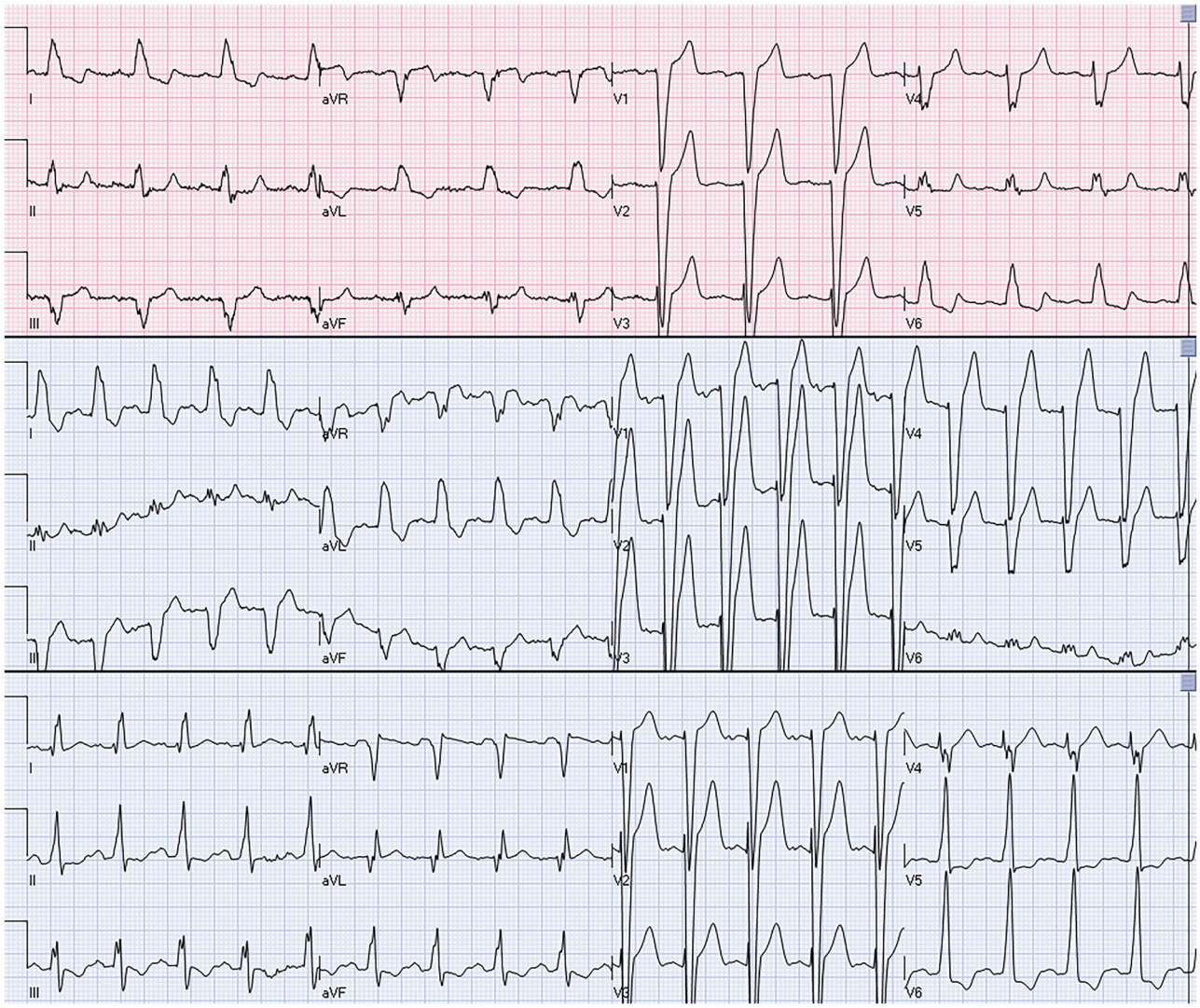

Fig. 1 Serial ECGs of a patient with LBBB. There are significant changes in the magnitude of ST elevation in the anterior leads that appear rate dependent

49%) [10, 11]. Another limitation is that the Sgarbossa criteria utilize an absolute cutoff (5 mm) instead of proportional definitions for discordant STE. It is expected that the absolute magnitude of STE be proportional to the QRS amplitude, and thus, should be adjusted. It is also important to recall that in patients with LBBB, the magnitude of ST deviation varies with changes in heart rate, QRS duration and axis and with the positioning of the electrodes (Fig. 1) [13]. Therefore, some means of adjudicating baseline excessive STE, rather than absolute cut-offs, are warranted.

Table 1 Sgarbossa criteria individual component performance [9]

Criterion	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
ST segment elevation ≥ 1 mm and concordant with QRS complex	73 (64–80)	92 (86–96)	9.54 (3.1–17.3)	0.3 (0.22–0.39)
ST-segment depression > 1 mm in leads V1, V2 or V3	25 (18–34)	96 (91–99)	6.58 (2.6–16.1)	0.78 (0.7–0.87)
ST-segment elevation ≥ 5 mm and discordant with QRS complex	31 (23–39)	92 (85–96)	3.63 (2.0–6.8)	0.75 (0.67–0.86)

Table 2 Sgarbossa criteria performance with angiographic adjudication

Author	Number of patients (AMI)	Endpoint	Sgarbossa Sensitivity[a]	Sgarbossa Specificity[a]
Smith (derivation) [11]	33	Angiographic evidence of either occlusion (TIMI 0 or 1) or stenosis with either thrombosis or ulcerated culprit lesion and peak 24 h cardiac troponin I ≥ 10 ng/mL (equivalent to 10,000 ng/L; 300x the upper reference limit)	52 (95% CI 34–69)	98 (95% CI 93–100)
Smith (validation) [10]	45	1. Acute culprit lesion with TIMI 0 to 1 flow or description of an acute thrombotic occlusion or 2. Presumed acute occlusion with significant cardiac outcome, defined as any of the following: (a) Catheterization showing an acute but nonocclusive culprit lesion with very elevated cardiac biomarker (troponin I ≥ 10.0 ng/mL, troponin T ≥ 1.0 ng/mL, or CK-MB ≥ 80 ng/mL); (b) If no angiography done, then very elevated cardiac biomarker and a new or assumed new regional wall motion abnormality on echocardiography; (c) ECG positive for any criteria with death before attempted emergent cardiac catheterization could be done	49 (95% CI: 34–63)	100 (95% CI: 98–100)
Di Marco [12]	54	Acute coronary occlusion with TIMI 0 or an acute lesion with TIMI flow ≥ 1 associated with a significant rise in cardiac biomarkers (ratio of the peak value of the biomarkers to the upper normal limit [troponin I or T ≥ 10 ng/L or CK-MB ≥ 5 IU/L])*	35% (95% CI: 24–49%)	98% (95% CI: 92–99%)

[a]Score ≥ 3

*This definition does not limit the study population to OMI, but would rather include almost all AMI

Modified Sgarbossa Criteria

Derived in 2012 and validated in 2015, the Smith-Modified Sgarbossa criteria [10, 11] kept the concordant STE and STD in V1–V3 and altered the 3rd criterion (excessively discordant STE) to require 1) ≥ 1 mm STE and 2) an STE to S-wave amplitude ratio ≥ 0.25 [11]. An additional single criterion was derived: any excessively discordant ST deviation (STD or STE)/(S or R) ≥ 30%. The

Table 3 Sgarbossa criteria performance with biomarker adjudication

Author	Number of patients (AMI)	Endpoint	Sgarbossa Sensitivity[a]	Sgarbossa Specificity[a]
Sgarbossa (validation) [9]	22	Acute myocardial infarction documented by serum enzyme (CK-MB) elevation	36%	96%
Tabas [44]	890	High-specificity cardiac marker testing (creatine kinase-MB or troponin), high specificity cardiac marker testing or no confirmation of AMI with marker testing	20% (95% CI: 18%- 23%)	98% (95% CI: 97%, 99%)
Gregg [15]	143	Discharge diagnosis of AMI	13.3%	97.9%
Nestelberger [7]	75	Evidence of myocardial necrosis in association with a setting consistent with myocardial ischemia. At least one hs-cTnT value above the 99th percentile along with a significant rise and/or fall (rise or fall of hc-cTnT by at least 10 ng/L within 6 h, or 6 ng/L within 3 h	3% (95% CI: 0 to 9%)	99% (95% CI: 97 to 100%)

[a]Score ≥ 3

ratio variables were determined by whether the QRS was mostly positive or negative.

The reference standard for both the derivation and validation studies was OMI defined as angiographic evidence of occlusion (thrombolysis in myocardial infarction flow 0–1) or stenosis with either thrombosis or ulcerated culprit lesion and very elevated peak 24 h cardiac troponin-I (cTnI) level ≥ 10 ng/mL [11]. Compared to the original Sgarbossa criteria, the derivation study found Smith's criteria to improve sensitivity and to maintain specificity (Tables 2 and 4) [11]. The substitution of the 3rd criterion with a proportion (ST/S ratio ≤ − 0.25) was subsequently validated in a study that included 45 OMI patients (Table 4) [10]. It remained more sensitive than both the weighted and unweighted Sgarbossa criteria. Smith's secondary single criterion of "overall proportional discordance" demonstrated good accuracy for OMI (sensitivity 100%, specificity 88%) in the derivation, and it remained specific for OMI (98%) but less sensitive (64%) in the validation study [10]. Combining this single criterion with the first two components of Sgarbossa criteria yielded a sensitivity of 100% and specificity of 86% (derivation) [11]. Di Marco et al. included both the Sgarbossa and Smith criteria and the overall proportional discordance criterion in their analysis. Results showed a Sgarbossa score ≥ 3 and/or discordant STE with an ST/S ratio ≤ − 0.25 to have low sensitivity and high specificity (Table 4) while discordant ST deviation with ST/S or ST/R ratio ≤ − 0.3 alone had sensitivity of 26% but a specificity of 99% [12].

One study sought to identify unique ECG trends in patients with OMI and to compare their accuracy of diagnosis to the Smith criteria [14]. They found that patients with OMI had significantly lower ΣQRS amplitude across 12 leads on the ECG compared to non-OMI patients. A cutoff of < 90 mm yielded a specificity of 92% but a sensitivity of 33%. Non-concave ST segment morphology on ECG was also tested and found to be specific (91%) but insensitive (55%) for OMI diagnosis. There was also a notable association with elevated T-wave/QRS amplitude ratio > 1.25 with OMI but the accuracy was still inferior to the Smith criteria (Table 4). Comparison studies of the Smith S wave criterion (ST/S > 0.25) and the original Sgarbossa criteria (score ≥ 3) using angiographic or biomarker reference standards have consistently shown the Smith criterion to be more sensitive and similarly as specific as the original Sgarbossa criteria (Tables 4 and 5).

Selvester and Philips Criteria

The Selvester rule requires STE greater than the STEMI threshold (2 mm in V2 and V3; 1 mm for all other leads) plus 10% of |R − S| amplitude for a patient with LBBB to

Table 4 Smith criteria performance with angiographic adjudication

Author	Number of patients (AMI)	Endpoint	Smith criteria Sensitivity (%)	Smith criteria Specificity (%)
Smith (derivation) [11]	33	Angiographic evidence of either occlusion (TIMI 0 or 1) or stenosis with either thrombosis or ulcerated culprit lesion and peak 24 h cardiac troponin I ≥ 10 ng/mL	91 (76–98)[a]	90 (83–95)[a]
Smith criteria Meyers et al. (validation) [10]	45	1. Acute culprit lesion with TIMI 0 to 1 flow or description of an acute thrombotic occlusion or 2. Presumed acute occlusion with significant cardiac outcome, defined as any of the following: (a) Catheterization showing an acute but nonocclusive culprit lesion with very elevated cardiac biomarker (troponin I ≥ 10.0 ng/mL, troponin T ≥ 1.0 ng/mL, or CK-MB ≥ 80 ng/mL); (b) If no angiography done, then very elevated cardiac biomarker and a new or assumed new regional wall motion abnormality on echocardiography; (c) ECG positive for any criteria with death before attempted emergent cardiac catheterization could be done	80 (68–92)[a]	99 (98–100)[a]
Di Marco [12]	54	Acute coronary occlusion with TIMI 0 or an acute lesion with TIMI flow ≥ 1 associated with a significant rise in cardiac biomarkers (ratio of the peak value of the biomarkers to the upper normal limit [troponin I or T ≥ 10 or CK-MB ≥ 5])*	67 (53–78)[a]	90 (82–95)[a]

[a]Smith criterion ST/QRS ratio ≤ − 0.25 in combination with Sgarbossa rules 1 + 2

*This definition does not limit the study population to OMI but would rather include almost all AMI

Table 5 Smith criteria performance with biomarker adjudication

Author	Number of patients (AMI)	Endpoint	Smith criteria Sensitivity (%)	Smith criteria Specificity (%)
Gregg [15]	143	Discharge diagnosis of AMI	20.3[a]	94.9[a]
Nestelberger [7]	75	Evidence of myocardial necrosis in association with a setting consistent with myocardial ischemia. Myocardial necrosis meant at least one hs-cTnT value above the 99th percentile along with a significant rise and/or fall (rise or fall of hc-cTnT by at least 10 ng/L within 6 h, or 6 ng/L within 3 h.*	12 (6–22)[b]	97 (93–99)[b]

[a]Smith criterion ST/QRS ratio ≤ -0.25 alone

[b]Smith criterion ST/QRS ratio ≤ -0.25 in combination with Sgarbossa rules 1 + 2

*This definition does not limit the study population to OMI but would rather include almost all AMI

qualify for a diagnosis of OMI [15]. One study assessed the Selvester Rule in combination with the first two components of the Sgarbossa criteria [16]. The addition of the Selvester rule significantly improved sensitivity (to 39.1%) and maintained specificity (89.1%) for AMI detection compared to the original Sgarbossa criteria. However, weaknesses of the study include pooling patients from multiple sources across different time periods and not specifying whether AMI diagnosis was confirmed enzymatically or with concomitant angiography. Dodd et al. compared the Smith ST/S ratio rule to the Selvester rule for diagnosing angiographic OMI [17]. Sensitivities of both rules alone and in combination with the Sgarbossa's first two criteria were significantly better than both the weighted and unweighted Sgarbossa criteria (Selvester sensitivity 88%, specificity 92% alone; sensitivity 91%, specificity 91% in combination with Sgarbossa; Smith sensitivity 91%, specificity 90% in combination). There was no significant difference in sensitivity or specificity between the Smith and Selvester rules.

The Philips QRS criterion relies on QRS area. STE must be $\geq 105\%$ QRS area + 100 μV to be positive for OMI [15]. Gregg et al. used the Philips criterion, Selvester score, and Smith S-wave criterion to replace the discordant Sgarbossa criterion [15]. The reference definition for AMI in this study was discharge diagnosis, but the diagnosis of AMI included both OMI and Non-Occlusion MI. The highest specificity and lowest sensitivity were seen with the original Sgarbossa criteria and a score ≥ 3 (Table 3) [15]. Meanwhile, the Selvester rule substitution showed the highest sensitivity (30.1%) but lower specificity (93.2%) [15].

Barcelona Criteria

More recently, a newer ECG criterion for STEMI equivalent (i.e., OMI) diagnosis in LBBB was described as the BARCELONA algorithm in a large retrospective observational cohort ($n = 484$). This algorithm defined a LBBB patient to have STEMI equivalent if any of the following criteria are present [18]:

1. ST deviation ≥ 1 mm concordant with QRS polarity in any ECG lead
2. ST deviation ≥ 1 mm discordant with QRS polarity, in any lead with maximal QRS (R or S wave) voltage ≤ 6 mm.

The BARCELONA algorithm showed a significantly higher sensitivity than the Sgarbossa and Smith criteria, as well as a high negative predictive value and good specificity, achieving a diagnostic accuracy comparable to that obtained by ECG diagnosis of STEMI in patients without LBBB (Table 6) [18].

Although the BARCELONA algorithm was validated against one of the largest cohorts of LBBB patients, several major methodological flaws are notable. First, the study's case population was comprised of selected patients referred for primary PCI—which does not appropriately represent the general population of ED patients with LBBB and suspected ACS. Second, the control population consisted of patients with no clinical concern for ACS, likely overestimating the specificity of all strategies studied [19]. Third, and most important, the primary reference standard in the Barcelona study was MI defined as any culprit lesion of any thrombolysis in myocardial infarction (TIMI) flow score with a rise in cardiac troponin above the upper reference limit. This definition thereby encompasses any type-1 AMI (STEMI and NSTEMI equivalent [20].

Furthermore, the Barcelona criteria consider any concordant STD of ≥ 1 mm in *any* lead to be pathologic (compared to the original Sgarbossa criteria, which only considered concordant STD in leads V1–V3). However, Dodd assessed their cohort of LBBB with OMI by analyzing concordant STD of ≥ 1 mm in any lead and found that single criterion to be 61% sensitive and 95% specific [14]. A rule which includes this criterion or a high ST/R or ST/S ratio improved sensitivity to 91% but lowered specificity to 76% [14]. This calls into question the Barcelona criteria's extension of concordant STD to any lead.

Table 6 All ECG performances

Criteria	Description	Sensitivity	Specificity
Sgarbossa	1. ST elevation ≥ 1 mm (100 μV) and concordant with QRS (score 5) 2. ST depression ≥ 1 mm (100 μV) in leads V1–3 (score 3) 3. ST elevation ≥ 5 mm (500 μV) and discordant with QRS (score 2)	20% [44][a] (95% CI 18–23%)	98% [44][a] (95% CI 97–99%)
Selvester 10% RS	ST elevation which is 10% or more of |S|-|R| plus STEMI limits (ST elevation required for the given lead)	30.1% [15][b]	93.2% [15][b]
Smith 25% S Wave Single criterion	ST elevation 25% or more of the S-wave amplitude	79% in Derivation [11] 51% in Validation [10]	93% in derivation [11] (9/129) 98.5% in validation [10] (3/249)
Smith 25% of S-Wave in combination with 2 other criteria	25% criterion OR concordant STE 1 mm in 1 lead OR concordant STD 1 mm in 1 lead of V1–V3	91% in Derivation [11] 80% in Validation [10]	90% in Derivation [11] 99% in Validation [10]
Excessive Discordance Proportional Rule	Excessively discordant ST-segment deviation (elevation or depression) defined by most negative ST/S ratio (ST/S < −0.30) in any lead with > 1 mm ST-segment elevation or depression	100% [11] Sensitivity was only 64% in the validation study; specificity was 98%.	88% [11]
Philips QRS Area	ST elevation ≥ 105% QRS area + 100 μV	23.8% [15]	95.8% [15]
BARCELONA*	1. ST deviation ≥ 1 mm (0.1 mV) concordant with QRS polarity in any ECG lead, thus including either: a. ST depression ≥ 1 mm (0.1 mV) concordant with QRS polarity in any ECG lead b. ST elevation ≥ 1 mm (0.1 mV) concordant with QRS polarity in any ECG lead (Sgarbossa score 5) 2. ST deviation ≥ 1 mm (0.1 mV) discordant with QRS polarity, in any lead with max (R | S) voltage ≤ 6 mm (0.6 mV)	93% [18] (95% CI 80–97%)	94% [18] (95% CI 86–98%)

[a]For a total score ≥ 3

[b]In combination with Sgarbossa criteria

*Outcome definitions were extremely flawed such that nearly all AMI (whether OMI or Non-OMI) would have been included

The reliability of "excessive discordance," whether STE or STD, is also controversial. Smith et al. first studied excessive discordant STD in LBBB, finding the optimal cutoff to be 30% of the preceding R wave [11]. However, the validation study did not replicate the observed sensitivity (though specificity remained very high) [10]. Therefore, if present, STD > 30% of the preceding R-wave has a very high positive likelihood ratio, but the negative likelihood ratio is inadequate.

Additionally, the Barcelona algorithm's second criterion considers discordant STD > 1 mm to be significant only in leads with max R or S voltage ≤ 6 mm. This is distinct from the Smith criterion, which defines discordant ST deviation to be at least 20–25% of preceding R or S wave amplitude, regardless of QRS voltage. The Barcelona criteria's use of a max R or S voltage of 6 mm translates to a lower minimum percentage of 17% (1 mm minimum ST deviation/6 mm maximum R/S amplitude). Moreover, under the Barcelona rule, excessive proportionally discordant ST deviation in leads with R or S amplitude > 6 mm would not be considered pathologic, regardless of percentage deviation. These features must necessarily reduce the Barcelona criteria's sensitivity for OMI [19]. See Figs. 2, 3 and 4 which for this very reason are positive by the Smith criteria and negative by Barcelona, with further explanation below.

These issues with the Barcelona criteria may manifest as incorrect diagnoses for patients under certain circumstances. For example, Fig. 2 displays the ECG of a patient diagnosed with non-ischemic cardiomyopathy yet fulfills the discordant ST deviation component of the Barcelona

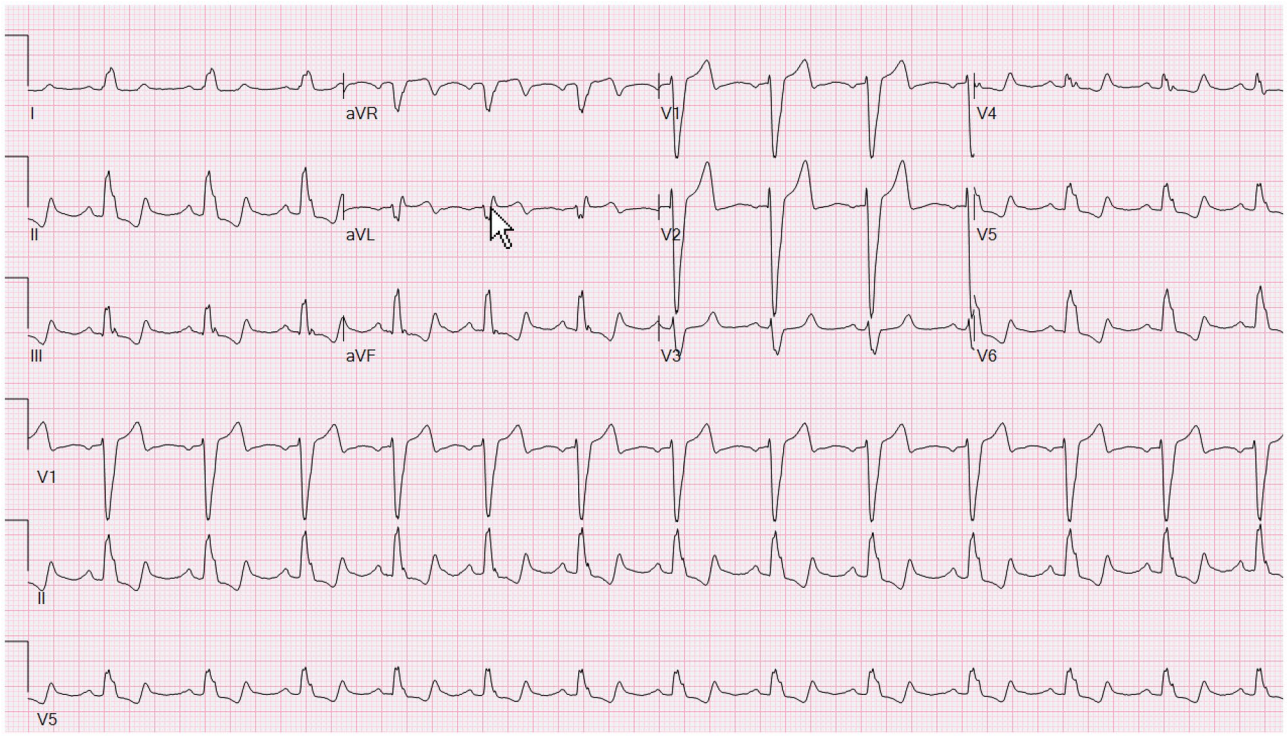

Fig. 2 An ECG of a patient with nonischemic dilated cardiomyopathy showing LBBB. There is discordant ST depression > 1 mm in leads V4-V5. The QRS amplitude in these leads is less than 6 mm. Therefore, the BARCELONA criteria for OMI are met and are thus falsely positive, whereas the Sgarbossa and Smith criteria are not met and are true negatives

criteria. If the Smith criteria are applied here, however, there is no fulfillment of any criteria. Figure 3 depicts the ECG of a patient with 100% acute thrombotic LAD occlusion but no concordant ST deviation. It is positive by the Smith criteria due to excessively discordant STE (ST/S > 25%) in V2, V3, and V4. However, the ECG contains no leads with maximum R or S wave ≤ 6 mm (other than aVR), and therefore is a false negative by the Barcelona algorithm [19]. Figure 4 shows the ECG of another patient with LBBB and an acute LAD occlusion. There is no concordant ST deviation but there is discordant STE in V1–V5 which meets the Smith criterion in all 5 consecutive leads [19].

Overall, the Barcelona criteria may have utility for OMI diagnosis in LBBB but there is a significant need for further validation studies addressing some of the mentioned concerns and methodologic weaknesses before

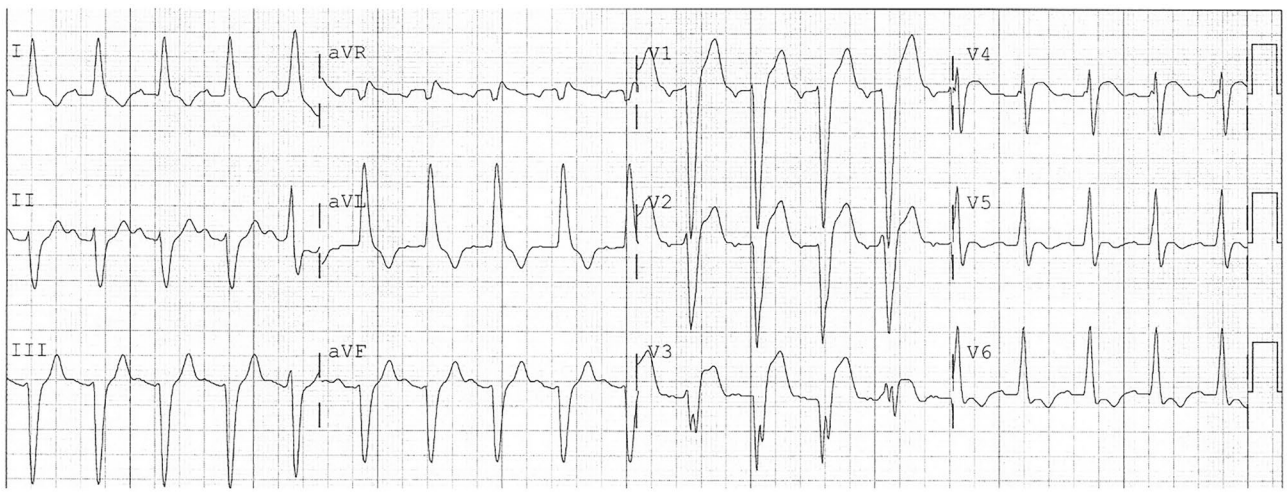

Fig. 3 An ECG of a patient with 100% acute thrombotic LAD occlusion. The ECG meets Smith criteria due to excessively discordant STE (ST/S > 25%) in V2, V3, and V4. However, there are no leads with maximum R or S wave 6 mm or less (other than aVR), and therefore is a false negative by the Barcelona algorithm. (Images are used with permission from Dr. Smith's ECG Blog.)

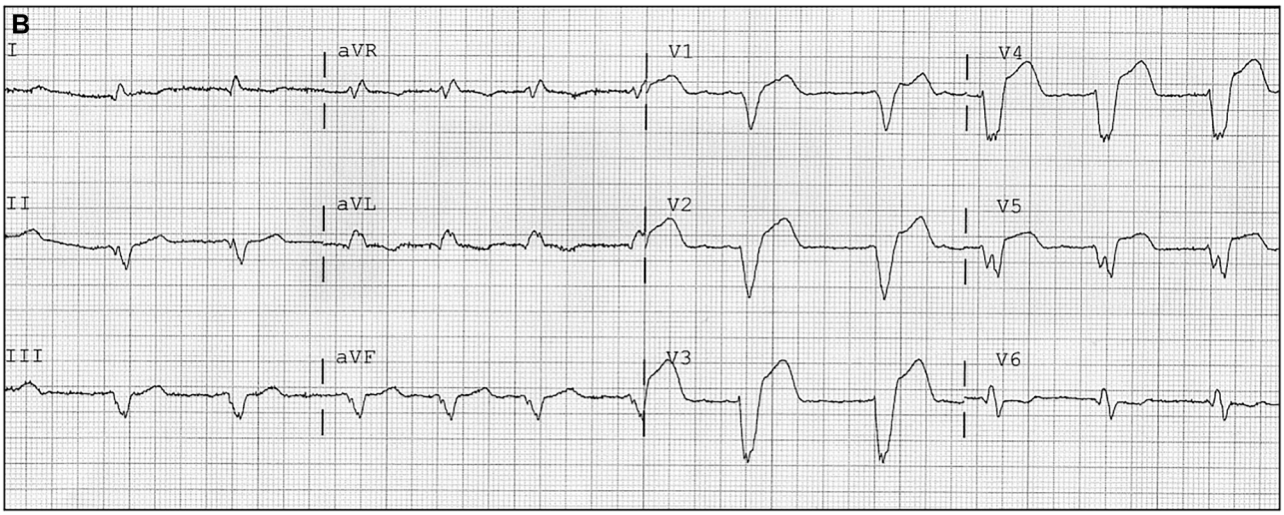

Fig. 4 ECG of a patient with LBBB and an acute LAD occlusion with a TIMI flow score of 0. There is no concordant STE or STD but there is discordant STE in V1-V5 which meets the Smith criterion in all 5 consecutive leads. Meanwhile, the ECG fulfills the discordant Barcelona criterion only in V5, because V1-V4 have predominant S waves which are greater than 6 mm in amplitude. (Images are used with permission from Dr. Smith's ECG Blog; and also reprinted from Smith et al. Ann Emerg Med. 2012 December 01;60(6): 766–776. https://doi.org/10.1016/j.annemergmed.2012.07.119, with permission from Elsevier) [11]

any consideration for widespread application and official acceptance.

Future Considerations

Although some of the aforementioned criteria demonstrate good diagnostic utility for OMI diagnosis in LBBB patients (Table 6), none have achieved widespread acceptance. Due to the lack of a consensus opinion on which criterion is superior and recommended, some studies have continued to study ECG variables to improve diagnostic accuracy. Since QT prolongation is one important feature of OMI, and the T-wave peak to T-wave end (TpTe) interval appears to be the most accurate means of measuring prolonged repolarization in LBBB, Dodd and Smith retrospectively compared QT, JT, and TpTe intervals in patients with LBBB and angiographically proven OMI to those in patients without OMI [21]. They found that in patients with LBBB and OMI, TpTe is longer as compared to patients without OMI [21]. This observation requires further derivation studies to identify a specific cutoff value before any implementation.

Additionally, the multitude of criteria discussed lacks studies on applicability to subset populations with pathophysiology akin to AMI presentation. For example, many patients with cardiomyopathy (ischemic or nonischemic) have LBBB and frequently present with symptoms compatible with AMI (pulmonary edema, hypotension, etc.). Many have positive cardiac markers due to type-2 AMI or acute or chronic (nonischemic) myocardial injury. Many of these patients have low voltage QRS amplitudes and thus, over diagnosis of OMI could occur with the BARCELONA criteria.

American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines

The most recent 2013 ACC/AHA STEMI guidelines now no longer regard new LBBB as an automatic STEMI equivalent [22]. ECGs of patients presenting with LBBB and presumed AMI are a frequent cause of delay or lack of reperfusion therapy because of the concern of the validity of the ECG criteria for AMI diagnosis and the risk of therapy. The guidelines acknowledge that most cases of LBBB at time of presentation are "not known to be old" because prior ECGs are not available for comparison [22]. Since new or presumably new LBBB at presentation occurs infrequently and may interfere with STE analysis, it is not considered diagnostic of OMI (STEMI equivalent) in isolation. The guidelines do recognize the criteria for ECG diagnosis of AMI in the setting of LBBB that have been proposed but overall advocate for the use of transthoracic echocardiography, cardiac troponin levels, and patient clinical assessment to aid diagnosis [22]. However, if doubt persists, invasive angiography may be necessary to guide therapy in the appropriate clinical context. As for patients with suspected AMI and LBBB (new or old) with hemodynamic instability or acute heart failure, the recommendation remains to pursue reperfusion therapy with either PCI or fibrinolytics immediately, regardless of symptom onset timing [22].

The ESC guidelines acknowledge the various criteria developed to assist with diagnosis and that the presence of concordant STE appears to be one of the best indicators of ongoing OMI [23]. However, they recognize the lack of diagnostic certainty with these complex algorithms. The ESC guidelines consequently recommend that patients with a clinical suspicion of ongoing refractory myocardial ischemia, "regardless of ECG or biomarker findings," should be managed in a way similar to STEMI patients, regardless of the presence or absence of LBBB, or whether the LBBB is previously known [23]. They also remark that the presence of a (presumed) new LBBB alone is not, by itself, predictive of OMI or even of AMI [23].

Cai et al. also proposed a diagnosis and triage algorithm featuring both the original and Smith modified criteria to better identify OMI among patients presenting with chest pain and new or presumably new LBBB [24]. The algorithm begins with clinical presentation. If patients with suspected AMI and LBBB present with hemodynamic instability or acute heart failure, primary PCI should be considered [24]. If a patient's clinical status is stable, the Sgarbossa criteria are then assessed [24]. In those not fulfilling these two criteria, the Smith criterion of an ST/S ratio − 0.25 or less is then utilized. If any of these criteria is fulfilled, the algorithm recommends primary PCI or fibrinolysis. However, if none of these criteria are met, such patients are to be evaluated with serial ECGs, serial specific biomarker assays and echocardiography [24]. Abnormal findings here are reason to pursue PCI or fibrinolysis, but if results are normal, the recommendation is non-invasive evaluation [24]. Lai et al. assessed this algorithm's performance in a small retrospective study and noted a sensitivity of 93.8% for identifying culprit lesions in patients with LBBB presenting with signs and symptoms of ACS [25••].

Pacing Modalities and Related Electrocardiographic Changes

Right Ventricular Pacing

Diagnosis of AMI in patients who have RVP presents a similar challenge to that of LBBB [26]. Bertel et al. found that patients with RVP tend to be older with more comorbidities and higher rates of heart failure upon presentation with AMI [27]. These patients also had markedly delayed door-to-balloon times for PCI in comparison to patients without RVP. Crude mortality was also higher for RVP patients [27]. The most recent ACC/AHA STEMI guidelines from 2013 offer no formal recommendations for diagnosing AMI in RVP patients [22]. In 2018, the ESC guidelines and the Fourth UDMI suggested utilizing the

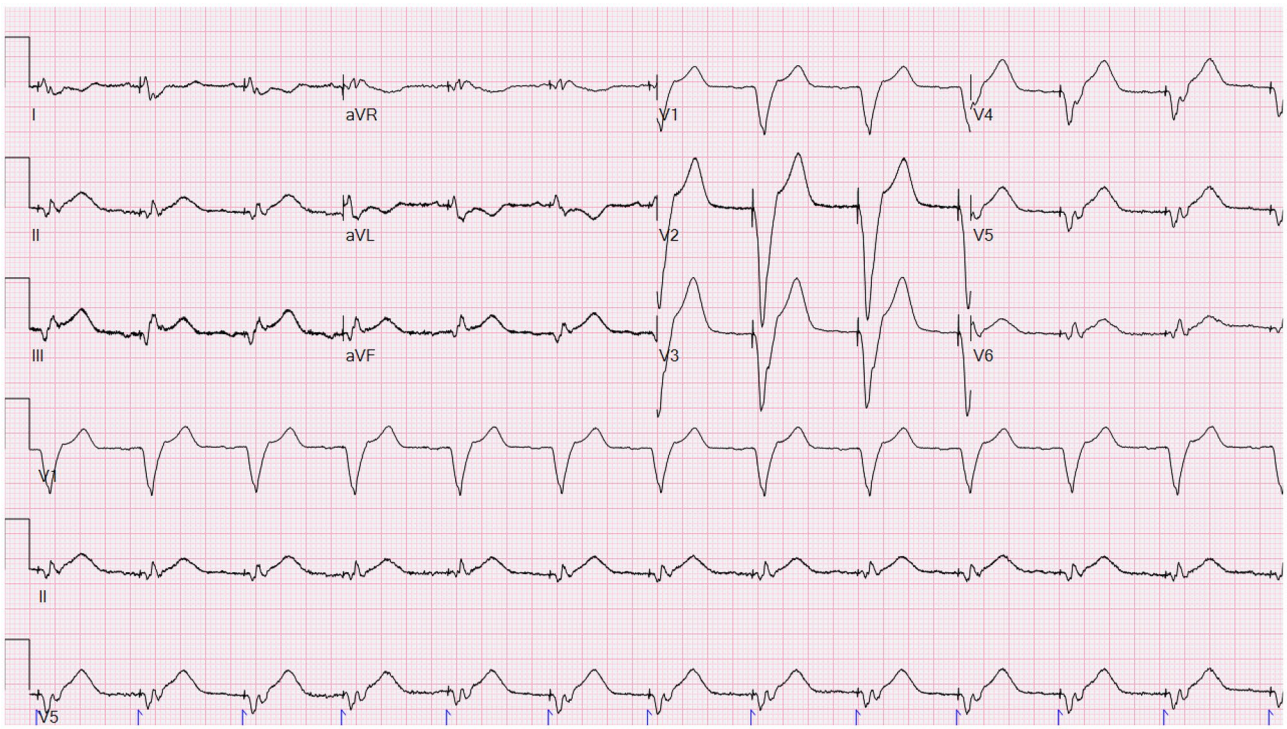

Fig. 5 OMI in a patient with RVP showing concordant ST elevation (> 1 mm) in the inferior leads (II, III, and AVF)

original Sgarbossa criteria for diagnosis of AMI in both LBBB and ventricular paced rhythms (Fig. 5) [1, 23]. Those guidelines cite ECG similarities between the two conditions but failed to highlight the low sensitivity of the original Sgarbossa criteria.

Sgarbossa et al. conducted a retrospective study comparing 17 ventricular-paced ECG controls with 17 ventricular-paced ECGs with AMI, confirmed by CK-MB [28]. The criteria identified were identical to the LBBB AMI criteria, except the point scoring system was not used when the criteria were applied. Maloy et al. retrospectively analyzed 57 patients with RVP ECGs and an AMI diagnosed by elevated cardiac markers and compared them with a control group of 99 patients with RVP ECGs and negative cardiac markers [29]. The authors concluded that the most specific Sgarbossa criterion in identifying AMI was STE > 5 mm discordant with the QRS complex. For STE ≥ 5 mm discordant with the QRS complex, the sensitivity for detecting AMI was 10% (95% CI = 5%–21%), specificity 99% (95% CI = 93%–99%), with a likelihood ratio of 5.2 (95% CI = 1.3–21%)[29].

Although the Sgarbossa criteria shows good specificity for detection of AMI in RVP patients, a more recent analysis compared the Selvester and Smith criteria against the Sgarbossa criteria for diagnosing OMI in RVP patients. The study defined OMI with angiographic and biochemical criteria: evidence of acute occlusion (TIMI flow 0 or 1) or coronary stenosis with peak 24 h cardiac troponin-I levels ≥ 10 ng/mL. The third component of the Sgarbossa criteria was substituted with the Selvester or Smith rules. This study found the Selvester criteria to have the best sensitivity of the three while the most specific was Sgarbossa's [30], and the most accurate was the Smith criteria (Table 7).

The Barcelona criteria have not yet been studied in this patient population. However, the previously mentioned concerns about the Barcelona criteria and the possibility of overdiagnosis of OMI may still be applicable to patients with RVP (Fig. 6).

The largest and most recent study of OMI in patients with a ventricular paced rhythm is the Paced Electrocardiogram Requiring Fast Emergent Coronary Therapy (PERFECT) study [31]. This retrospective case–control included adult patients with ventricular paced rhythms and symptoms of ACS who presented emergently to 16 international cardiac referral centers between January 2008 and January 2018. It included patients with ventricular paced rhythm presenting with symptoms of ACS. The OMI group (59 patients) was defined angiographically as TIMI grade 0 to 1 flow, or angiographic evidence of coronary thrombosis and peak cardiac troponin-I ≥ 10.0 ng/mL or troponin-T ≥ 1.0 ng/mL. There

Table 7 ECG criteria performance in right ventricular pacing

Author	Number of patients (OMI)	Outcome	Sgarbossa Sensitivity (%)	Sgarbossa Specificity (%)	Smith Sensitivity	Smith Specificity	Selvester Sensitivity	Selvester Specificity
Freitas [30]	26	Evidence of acute occlusion (thrombolysis in myocardial infarction grade (TIMI) flow 0 or 1) or coronary stenosis with peak 24 h cardiac troponin level ≥ 10 ng/mL	15.4 (4.4–34.9)	100 (80.5–100)	34.6 (17.2–55.7)	76.5 (50.1–93.2)	38.5 (20.2–59.4)	70.6 (44.0–89.7)
Dodd [31]	59	TIMI grade 0 to 1 flow, or angiographic evidence of coronary thrombosis and peak cardiac troponin-I ≥ 10.0 ng/mL or troponin-T ≥ 1.0 ng/mL	56%[a] (95% CI 42–69)	97% (95% CI 92–99)	81%[a] (95% CI 69–90)	96% (95% CI 90–99)	-	-

[a]Extension of 2nd criterion (concordant ST depression > 1 mm) from V1–V3 to V1–V6 yielded a sensitivity of 86%

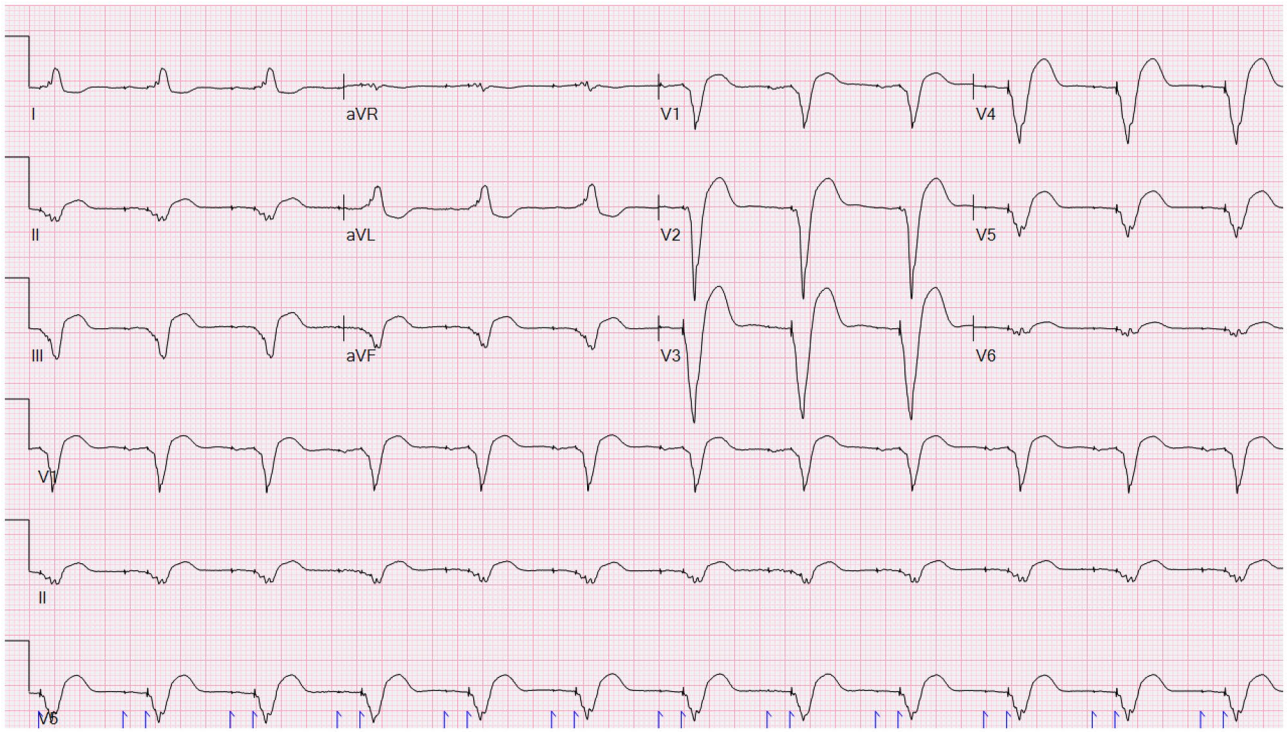

Fig. 6 ECG of a patient with AV sequential pacing fulfilling the Barcelona criteria (discordant ST deviation) from a patient with non-ischemic dilated cardiomyopathy without acute coronary syndrome

were two control groups: the "Non-OMI-Angio" group consisted of patients that underwent coronary angiography but did not meet the definition of OMI; the "No OMI" control group consisted of randomly selected emergency department patients without OMI who did not have an angiogram. Results showed that the Smith's criteria were more sensitive than the original Sgarbossa's (Table 7) and were 86% sensitive if concordant STD was extended out to lead V6 (all precordial leads, since [unlike LBBB] RVP results in a negative QRS in all precordial leads). The 2 rules had similar specificity (Table 7).

This variability in accuracy between the 2 criteria can be seen in Fig. 7a. This ECG from a patient with atrial and ventricular paced rhythm is negative for OMI by the original Sgarbossa criteria, but it fulfills the Smith criteria with discordant STE with an ST/S ratio > 25% in leads II and V5–V6. There is also excessively discordant STD in V2, although this criterion was not validated in the PERFECT study. Angiography ultimately revealed a 100% occlusion of a dominant circumflex artery. Moreover, the ECG following PCI showed normal ST/S ratios (< 25%) and resolution of the excessively discordant STD in V2 (Fig. 7b).

Biventricular Pacing

Cardiac resynchronization therapy, also known as biventricular pacing (BiV), uses an implanted cardiac pacing device that provides simultaneous electrical activation of the left ventricle and right ventricle. In patients with BiV pacing, AMI can be particularly challenging to diagnose due to the variations in impulse timing and lead placement. Most patients who are BiV paced will show a RBBB pattern in V1 on the ECG, and the QRS duration is shorter than during LV or RV pacing alone [32]. While BiV pacing narrows the QRS compared to no pacing, patients with an indication for BiV pacing have an abnormal ECG with wide QRS at baseline. It is unclear what criteria thresholds should be used for these patients. Since they do not have LBBB morphology, there is no justification to use Sgarbossa, Selvester or Smith criteria. To date, there is no consensus on the ECG criteria for AMI in this population. Research for this subject is mainly limited to a few case reports. For instance, in 2011 Ukena et al. reported a 53-year-old patient with a BiV device that had 100% occlusion of the LAD and ECG demonstrated 0.1–0.3 mV STE in the lateral leads [33]. Karumbaiah et al. described a 70-year-old woman with a BiV pacing and occluded proximal left LAD. Her ECG showed 2–3 mm STE in leads V1–V2, concordant with the QRS complex, and STE in V3–V5, discordant with QRS complex [34]. Given

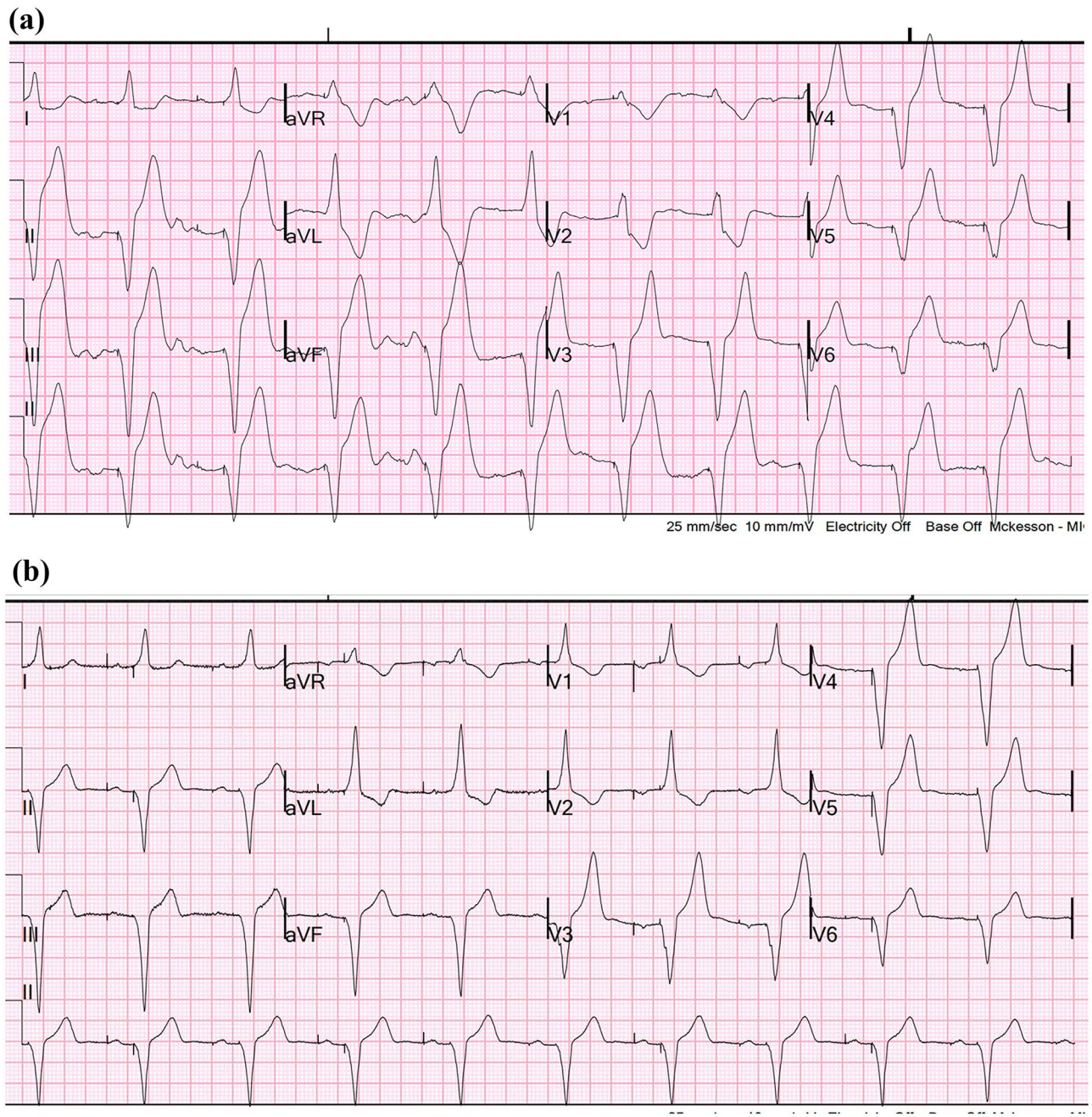

Fig. 7 **a)** ECG of a patient with atrial and ventricular paced rhythm and 100% dominant circumflex occlusion. This ECG is negative for OMI by the original Sgarbossa criteria, but it fulfills the Smith criteria with discordant STE with an ST/S ratio > 25% in leads II and V5–V6. There is also excessively discordant STD in V2. **b)** Post-PCI ECG in the same patient as above. Compared to Fig. 7a, this ECG shows normalized ST/S ratios (< 25%) and resolution of the excessively discordant STD in V2. (Images are used with permission from Dr. Smith's ECG Blog.)

that there are only two cases where the use of Sgarbossa criteria have been mentioned, there is poor utility in assessing its sensitivity.

Based on the above case studies and the review conducted by Barold et al. regarding typical and atypical ECG features in BiV pacing, STE > 1 mm in leads V1–V2 may be enough to diagnose anterior AMI in those who are BiV paced from the basal LV and RV apex [32, 34, 35]. This is because BiV pacing from the area produces a positive QRS complex in V1 resembling a RBBB. Thus, BiV pacing

may have ischemic changes that mimic those seen with normal sinus rhythm and RBBB. Walsh et al. described a patient with a BiV device found to have acute posterior AMI with an ECG demonstrating concordant STD > 1 mm in the right precordial leads (V2 and V3) [36]. The patient was also noted to have new discordant STE in leads II, III and aVF with a new reciprocal STD < 1 mm in aVL, consistent with inferior OMI.

The aforementioned PERFECT study [31] notably included a significant number of BiV patients (82/251). There were a higher proportion of patients with BiV in the "No OMI" control group than the OMI group. Interestingly enough, sensitivity analyses evaluating performance of the Smith criteria on subgroups of patients with RVP (OMI $n = 48$, No OMI $n = 56$) yielded similar results (sensitivity 83% [95% CI 70–93] and specificity 98% [95% CI 90–100]) as the full patient cohort [31]. These maintained sensitivity and specificity results across subgroups of paced patients (single vs. BiV) may suggest some diagnostic utility of the Smith criteria for OMI diagnosis in BiV patients, but further studies are warranted. Most of the patients with BiV pacing have cardiomyopathy and often present with symptoms compatible with ACS, with or without increased serum troponin. How to reliably distinguish OMI from Non-Occlusion MI or nonspecific acute myocardial injury is unclear. This, coupled with the increased number of BiV pacing in the general population, reveals a need for further research in the area.

His-Bundle Pacing

His-bundle pacing (HBP) has been used for cardiac resynchronization therapy with high implant success rates and significant QRS narrowing [37]. HBP is further subdivided into two main categories: selective and nonselective. Selective HBP activates only the His-bundle whereas nonselective HBP also activates adjacent ventricular myocardium. In selective HBP, the QRS morphology should be identical to the native QRS morphology [38]. Meanwhile, nonselective pacing entails concomitant activation of adjacent ventricular tissue in addition to stimulation of the His-bundle, resulting in a QRS interval that would be slightly longer than that of the intrinsic QRS. However, the morphology and axis of the QRS should be similar without significant ST deviations that would obfuscate the diagnosis of OMI. Therefore, HBP theoretically should not interfere with the diagnosis of OMI. One theoretical scenario which could produce confusion is HBP in patients with underlying LBBB. In patients with LBBB, HBP is usually associated with three different thresholds. These include one for the activation of the His-bundle, one for activation of nonselective adjacent ventricular tissue, and one for correction of the LBBB [38].

Correction of the LBBB would yield a narrow QRS without associated ST deviation that would interfere with OMI diagnosis. Failure to correct a LBBB would carry the same previously discussed diagnostic challenges associated with a baseline LBBB. Moreover, long-term data regarding the durability of HBP and stability of capture thresholds remains limited. In an observational study LBBB correction thresholds were stable over a period of 3 years follow-up [39]. However, it is plausible that LBBB correction thresholds may rise over time. A patient with previously corrected LBBB and HBP-associated narrow QRS could have their ECG revert back to their previous LBBB pattern. This could cause confusion as a cursory glance of ECGs may be interpreted as a "new left bundle branch block," which could prompt an otherwise unwarranted, extensive cardiac evaluation.

Left Ventricular Pacing

Left bundle branch pacing (LBBP) has emerged as another physiologic alternative to RVP [40]. It involves direct stimulation of the left bundle distal to the conduction block through pacing lead placement via a trans-ventricular septal approach [41]. Compared to HBP, LBBP offers the advantages of being easier to implant and having lower, more stable capture thresholds [40, 42].

LBBP typically produces an incomplete right bundle branch block pattern, with some heterogeneity in ECG patterns based on the selectivity of pacing impulses [40, 43]. Selective LBBP is characterized by an isoelectric line between the pacing impulse and the start of the QRS. V1 characteristically has an "rsR'" pattern with a wide R' wave while the lateral leads I, V5–V6 have wide, notched S deflections [43].

There is no data regarding the diagnosis of OMI in patients with LBBP. However, given the expected incomplete right bundle branch block appearance, theoretically there should be little diagnostic dilemma. Right bundle branch blocks may be associated with STD and T wave inversions in leads V1–V3 and thus may create diagnostic difficulties in the diagnosis of inferolateral OMI.

Recommendations

The multitude of aforementioned criteria for OMI diagnosis has a variety of strengths and weaknesses, as delineated above. Specifically, there appears to be some utility of these criteria in patients with LBBB and RVP with new supportive data emerging rapidly. However, there is no consensus or guideline recommendation on which criteria is the best. Although data is limited, we recommend utilizing the Cai algorithm, which combines clinical assessment with

elements of the original Sgarbossa criteria and the Smith criterion, for LBBB and RVP patients with suspected OMI. We recommend use of the Cai algorithm for the following reasons. The Smith criteria were developed using sound methodologic criteria for OMI, requiring either TIMI-0/1 flow or TIMI-2/3 flow and a very high peak troponin, a value that that is shown to be consistent with OMI (peak troponin at least 100X the URL). The Smith criteria were derived and then validated for LBBB as well as for paced rhythm. The Cai algorithm starts with use of the ACC/AHA and European guidelines, which recommend immediate angiogram for patients with suspected ACS and hemodynamic instability or heart failure, regardless of ECG findings. In the absence of these physiologic abnormalities, it then uses the most specific element of the original Sgarbossa criteria, which is concordant ST deviation of at least 1 mm in at least 1 lead. In the absence of concordance, it then uses excessively discordant ST elevation at an ST/S ratio of 25%, which Smith et al. have shown to be very specific. The combination of all 3 criteria can be both sensitive and specific. Thus, the algorithm incorporates the ACC/AHA and ESC guidelines with the specific and sensitive Smith ECG criteria.

Compliance with Ethical Standards

Conflict of Interest The authors of this manuscript declare that there is no conflict of interest for this manuscript. These authors include Muzamil Khawaja, Janki Thakker, Riyad Kherallah, Yumei Ye, Stephen W. Smith, and Yochai Birnbaum.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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