Electrocardiographic Diagnosis of Acute Coronary Occlusion Myocardial Infarction in Ventricular Paced Rhythm Using the Modified Sgarbossa Criteria

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Study objective: Ventricular paced rhythm is thought to obscure the electrocardiographic diagnosis of acute coronary occlusion myocardial infarction. Our primary aim was to compare the sensitivity of the modified Sgarbossa criteria (MSC) to that of the original Sgarbossa criteria for the diagnosis of occlusion myocardial infarction in patients with ventricular paced rhythm.

Methods: In this retrospective case-control investigation, we studied adult patients with ventricular paced rhythm and symptoms of acute coronary syndrome who presented in an emergency manner to 16 international cardiac referral centers between January 2008 and January 2018. The occlusion myocardial infarction group was defined angiographically as thrombolysis in myocardial infarction grade 0 to 1 flow or angiographic evidence of coronary thrombosis and peak cardiac troponin I $\geq$10.0 ng/mL or troponin T $\geq$1.0 ng/mL. There were 2 control groups: the "non-occlusion myocardial infarction-angio" group consisted of patients who underwent coronary angiography for presumed type I myocardial infarction but did not meet the definition of occlusion myocardial infarction; the "no occlusion myocardial infarction" control group consisted of randomly selected emergency department patients without occlusion myocardial infarction.

Results: There were 59 occlusion myocardial infarction, 90 non-occlusion myocardial infarction-angio, and 102 no occlusion myocardial infarction subjects (mean age, 72.0 years; 168 [66.9%] men). For the diagnosis of occlusion myocardial infarction, the MSC were more sensitive than the original Sgarbossa criteria (sensitivity 81% [95% confidence interval [CI] 69 to 90] versus 56% [95% CI 42 to 69]). Adding concordant ST-depression in V4 to V6 to the MSC yielded 86% (95% CI 75 to 94) sensitivity. For the no occlusion myocardial infarction control group of ED patients, additional test characteristics of MSC and original Sgarbossa criteria, respectively, were as follows: specificity 96% (95% CI 90 to 99) versus 97% (95% CI 92 to 99); negative likelihood ratio (LR) 0.19 (95% CI 0.11 to 0.33) versus 0.45 (95% CI 0.34 to 0.65); and positive LR 21 (95% CI 7.9 to 55) versus 19 (95% CI 6.1 to 59). For the non-occlusion myocardial infarction-angio control group, additional test characteristics of MSC and original Sgarbossa criteria, respectively, were as follows: specificity 84% (95% CI 76 to 91) versus 90% (95% CI 82 to 95); negative LR 0.22 (95% CI 0.13 to 0.38) versus 0.49 (95% CI 0.35 to 0.66); and positive LR 5.2 (95% CI 3.2 to 8.6) versus 5.6 (95% CI 2.9 to 11).

Conclusion: For the diagnosis of occlusion myocardial infarction in the presence of ventricular paced rhythm, the MSC were more sensitive than the original Sgarbossa criteria; specificity was high for both rules. The MSC may contribute to clinical decisionmaking for patients with ventricular paced rhythm. [Ann Emerg Med. 2021;■:1-13.]

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INTRODUCTION

Background and Importance

Patients with ventricular paced rhythm and symptoms consistent with acute coronary syndrome (ACS) pose a diagnostic challenge due to a long-held misperception that myocardial infarction cannot be diagnosed from the 12-lead electrocardiogram (ECG) in the setting of ventricular paced rhythm.[1,2] This decades-old belief, previously also held for left bundle branch block, was based on the fact that both ventricular paced rhythm and left bundle branch block cause secondary repolarization abnormalities and may

obscure Q-waves on the ECG.[3,4] Q-waves defined the diagnosis of myocardial infarction before modern cardiac imaging was widely available. However, Q-waves diagnose old myocardial infarction, and the notion that myocardial infarction cannot be diagnosed in patients with ventricular paced rhythm or left bundle branch block was inaccurately extended to include the diagnosis of acute myocardial infarction. Immediate ECG diagnosis of an acute coronary lesion resulting in occlusion myocardial infarction is critical in the modern reperfusion era.[5] It would be a significant advancement if such a diagnosis could be rapidly made with the ECG.[5-7] Despite this, standardized criteria for diagnosing occlusion myocardial infarction in the presence of ventricular paced rhythm have not been established. Patients with ventricular paced rhythm and occlusion myocardial infarction are, therefore, less likely to receive emergency reperfusion therapy, and they have higher adjusted mortality rates than patients with native cardiac conduction.[8,9] Furthermore, patients with ventricular paced rhythm who undergo rapid reperfusion therapy have a lower adjusted mortality rate than those who do not.[8,9]

The most recent American College of Cardiology and American Heart Association ST-elevation myocardial infarction (STEMI) guidelines give no direction on diagnosing occlusion myocardial infarction in patients with ventricular paced rhythm.[10] In 2018, the European Society of Cardiology guidelines[11] and the fourth universal definition of myocardial infarction[12] suggested utilizing the original Sgarbossa criteria (Figures 1A to 1C) for diagnosis of occlusion myocardial infarction in both left bundle branch block[13,14] and ventricular paced rhythm.[15-17] Those guidelines cite ECG similarities between the 2 conditions but fail to highlight the low sensitivity of the original Sgarbossa criteria. There are 2 primary reasons for this low sensitivity.[18,19] First, the derivation of the original Sgarbossa criteria utilized a biomarker (creatinine kinase-MB) definition of AMI, resulting in a case group of patients with both occlusion myocardial infarction and nonocclusion myocardial infarction. Second, the 5-mm discordant ST-elevation criterion of the original Sgarbossa criteria is absolute and not based upon the electrocardiographic principle of proportionality. Smith et al[18] derived the modified Sgarbossa criteria (MSC) (Figures 1D to 1F) utilizing angiographic outcomes and defining excessively discordant ST-elevation relative to the amplitude of the preceding S-wave. In both the derivation and validation studies of the MSC, sensitivity was significantly higher than that of the original Sgarbossa criteria (91% versus 52% and 80% versus 49%, respectively; $P<.001$ for all) and high specificity was maintained (90% versus 98% and 99% versus 100%, respectively; P=NS for all).[20]

Goals of This Investigation

The primary objective of the Paced Electrocardiogram Requiring Fast Emergent Coronary Therapy (PERFECT) study was to compare the sensitivity and specificity of the MSC with those of the original Sgarbossa criteria for the diagnosis of occlusion myocardial infarction in patients with ventricular paced rhythm. We hypothesized that the MSC would be more sensitive than the original Sgarbossa criteria while maintaining high specificity.

METHODS

Study Design and Setting

The PERFECT study (ClinicalTrials.gov NCT02765477) was a multicenter, observational case-control investigation. We identified adult subjects who presented to 16 international centers from January 2008 to January 2018 with symptoms concerning for ACS and with ventricular paced rhythm on the ECG. Study site details can be found in Table E1 (available at http://www.annemergmed.com/). The study protocol was approved by the ethics committee or institutional review board at each center. We mitigated risks of data error and bias by adhering to strict methodology and best practices for observational diagnostic accuracy studies.[21-23]

Selection of Participants

Subjects in the occlusion myocardial infarction and control groups were included if they met the following criteria: ≥18 years old, presented in an emergency manner with symptoms of ACS (atraumatic chest pain, dyspnea, or suspected ischemic-equivalent symptoms [eg, pain in the epigastrium, shoulder, jaw, throat, or arm or nausea, vomiting, or diaphoresis]), had an ECG showing ventricular paced rhythm on all 12 leads, and had 1 or more cardiac troponin levels measured during the index visit. Patients were excluded for documented absence of symptoms at the time of preangiography ECG recording and absence of ventricular paced rhythm on all 12 leads on any preangiography ECG. For the primary analysis, physiologic exclusion criteria also included the following: pulse rate >130 beats/min, diastolic blood pressure >120 mm Hg, presence of pulmonary edema necessitating positive pressure ventilation, and initial serum potassium level >5.5 mEq/L (5.5 mmol/L). These physiologic exclusion criteria were included as they often distort the

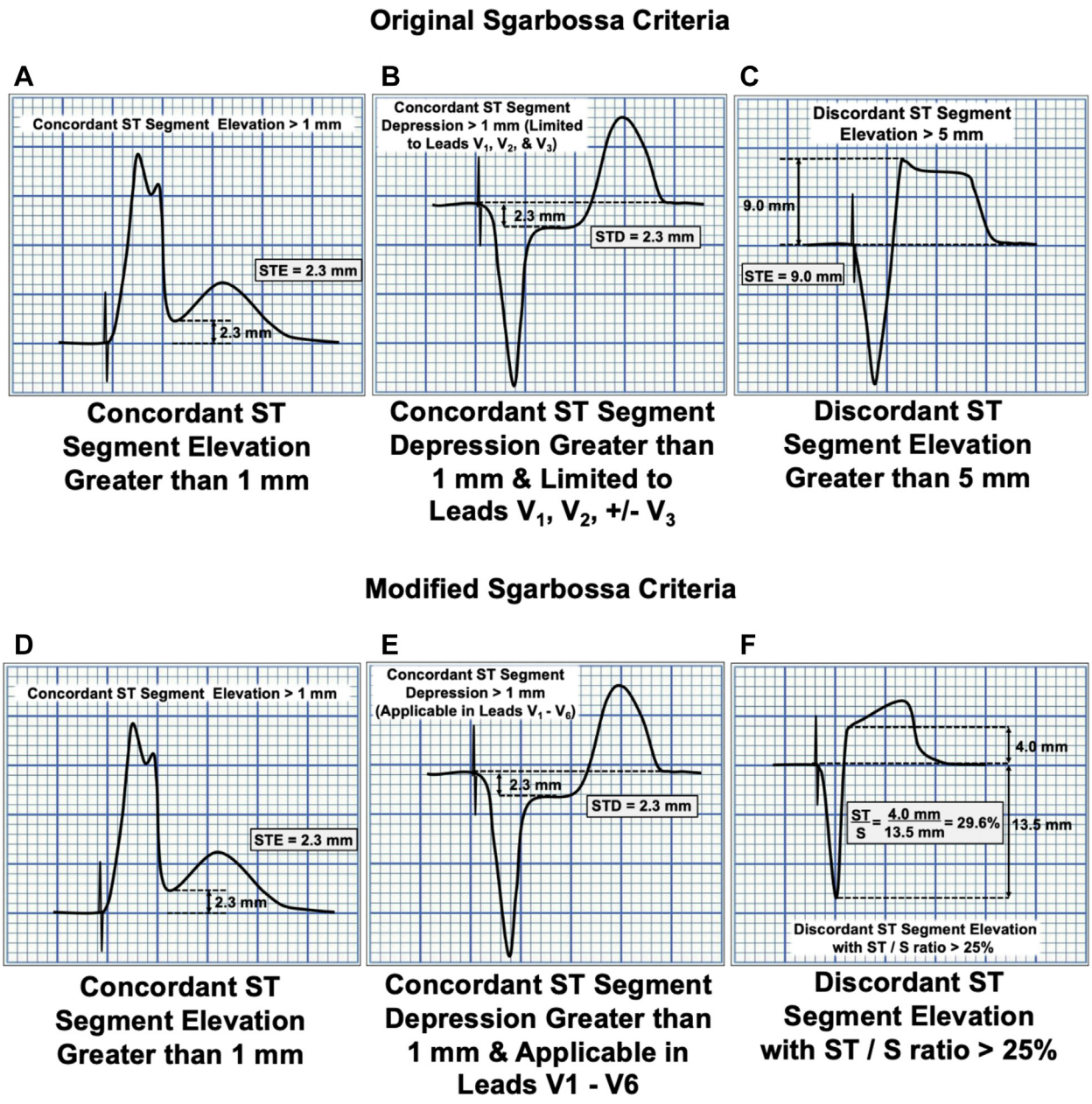

Figure 1. Schematics of the original and modified Sgarbossa criteria. *A-C*, original Sgarbossa criteria. *D-F*, MSC. *A,* Concordant ST-segment elevation (STE) more than 1 mm. *B,* Concordant ST-segment depression (STD) more than 1 mm. *C,* Discordant STE more than 5 mm. *D,* Concordant STE more than 1 mm. *E,* Concordant STD more than 1 mm. *F,* Discordant STE with ST-segment to S-wave ratio more than 25%. *STD*, ST-segment depression; *STE*, ST-segment elevation.

ECG or indicate critical illness necessitating invasive workup regardless of the ECG; the criteria were also utilized in the derivation of the MSC for left bundle branch block.[18]

Search methods varied somewhat by institution due to differences in available administrative databases (see "Detailed Search Methods" section and Table E1 [available at http://www.annemergmed.com/]). Sites sought to identify both a group of consecutive patients referred for coronary angiography due to high suspicion of ACS and a group of consecutive patients who presented to the emergency department (ED) with ventricular paced rhythm and symptoms of ACS. This was accomplished as described below.

All sites identified consecutive patients with ventricular paced rhythm who presented in an emergency manner and underwent coronary angiography during the index visit. Emergency presentation was defined as arrival by 1 of 3 routes: directly through the study site ED, as a transfer or referral patient from the ED of another institution, or as a

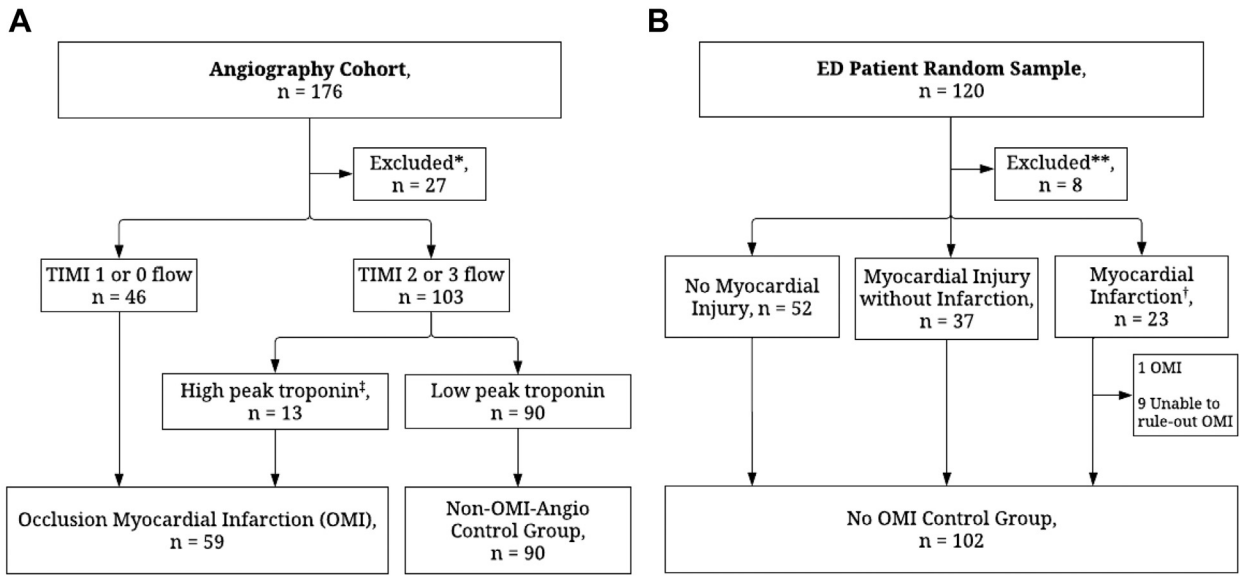

Figure 2. Patient flow diagram for case and control groups. This flow diagram depicts the patients considered for inclusion in the study case and control groups. *A,* The angiogram cohort was divided into occlusion myocardial infarction and non-occlusion myocardial infarction-angio groups. *B,* The ED patient random sample served as the primary control group. *Reasons for exclusion were need for positive pressure ventilation, n=16; diastolic blood pressure >120 mm Hg, n=5; serum potassium >5.5 mEq/L (5.5 mmol/L), n=4; uninterpretable ECG, n=3; heart rate >130 beats/min, n=1. **Reasons for exclusion were positive pressure ventilation, n=5; serum potassium >5.5 mEq/L (5.5 mmol/L), n=2; diastolic blood pressure >120 mm Hg, n=1. †Of the 23 patients with myocardial infarction in the ED patient random sample, the 10 who were excluded had adjudicated type 1 myocardial infarction. The remaining 13 who were included in the no occlusion myocardial infarction control group were all adjudicated as type 2 myocardial infarction. ‡High peak troponin was defined as cardiac troponin I ≥10 ng/mL or troponin T ≥1.0 ng/mL, per site-specific assays.

direct admission to the study site's catheterization laboratory by an ambulance service. Board-certified cardiologists adjudicated angiography reports (and cineangiography images when necessary) to identify culprit lesions and to determine thrombolysis in myocardial infarction (TIMI) flow state.[24] Adjudicators were blinded to subjects' ECGs and information on subjects' clinical courses; such information was also redacted from angiography reports. After adjudication, this angiography cohort was divided into 2 subgroups: occlusion myocardial infarction and non-occlusion myocardial infarction-angio (Figure 2A).

Five of the 16 study sites were also able to identify an additional control group of consecutive patients who presented to the ED with ventricular paced rhythm and symptoms of ACS (Table E1, available at http://www.annemergmed.com/). Subjects were randomly selected from this list, and adjudication for myocardial infarction subtype was performed according to the third universal definition of myocardial infarction (Figure 2B).[25-27]

Patient Group Definitions and Rationale

Occlusion myocardial infarction group. Occlusion myocardial infarction was defined angiographically as an acute "culprit" coronary lesion with either 1) TIMI 0 to 1 flow or 2) TIMI 2 to 3 flow that was intervened on and had an associated high peak cardiac troponin level (troponin I ≥10 ng/mL or troponin T ≥1.0 ng/mL per site-specific assays). This outcome definition has been used in multiple prior studies of ventricular paced rhythm and left bundle branch block.[17,18,20,28-32]

Non-occlusion myocardial infarction-angio control group. The non-occlusion myocardial infarction-angio group consisted of patients who underwent coronary angiography for presumed ACS but did not meet the definition of occlusion myocardial infarction cited above. These patients either had culprit arteries with TIMI 2 to 3 flow without very high peak troponin or no coronary culprits at all.

No occlusion myocardial infarction control group. The no occlusion myocardial infarction group consisted of consecutive patients who presented to the ED for whom occlusion myocardial infarction could be definitively ruled out. Subjects were included in the no occlusion myocardial infarction group if they had: no acute myocardial injury, acute myocardial injury without acute myocardial infarction, or adjudicated type 2 myocardial infarction (ie, clear nonACS etiology of elevated troponin and no new wall motion abnormality on echocardiogram).

Any patient from this consecutive group of ED control patients who ruled in for type 1 myocardial infarction and also had an angiogram was assigned to the occlusion myocardial infarction or non-occlusion myocardial infarction-angio group, depending on the results of the angiogram and troponin testing.

Rationale for Patient Groups

The 3 patient groups analyzed in this study were chosen based on the pathophysiology of ACS and to mimic clinical decisionmaking. It is important to understand that ACS is a dynamic process, with coronary artery thromboses that are continuously lysing and propagating. Because the ECG and the angiogram are recorded at separate times, the ECG may not perfectly represent the angiogram that is done many minutes to hours later. Among patients with normal cardiac QRS conduction (ie, not ventricular paced rhythm or left bundle branch block) and true positive STEMI on the ECG who undergo immediate primary percutaneous coronary intervention, 28% have a culprit lesion with TIMI 2 to 3 flow at the time of the angiogram. This is presumed to be due to spontaneous reperfusion (ie, autolysis) just prior to percutaneous coronary intervention.[33] That is, the artery may be occluded at the time of the ECG but open at angiography. In such patients, a simple angiographic outcome of TIMI 0 to 1 is insufficient for evaluation of the diagnostic characteristics of the ECG recorded previously. In other words, in a hypothetical study of the ECG in occlusion myocardial infarction in *normal conduction*, the diagnosis of true STEMI would be falsely positive in 28% of cases if the outcome variable was simply angiographic TIMI 0 to 1 flow. An examination of previous studies of STEMI and non-STEMI (NSTEMI) in normal QRS conduction shows a rough correlation of true STEMI with a large infarct size as measured by peak cardiac troponin I $\geq$10.0 ng/mL or cardiac troponin T $\geq$1.0 ng/mL.[17,18,20,28-32] For these reasons, prior studies of occlusion myocardial infarction in left bundle branch block and in normal cardiac conduction utilized a composite outcome of either 1) TIMI 0 to 1 flow or 2) a culprit lesion with TIMI 2 to 3 flow *plus* very high troponin.[5-7,17,18,20] The same composite outcome was used in the present study.

Patients in the occlusion myocardial infarction group are presumed to have better outcomes if they undergo emergency reperfusion therapy. In practice, these patients must be primarily identified by the ECG because diagnosis by troponin is delayed. At the present time, this group is not identified early because clinicians have no guidelines for doing so. Moreover, it is often not even recognized that it is *possible* for the ECG to diagnose occlusion myocardial infarction in those with ventricular paced rhythm.

Detailed Search Methods

If available, institutions searched cardiovascular imaging system databases containing ECG and cardiac catheterization results. A text search was performed to identify ECGs containing the characters "vent* AND pac*" in either the automated ECG interpretation or physician overread. Search results were limited to ECGs performed in the ED or cardiac catheterization laboratory. Control patients were randomly selected from this ECG list. Random selection was performed by exporting the data into a Microsoft Excel (Microsoft Corporation, Redmond, WA) spreadsheet and adding a column with a random number generated by the RAND function. The list was then sorted numerically based on the randomly assigned number, and the list was screened in numerical order. Sites were asked to identify 5 control group patients for every occlusion myocardial infarction patient identified. To identify occlusion myocardial infarction and non-occlusion myocardial infarction-angio patients, the ECG list was filtered to identify patients who also underwent left heart catheterization. This second level filtering was to occur after selection of control patients and prior to adjudication. Data was collected for all patients who underwent left heart catheterization to complete the occlusion myocardial infarction and non-occlusion myocardial infarction-angio groups.

If cardiovascular imaging system database access was not available, institutions searched either databases of emergency left heart catheterization procedures to identify patients with ventricular paced rhythm; pacemaker databases to identify patients who presented to the ED or cardiac catheterization laboratory; or by procedural terminology codes to identify patients who underwent cardiac catheterization or coronary intervention (G0290, G0291, 92980, 92981, 92982, 92984, 92995, 92996, 92973, 93508, 93510, 93526, 93539, 93540, 93543, or 93545) and then identified patients with ventricular paced rhythm from that list. A list of search methods utilized at each institution can be found in Table E1 (available at http://www.annemergmed.com/).

Data Collection and Measurements

Data abstractors and adjudicators were provided with standardized data coding guidelines and training. Data abstractors were not strictly blinded to the study hypothesis. Data adjudicators were blinded to clinical group assignment and potentially biasing clinical information, as aforementioned. Study investigators

performed weekly data quality monitoring and were available for on-demand feedback and retraining.

Demographic and clinical data were collected and managed using a standardized, web-based Research Electronic Data Capture (REDCap) tool hosted by Hennepin County Medical Center. Data included patient demographics, medical history, cardiovascular risk factors, pacemaker history, index visit arrival date/time, presenting symptoms, initial vital signs, clinical course, laboratory data (eg, cardiac troponin level), all ECGs performed during the index visit, details of echocardiograms, coronary angiography details and reports, cardiovascular intervention details (eg, percutaneous coronary intervention or coronary artery bypass grafting), and discharge date/time and diagnoses. If available, ECGs and cardiac troponin levels obtained at referring facilities or by ambulance services were also collected.

The process to identify the ECG utilized for analysis was chosen to mimic clinical decisionmaking and mirror prior studies.[18,34,35] For every subject, one study investigator (KWD), blinded to clinical data and patient group allocation, reviewed all ECGs obtained prior to angiography. The first ECG meeting either of the Sgarbossa concordance criteria (ie, $\geq$1 mm concordant ST-elevation in any lead or $\geq$1 mm concordant ST-depression in V1 to V3) was chosen for analysis. If no ECG met concordance criteria, the ECG with the highest ratio of discordant ST-elevation in any lead and all ECGs meeting the original Sgarbossa criteria excessive discordance criterion (ie, $\geq$5 mm discordant ST-elevation) were chosen.

ECG measurements were performed by members of the ECG Core Laboratory in a blinded fashion.[18,36] Measurements were performed on the first electrically paced, interpretable QRS-TU complex in each lead. Measurements included Q-, R-, and S-wave amplitudes and ST-segment amplitude at the J-point. All measurements were performed to the nearest 0.5 mm (0.05 mV) relative to the isoelectric baseline. The isoelectric baseline was defined by the segment immediately preceding the right ventricular pacing impulse (ie, at the onset of the QRS complex). Visual inspection was utilized to determine if the majority of the QRS complex area was positive or negative. ST-segment discordance was defined when the ST-T area was mostly opposite to the QRS area respective to the isoelectric baseline. High interobserver agreement with these measurement methods has been previously established.[20]

Outcomes

The study's primary objective was to compare the sensitivity of the MSC to that of the original Sgarbossa criteria for diagnosis of occlusion myocardial infarction in patients with ventricular paced rhythm and symptoms consistent with ACS; specificity and positive and negative likelihood ratios were also assessed. We also analyzed a modification of the MSC in which the $\geq$1 mm of concordant ST-depression criterion was expanded to include leads V4 to V6. This preplanned modification accounted for the fact that a dominant QS-wave pattern (negative QRS area) is often seen throughout the precordial leads in ventricular paced rhythm, whereas left bundle branch block has a monophasic R-wave pattern (positive QRS area) in V5 and V6.[37]

Unless otherwise noted, analyses in this manuscript utilized the "unweighted" original Sgarbossa criteria. For left bundle branch block, the original Sgarbossa criteria used a point system, and 3 points were required for diagnosis. Discordant ST-elevation of 5 mm or more counted for only 2 points, which was insufficient to make the diagnosis of occlusion myocardial infarction. The point system made it challenging to diagnose a mid left anterior descending artery occlusion because a mid left anterior descending artery occlusion is unlikely to manifest concordant ST-elevation on the ECG. An unweighted original Sgarbossa criteria gives equal weight to each of the 3 original Sgarbossa criteria so that more than 5 mm of ST-elevation alone can be utilized for the diagnosis of occlusion myocardial infarction. In left bundle branch block, the unweighted original Sgarbossa criteria is more sensitive than the weighted point system.[20] The unweighted original Sgarbossa criteria have also been utilized in previous studies of the original Sgarbossa criteria in patients with ventricular paced rhythm.[16,38]

Analysis

Results are descriptive, reported as numbers (percentages), medians and interquartile ranges (IQRs), or sensitivity, specificity, and likelihood ratios with 95% confidence intervals (95% CIs). Statistics were computed using Stata Statistical Software version 16 (StataCorp LP; College Station, TX) and bootLR (https://abfriedman.shinyapps.io/bootLRshiny/).[39]

RESULTS

Characteristics of Study Subjects

Our search methods identified 176 subjects with ventricular paced rhythm and symptoms of ACS who underwent coronary angiography during the index visit (Figure 2A). Twenty-seven patients were excluded based on predefined exclusion criteria, including 7 later adjudicated as having TIMI 0 to 1 flow and 20 with TIMI 2 to 3 flow.

Table 1. Demographic and clinical characteristics of patients.

Patient Characteristics	Occlusion Myocardial Infarction (n=59)	Non-Occlusion Myocardial Infarction-Angio (n=90)	No Occlusion Myocardial Infarction (n=102)
Age, median (IQR), yr	78 (71-82)	73 (68-81)	69 (60-82)
Sex, No. (%)			
Male	44 (75%)	65 (72%)	59 (58%)
Female	15 (25%)	25 (28%)	43 (42%)
Symptoms, no. (%)			
Chest pain	56/59 (95%)	74/86 (86%)	55/96 (57%)
Dyspnea	31/55 (56%)	48/84 (57%)	68/97 (70%)
Both chest pain and dyspnea	30/55 (55%)	40/83 (48%)	32/92 (35%)
No chest pain or dyspnea (other symptoms)	0	5/90 (6%)‡	2/102 (2%)§
Cardiovascular disease risk factors, no. (%)			
Cerebrovascular disease	7/45 (16%)	15/72 (21%)	22/43 (51%)
Chronic kidney disease	20/52 (38%)	29/84 (35%)	31/72 (43%)
Diabetes mellitus	33/54 (61%)	47/89 (53%)	30/67 (45%)
Dyslipidemia	48/58 (83%)	76/89 (85%)	57/72 (79%)
Hypertension	50/58 (86%)	82/88 (93%)	79/92 (86%)
Obesity	19/56 (34%)	30/75 (40%)	38/78 (49%)
Peripheral vascular disease	8/41 (20%)	11/53 (21%)	7/25 (28%)
Tobacco abuse	21/26 (81%)	40/49 (82%)	42/65 (65%)
Family history of early coronary artery disease	6/38 (16%)	9/29 (31%)	6/26 (23%)
Known coronary artery disease, no. (%)	39/55 (71%)	75/85 (88%)	68/81 (84%)
Prior myocardial infarction	25 (45%)	49 (58%)	47 (58%)
Prior percutaneous coronary intervention	22 (40%)	38 (45%)	31 (38%)
Prior coronary artery bypass grafting	20 (36%)	35 (41%)	21 (26%)
Other known coronary artery disease*	10 (18%)	26 (31%)	26 (32%)
Any known coronary artery disease *or* 3+ cardiovascular risk factors, no. (%)	51 (86%)	81 (95%)	81 (80%)
Ventricular lead arrangement, no. (%)			
Right ventricle	48 (81%)	64 (71%)	56 (55%)
Biventricular	11 (19%)	26 (29%)	45 (45%)
Means of arrival to study site, no. (%)			
Directly to ED	41 (70%)	70 (78%)	102 (100%)‖
Transfer from outside facility	18 (30%)	20 (22%)	Not applicable
Time to coronary angiography†, median (IQR), min	346 (72-1078)	1955 (1136-3712)	Not applicable
Peak cardiac troponin, median (IQR), ng/mL			
Troponin I	14.32 (4.98-47.2)	0.13 (0.04-0.87)	0.03 (0.01-0.06)
Troponin T	3.44 (2.14-8.26)	0.21 (0.08-0.81)	0.02 (0.00-0.05)
In-hospital mortality, No. (%)	7 (12%)	3 (3%)	3 (3%)

*Other known coronary artery disease was defined as >50% stenosis on prior coronary angiography.
†Defined as the time from arrival at the study site (not transferring facility, if applicable) to the start of coronary angiography procedure.
‡Five patients in the non-occlusion myocardial infarction-angio group had no chest pain or shortness of breath but presented with acute coronary syndrome-equivalent symptoms (shoulder/arm pain, n=1; ventricular tachycardia, n=2; syncope, n=1; jaw pain, n=1).
§Two patients in the no occlusion myocardial infarction group had no chest pain or shortness of breath but presented with acute coronary syndrome-equivalent symptoms (shoulder/arm pain, n=1; jaw pain, n=1).
‖By definition, all patients in the no occlusion myocardial infarction group presented to the study site ED.

In total, 59 subjects met the definition of occlusion myocardial infarction (46 with TIMI 0 to 1 flow and 13 with TIMI 2 to 3 flow plus high cardiac troponin due to acute coronary thrombosis). The remaining 90 subjects from the angiography cohort comprised the non-occlusion myocardial infarction-angio control group.

Table 2. Test characteristics for diagnosis of occlusion myocardial infarction in patients with ventricular paced rhythm.

	Occlusion Myocardial Infarction (n=59)	Non-Occlusion Myocardial Infarction-Angio Control Group (n=90)			No Occlusion Myocardial Infarction Control Group (n=102)		
Diagnostic Criteria	Sensitivity (95% CI)	Specificity	Negative likelihood ratio	Positive likelihood ratio	Specificity	Negative likelihood ratio	Positive likelihood ratio
MSC	81% (69-90)	84% (76-91)	0.22 (0.13-0.38)	5.2 (3.2-8.6)	96% (90-99)	0.19 (0.11-0.33)	21 (7.9-55)
MSC with concordant ST-depression V1 to V6	86% (75-94)	83% (74-90)	0.16 (0.085-0.31)	5.2 (3.2-8.3)	96% (90-99)	0.14 (0.07-0.27)	22 (8.4-58)
Original Sgarbossa criteria	56% (42-69)	90% (82-95)	0.49 (0.35-0.66)	5.6 (2.9-11)	97% (92-99)	0.45 (0.34-0.61)	19 (6.1-59)

There were 120 subjects randomly selected from a group of ED patients with ventricular paced rhythm and symptoms of ACS, of which 8 met predefined exclusion criteria (Figure 2B). Of the remaining 112 patients, 52 had no myocardial injury, 37 had myocardial injury without myocardial infarction, and 23 had myocardial infarction. Of the 23 patients with myocardial infarction, 13 had type 2 acute myocardial infarction and 10 had type 1 acute myocardial infarction. One patient with type 1 acute myocardial infarction was already included in the occlusion myocardial infarction group. The remaining 9 patients adjudicated as type 1 acute myocardial infarction all had chest pain and discharge diagnoses of acute myocardial infarction, but they had to be excluded because none underwent coronary angiography to diagnose or exclude occlusion myocardial infarction (median [IQR] peak cardiac troponin 0.52 [0.05 to 2.5] ng/mL, and one patient had an ECG positive by the MSC). The resulting no occlusion myocardial infarction control group consisted of 102 subjects.

Clinical characteristics of study subjects are presented in Table 1. Subjects in the occlusion myocardial infarction group had higher peak troponin levels and were more likely to die during the index hospitalization. Subjects in the no occlusion myocardial infarction group were more commonly women and more likely to have biventricular pacing. The median (IQR) times to coronary angiography were 346 (72 to 1078) minutes for patients with occlusion myocardial infarction and 1955 (1136 to 3712) minutes for patients in the non-occlusion myocardial infarction-angio group. In the occlusion myocardial infarction group, culprit arteries included the following coronary arteries and their major branches: left anterior descending coronary artery (n=21), right coronary artery (n=18), left circumflex artery (n=13), ramus intermedius (n=2), coronary graft to the right coronary artery (n=5), and coronary graft to the left circumflex artery (n=2).

Main Results: Sensitivity of the Modified and Original Sgarbossa Criteria for Diagnosis of Occlusion Myocardial Infarction

For diagnosis of occlusion myocardial infarction in patients with ventricular paced rhythm, sensitivity of the MSC was 81% (95% CI 69 to 90), and that of the original Sgarbossa criteria was 56% (95% CI 42 to 69). When the concordant ST-depression criterion was extended to also include leads V4, V5, and V6, sensitivity of the MSC was 86% (95% CI 75 to 94) (Table 2). When Sgarbossa's point system was applied, the sensitivity of the resulting "weighted" original Sgarbossa criteria was 53% (95% CI 39 to 66).

The concordance criteria shared between the MSC and original Sgarbossa criteria correctly identified 31 (53%) occlusion myocardial infarction patients. The original Sgarbossa criteria excessive discordance criterion (ie, >5 mm discordant ST-elevation) identified 2 (3%) additional occlusion myocardial infarction patients, while the MSC proportionally excessive discordance criterion (ie, ST-elevation to S-wave ratio ≥25%) identified 17 (29%) additional OMI patients (Tables E2 and E3 and Figure E1, available at http://annemergmed.com/).

Diagnostic Characteristics for the No Occlusion Myocardial Infarction Control Group

For the no occlusion myocardial infarction control group, the false positive rate for the MSC was 4 of 102 (specificity 96%; 95% CI 90 to 99), compared to 3 of 102 for the original Sgarbossa criteriaC (specificity 97%; 95% CI 92 to 99). Three of the 4 false positive subjects by MSC had baseline ECGs available from prior visits, and all of the available baseline ECGs also met the MSC (Tables E3, E4, and E7 and Figures E2 to E5, available at http://www.annemergmed.com/).

The positive likelihood ratios were 21 (95% CI 7.9 to 55) and 19 (95% CI 6.1 to 59) for MSC and original Sgarbossa criteria, respectively. The negative likelihood ratios were 0.19 (95% CI 0.11 to 0.33) and 0.45 (95% CI

0.34 to 0.65) for MSC and original Sgarbossa criteria, respectively (Table 2).

The MSC proportionally excessive discordance criterion was the most accurate single criterion, with sensitivity of 63% (95% CI 49 to 75) and specificity of 97% (95% CI 92 to 99) (Tables E3 and E4, available at http://www.annemergmed.com/).

There were no significant differences in test characteristics when the occlusion myocardial infarction group was restricted to subjects with TIMI 0 to 1 flow (n=46) or when physiologic exclusion criteria were rescinded (Tables E8 and E9, available at http://www.annemergmed.com/). Sensitivity analyses evaluating performance of the MSC on subgroups of patients with right ventricular pacing (occlusion myocardial infarction, n=48; no occlusion myocardial infarction, n=56) yielded similar results (sensitivity 83% [95% CI 70 to 93] and specificity 98% [95% CI 90 to 100]).

Diagnostic Characteristics for the Non-Occlusion Myocardial Infarction-angio Control Group

For the non-occlusion myocardial infarction-angio control group, the false positive rate for the MSC was 14 of 90 (specificity 84%, 95% CI 76 to 91), compared to 9 of 90 for the original Sgarbossa criteria (specificity 90%, 95% CI 82 to 95) (Tables E5 to E7, available at http://www.annemergmed.com/). Five of the 14 false positives by the MSC underwent percutaneous coronary intervention during the index hospitalization. The positive likelihood ratios for MSC and original Sgarbossa criteria, respectively, were 5.2 (95% CI 3.2 to 8.6) and 5.6 (95% CI 2.9 to 11). The negative likelihood ratios were 0.22 (95% CI 0.13 to 0.38) for MSC and 0.49 (95% CI 0.35 to 0.66) for original Sgarbossa criteria (Table 2 and Table E6 [available at http://www.annemergmed.com/]).

LIMITATIONS

The low prevalence of ventricular paced rhythm and occlusion myocardial infarction made it impractical to perform this trial in a prospective manner or as a cohort study. We therefore completed a case-control study across 16 international health systems and developed the largest database of patients with ventricular paced rhythm and angiographically proven occlusion myocardial infarction to date.

The fact that it took a search covering 10 years and 16 sites to accumulate 59 occlusion myocardial infarction subjects might be interpreted to imply a low prevalence of occlusion myocardial infarction in patients with ventricular paced rhythm and, consequently, a low positive predictive value of the MSC for this diagnosis. However, the low prevalence of occlusion myocardial infarction in ED patients with ventricular paced rhythm and symptoms of ACS is primarily due to the low prevalence of ventricular paced rhythm in ED patients with symptoms of ACS (approximately 2.5%) and not due to a low prevalence of occlusion myocardial infarction in the population with ventricular paced rhythm. Occlusion myocardial infarction is present in only 2% to 5%, and STEMI in 1% to 3%, of ED patients with normal cardiac conduction who are evaluated for ischemic symptoms.[26,40-43] Thus, the positive predictive value of the ECG is unlikely to be different in patients with ventricular paced rhythm or normal cardiac conduction. The relatively small sample size did result in notably wide confidence intervals, leading to near overlap in the upper and lower bounds of the 95% CIs for the sensitivity between original Sgarbossa criteria and MSC in the primary analysis.

It remains likely that some patients with ventricular paced rhythm and occlusion myocardial infarction were not identified; even the most rigorous of search methods may omit some subjects. Additional subjects may not have met the stringent inclusion criteria. Our utilization of troponin cutoffs in the group of patients with TIMI 2 to 3 flow may have eliminated subjects in which troponin levels were not measured to peak, rapid spontaneous reperfusion resulted in limited myocardial cell death, or only a small myocardial territory was at risk. However, our 78% rate of TIMI 0 to 1 flow is typical for STEMI studies, and the sensitivity and specificity in the TIMI 0 to 1 cohort were the same as those in the full population.[44] It is also likely that some patients with ventricular paced rhythm and occlusion myocardial infarction did not meet criteria for inclusion in the study because they did not undergo coronary angiography whatsoever.[8,9]

There was a higher proportion of patients with biventricular pacing in the no occlusion myocardial infarction control group than in the occlusion myocardial infarction group, which had the potential to introduce bias into the results. Sensitivity analyses were performed to account for this, and the resulting test characteristics were similar to those of the full patient cohort.

Additionally, there were variations between sites with respect to the search methods utilized, the numbers of patients contributed, and the means in which patients arrived at the study sites. These practices may introduce bias or limit external validity of the results. It is likely, however, that the larger number and variety of patients identified through this international collaboration outweighed any potential biases the methods may have introduced.

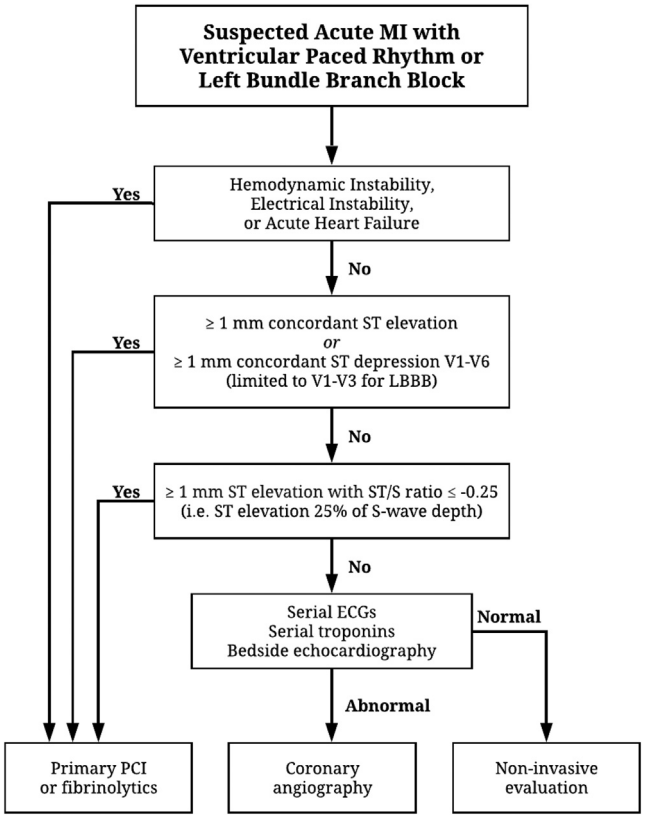

Figure 3. Algorithm for workup and treatment of suspected acute myocardial infarction in the setting of ventricular paced rhythm or left bundle branch block. This diagram depicts a proposed algorithm for diagnosing occlusion myocardial infarction in the setting of ventricular paced rhythm or left bundle branch block.

Most importantly, there is no reason to believe that any of these limitations disproportionately affected the diagnostic accuracy of either the MSC or the original Sgarbossa criteria. In other words, any bias would result in bias for both rules, not just one, so that the primary results of the study remain valid.

DISCUSSION

In this multicenter study of patients presenting in an emergency manner with symptoms of ACS and ventricular paced rhythm on ECGs, we validated the hypothesis that the MSC were more sensitive than the original Sgarbossa criteria for the diagnosis of acute occlusion myocardial infarction while maintaining comparably high specificity. In prior retrospective studies, Sgarbossa et al[15] (n=17) and Maloy et al[16] (n=57) found that the original Sgarbossa criteria had high specificity but low sensitivity for any acute myocardial infarction in patients with ventricular paced rhythm. Of 5,072 patients in a single-center, prospective registry of primary angiography performed for suspected occlusion myocardial infarction, Freitas et al[17] identified 43 patients with ventricular paced rhythm, of which 26 had occlusion myocardial infarction. The MSC had the highest accuracy of all criteria for the diagnosis of occlusion myocardial infarction, but the sensitivity was only 35%. However, Freitas et al only measured the ECG at "first medical contact," which was primarily the ECG obtained by out-of-hospital providers. Occlusion myocardial infarction is a dynamic process, and the value of multiple serial ECGs is well known.[42,45] If only a single, very early ECG is evaluated, ST-segment deviations may not be captured. It is also possible that subjects' symptoms had resolved at the time of the ECG tracing, which would suggest spontaneous coronary artery reperfusion and resolution of ECG findings consistent with occlusion myocardial infarction. Both of these were likely to have occurred in some subjects in Freitas et al's study. In our study, we performed rigorous chart review to determine patients' symptom status at the time of ECG recording. We then evaluated all preangiography ECGs obtained while the patient was symptomatic to determine if any ECG met the MSC or original Sgarbossa criteria. Our findings are consistent with those from prior studies utilizing similar methods in patients with left bundle branch block and angiographically proven occlusion myocardial infarction.[18,20]

The sensitivity of the MSC for occlusion myocardial infarction in our study was higher than the reported sensitivities of "STEMI criteria" for diagnosis of occlusion myocardial infarction in normal cardiac conduction, including criteria cited by the universal definition of myocardial infarction.[42,46-54] In a recent prospective, real-world study of 2,486 consecutive patients who presented to the ED with chest pain and normal cardiac conduction, Hillinger et al[42] identified 438 patients with acute myocardial infarction and 81 with adjudicated STEMI. STEMI criteria on the first ED ECG were only 35% sensitive for adjudicated STEMI. When all serial ECGs were assessed, STEMI criteria were 51% sensitive for adjudicated STEMI, 30% sensitive for occlusion myocardial infarction, and 9.4% sensitive for all acute myocardial infarction. In this study, we found the MSC to be 86% sensitive for the diagnosis of occlusion myocardial infarction in patients with ventricular paced rhythm. The higher sensitivity of the MSC may be partly due to the fact that, in contrast to STEMI criteria, the MSC take proportionality into account. Similar sensitivity was reported when the MSC were applied to patients with left bundle branch block.[18,20] These findings disprove the long-held misconception that the ECG is not helpful in the diagnosis of occlusion myocardial infarction in the presence of ventricular paced rhythm.

The specificity of the MSC was somewhat lower for patients in the non-occlusion myocardial infarction-angio group compared to the no occlusion myocardial infarction group. The vast majority of non-occlusion myocardial infarction-angio patients had type 1 myocardial infarctions with culprit arteries but with TIMI 2 to 3 flow and absence of very high troponin. Thus, this group is analogous to low-risk NSTEMI in normal cardiac conduction. Such patients require coronary angiography and possible percutaneous coronary intervention but not in an emergency fashion. Five of the 14 false positive subjects by the MSC in the non-occlusion myocardial infarction-angio group in this study underwent percutaneous coronary intervention; 9 did not need intervention at all. If the MSC were applied prospectively, these 14 patients may have undergone emergency, rather than delayed, coronary angiography. That is, they may have gone for coronary angiography and percutaneous coronary intervention more rapidly than thought to be necessary.

The no occlusion myocardial infarction group was the group that did not need coronary angiography at any time during the index visit and certainly not in an emergency manner. The MSC were very specific in this group, with few false positives. The critical and time-sensitive diagnostic differentiation that can be made by the MSC is to identify patients with occlusion myocardial infarction from all undifferentiated patients with symptoms of ACS who do not need emergency percutaneous coronary intervention.

Based on our findings, we recommend adding ventricular paced rhythm to the algorithm proposed by Cai et al[35] for the diagnosis of occlusion myocardial infarction in patients with left bundle branch block (Figure 3). Although such an algorithm would ideally be prospectively validated with clinical outcomes, the low prevalence of patients with both ventricular paced rhythm and occlusion myocardial infarction limits the feasibility of prospective studies. Currently, patients with ventricular paced rhythm and occlusion myocardial infarction do not receive optimal treatment and suffer from high mortality when compared to patients with normal cardiac conduction. In our occlusion myocardial infarction subjects with ventricular paced rhythm, we found a prolonged median time to reperfusion (5.8 hours) and a high in-hospital mortality (12%). Nine patients in our study with adjudicated type 1 acute myocardial infarctionI did not undergo coronary angiography, and 1 of those subjects did have an ECG positive by MSC. Rathore et al[8] and Rathore et al[9] found that patients with ventricular paced rhythm and acute myocardial infarction were less likely to undergo reperfusion therapy (adjusted relative risk 0.27, 95% CI 0.22 to 0.33) and have higher adjusted mortality at both 30 days (hazard ratio 1.21, 95% CI 1.12 to 1.31) and 1 year (hazard ratio 1.5, 95% CI 1.42 to 1.58) compared to patients with normal conduction.

In conclusion, the MSC are as specific and significantly more sensitive than the original Sgarbossa criteria for the diagnosis of occlusion myocardial infarction in the presence of ventricular paced rhythm. In patients with ventricular paced rhythm and symptoms concerning for ACS, the MSC aid in diagnosis of occlusion myocardial infarction and may inform the reperfusion decision.

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