The New England
Journal of Medicine

Volume 334 FEBRUARY 22, 1996 Number 8

ELECTROCARDIOGRAPHIC DIAGNOSIS OF EVOLVING ACUTE MYOCARDIAL INFARCTION IN THE PRESENCE OF LEFT BUNDLE-BRANCH BLOCK

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Abstract *Background.* The presence of left bundle-branch block on the electrocardiogram may conceal the changes of acute myocardial infarction, which can delay both its recognition and treatment. We tested electrocardiographic criteria for the diagnosis of acute infarction in the presence of left bundle-branch block.

Methods. The base-line electrocardiograms of patients enrolled in the GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial who had left bundle-branch block and acute myocardial infarction confirmed by enzyme studies were blindly compared with the electrocardiograms of control patients who had chronic coronary artery disease and left bundle-branch block. The electrocardiographic criteria for the diagnosis of infarction were then tested in an independent sample of patients presenting with acute chest pain and left bundle-branch block.

Results. Of 26,003 North American patients, 131 (0.5 percent) with acute myocardial infarction had left bundle-branch block. The three electrocardiographic criteria with independent value in the diagnosis of acute infarction in these patients were ST-segment elevation of 1 mm or more that was concordant with (in the same direction as) the QRS complex; ST-segment depression of 1 mm or more in lead V_1, V_2, or V_3; and ST-segment elevation of 5 mm or more that was discordant with (in the opposite direction from) the QRS complex. We used these three criteria to develop a scoring system (0 to 5), which allowed a highly specific diagnosis of acute myocardial infarction to be made.

Conclusions. We developed and validated a clinical prediction rule based on a set of electrocardiographic criteria for the diagnosis of acute myocardial infarction in patients with chest pain and left bundle-branch block. The use of these criteria, which are based on simple ST-segment changes, may help identify patients with acute myocardial infarction, who can then receive appropriate treatment. (N Engl J Med 1996;334:481-7.)

THE optimal use of coronary reperfusion therapies relies on a rapid diagnosis of evolving myocardial infarction.[1,2] For most patients presenting with cardiac chest pain, the electrocardiogram is a powerful aid in diagnosing the cause of the pain and selecting the appropriate therapy.[2] In patients who present with concomitant left bundle-branch block, however, the electrocardiographic manifestations of acute myocardial injury may be masked. During the past five decades, several electrocardiographic signs have been proposed to aid in the diagnosis of infarction in such patients, but because of methodologic limitations,[3-9] none of these signs have gained widespread acceptance. Many physicians believe that acute myocardial injury cannot be detected accurately in patients with left bundle-branch block.[10] We examined the value of the standard electrocardiogram for the diagnosis of acute myocardial infarction in the presence of left bundle-branch block in a large population of patients.

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Supported by grants from Bayer, Genentech, CIBA–Corning, ICI Pharmaceuticals, and Sanofi Pharmaceuticals.

METHODS

Derivation Sample

Criteria for the diagnosis of acute myocardial infarction in the presence of left bundle-branch block were developed from two populations (the study and control groups), which constituted the derivation sample. The study group consisted of the subgroup of North American patients enrolled in the GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial[11] who had acute myocardial infarction documented by serum enzyme changes and evidence of complete left bundle-branch block on their base-line electrocardiograms. The control group was assembled by randomly selecting from the Duke Databank for Cardiovascular Disease an equal number of patients with

stable, angiographically documented coronary artery disease and complete left bundle-branch block.[12] The patients in the control group did not have acute chest pain at the time of the electrocardiographic recording.

Electrocardiograms were digitally obtained at 100 Hz with a speed of 25 mm per second and an amplification of 10 mm per millivolt.

Definition of Left Bundle-Branch Block

The normal sequence of ventricular activation (depolarization and repolarization) can be altered by both left bundle-branch block and acute myocardial injury. To achieve a reasonable compromise between the electrocardiographic changes inherent in the two conditions,[13] we used the following definition of left bundle-branch block: a QRS duration of at least 0.125 second in the presence of sinus or supraventricular rhythm, a QS or rS complex in lead V_1, and an R-wave peak time of at least 0.06 second in lead I, V_5, or V_6 associated with the absence of a Q wave in the same lead.[7,14-16] Patients with electrocardiograms showing intermittent left bundle-branch block were excluded from the study.

Interpretation of Electrocardiograms

All the electrocardiograms were analyzed for signs of myocardial injury by one of four investigators who were unaware of both the patient's identity and the clinical variables. The signs examined[3-9,16-20] are shown in Table 1. The ST-segment deviation was measured at the J point. To assess interobserver variability, a random sample of 10 percent of the electrocardiograms were read by all four investigators.

Statistical Analysis

Interobserver agreement, as estimated with the kappa statistic, was greater than 0.85 for both QRS-complex and T-wave polarities. For both the terminal S wave in leads V_5 and V_6 and notching of at least 0.05 second of the S wave in lead V_3, the agreement was 0.77, but it was low (<0.55) for lead V_4, as well as for notching of at least 0.05 second of the R wave in lead I, aVL, V_5, or V_6. Measurements of ST-segment deviations were closely correlated among the four investigators (r>0.9 for all comparisons, by Pearson's correlation coefficient).

All electrocardiographic criteria were screened by univariate analysis (chi-square tests) to identify those associated with acute myocardial infarction. For ST-segment elevations, the receiver-operating-characteristic curves were constructed to evaluate the diagnostic performance of different combinations of the degree of elevation and number of leads exhibiting such elevation. Because a high specificity is desirable for the diagnosis of acute myocardial infarction,[21,22] we determined prospectively that the optimal cutoff point would correspond to the most sensitive degree of ST-segment elevation that had a specificity of at least 90 percent. Criteria for which the interobserver agreement was at least 0.7 and the univariate analysis showed statistical significance (P<0.1) were included in a stepwise logistic-regression model to identify independent criteria that were significant predictors of acute infarction (P<0.05). A scoring system for the diagnosis of infarction was developed from the coefficients assigned by the logistic model for each independent criterion, on a scale of 0 to 5. Receiver-operating-characteristic curves, kappa statistics, and correlation coefficients were estimated with True Epistat software.[23] Chi-square tests and logistic-regression analyses were performed with Egret software.[24]

The diagnostic performance of the model was then tested in an independent population of 45 patients with left bundle-branch block, acute chest pain, and a high likelihood of coronary artery disease (the validation sample). Included in this sample were patients in the GUSTO-1 registry and the GUSTO-2A (Global Use of Strategies to Open Occluded Coronary Arteries) study and the patients from GUSTO-1 subsequently found to have normal creatine kinase MB values.

Table 1. Electrocardiographic Criteria Analyzed in Patients with Left Bundle-Branch Block.

ST-segment elevation and its concordance or discordance with the QRS complex in every lead
ST-segment depression in every lead
Presence of Q waves in two contiguous precordial leads or in two limb leads (Q waves were considered present if they were ≥20 msec in lead V_4 or ≥30 msec in lead I, II, aVL, V_5, or V_6, regardless of width in leads V_1 to V_3)
R-wave regression from leads V_1 to V_4
QS pattern from leads V_1 to V_4
Positive T waves in lead V_5 or V_6
Notching ≥0.05 sec in the ascending limb of the S wave in lead V_3 or V_4 (sign of Cabrera)
Notching ≥0.05 sec in the ascending limb of R waves in lead I, aVL, V_5, or V_6 (sign of Chapman)
Terminal S wave in lead V_5 or V_6
Left-axis deviation

Table 2. Selected Characteristics of Patients with Left Bundle-Branch Block.*

Characteristic	Patients with Acute MI (N = 131)	Control Patients (N = 131)	P Value
Median age — yr (25th, 75th percentiles)	68.5 (62, 76)	68.0 (62, 74)	0.63
Male sex — no. (%)	84 (64)	78 (60)	0.52
Left-axis deviation — no. (%)†	37 (28)	63 (48)	0.002
Previous MI — no. (%)	34 (26)	77 (59)	<0.001
Median time to randomization — min (25th, 75th percentiles)	120 (90, 180)	—	—

*MI denotes myocardial infarction.

†A left-axis deviation was defined as a QRS axis of at least −30 degrees.

Results

Of the base-line electrocardiograms from the 26,003 North American patients, 145 met the criteria for left bundle-branch block. The diagnosis of acute myocardial infarction was confirmed by studies showing elevated creatine kinase MB levels in 131 of the patients. The electrocardiograms from these 131 patients were analyzed for the presence of the aforementioned diagnostic criteria. Selected base-line characteristics of the patients with acute myocardial infarction and the control patients are shown in Table 2.

Univariate Analysis

On the basis of the receiver-operating-characteristic curves, the maximal sensitivity with the target specificity (>90 percent) was achieved when at least one lead exhibited ST-segment elevation of at least 1 mm that was concordant with (in the same direction as) the QRS complex or at least 5 mm that was discordant with (in the opposite direction from) the QRS complex.

Electrocardiographic criteria with statistical significance for the diagnosis of acute myocardial infarction and their sensitivities, specificities, and likelihood ratios are listed in Table 3. The likelihood ratios indicate to what extent a particular criterion will increase or decrease the probability of infarction. The electrocardiographic criterion with the highest likelihood ratio was

Table 3. Results of the Univariate Analysis of Electrocardiographic Criteria.*

Criterion	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
	percent			
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 lead V_1, V_2, or V_3	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)
Positive T wave in lead V_5 or V_6	26 (19–34)	92 (86–96)	3.42 (0.18–65)	0.8 (0.72–0.9)
Left-axis deviation	72 (63–79)	48 (39–57)	1.38 (1.13–9.8)	0.59 (0.25–1.39)

*CI denotes confidence interval.

ST-segment elevation of at least 1 mm in leads with a QRS complex in the same direction. Similarly, the absence of this criterion was associated with the lowest likelihood ratio.

Multivariate Analysis and Index Scores for the Independent Electrocardiographic Criteria

All five electrocardiographic criteria associated with acute infarction in the presence of left bundle-branch block were included in a stepwise multiple logistic-regression model along with the variable "previous myocardial infarction." The model identified three independent predictors of acute myocardial infarction (Table 4 and Fig. 1). Figure 2 shows the predicted probability of infarction for each combination of criteria. A more accurate estimate of the probability of infarction can be obtained when the weight of each criterion, as determined by the logistic model, is used to develop a simple index score (Table 4).

The operating characteristics of the scoring system for the independent criteria provide a high discriminative power for the diagnosis of infarction (area under the curve, 0.874) (Fig. 3). For an accurate diagnosis, a specificity of 90 percent requires a minimal total score of 3. Patients presenting with ST-segment elevation of at least 5 mm in leads with a QRS complex in the opposite direction (score, 2) should therefore probably undergo further testing.

Testing of the Electrocardiographic Criteria in the Validation Sample

The criteria derived from the model and their index scores were tested in the validation sample, which included 22 patients with enzymatic evidence of acute necrosis and 23 with only unstable angina (the control group). As compared with the results in the derivation sample, the operating characteristics of the scoring system for the three criteria combined had a lower discriminative power for the diagnosis of infarction (area under the curve, 0.7). The sensitivities, specificities, likelihood ratios, and predictive values of the criteria (for an index score ≥3) in both samples are shown in Table 5.

Discussion

With the advent of effective reperfusion therapies, a rapid and accurate diagnosis of acute myocardial infarction has become essential.[22,25] Thrombolytic agents are most beneficial when administered promptly, and their erroneous use in patients with unstable angina or noncardiac chest pain is potentially dangerous.[11,26,27] Algorithms and predictive models developed to identify patients with ongoing myocardial ischemia or infarction[28-34] do not apply to patients with left bundle-branch block. The new appearance of bundle-branch block in a patient with acute chest pain is highly suggestive of infarction, and ischemic changes superimposed on a pattern of chronic left bundle-branch block are easy to recognize when a previous electrocardiogram is available for comparison. The timely availability of a previous electrocardiogram, however, is the exception rather than the rule. Physicians usually must decide to administer appropriate treatment or perform further testing on the basis of only the most recent electrocardiographic information. Our study suggests that in patients with left bundle-branch block, an examination of the electrocardiogram obtained at the time of presentation allows a diagnosis of acute myocardial infarction to be made with a high degree of confidence.

We found that ST-segment deviation was the only electrocardiographic finding that was useful in the diagnosis of acute myocardial infarction in the presence of left bundle-branch block. Previously proposed electrocardiographic signs involving the QRS complex were not useful. These discrepancies may be due to the fact that we analyzed electrocardiograms obtained on admission, thus detecting changes in the ST-segment (an early manifestation of acute coronary occlusion) rather than changes in the QRS complex (which indicate necrosis). Furthermore, the GUSTO-1 trial included patients with acute myocardial infarction, whereas previous studies of patients with left bundle-branch block have not always differentiated between acute and chronic infarction.[6-8]

Uncomplicated left bundle-branch block is characterized by secondary repolarization changes in a direction

Table 4. Odds Ratios and Scores for Independent Electrocardiographic Criteria.

Criterion	Odds Ratio (95% CI)	Score
ST-segment elevation ≥1 mm and concordant with QRS complex	25.2 (11.6–54.7)	5
ST-segment depression ≥1 mm in lead V_1, V_2, or V_3	6.0 (1.9–19.3)	3
ST-segment elevation ≥5 mm and discordant with QRS complex	4.3 (1.8–10.6)	2

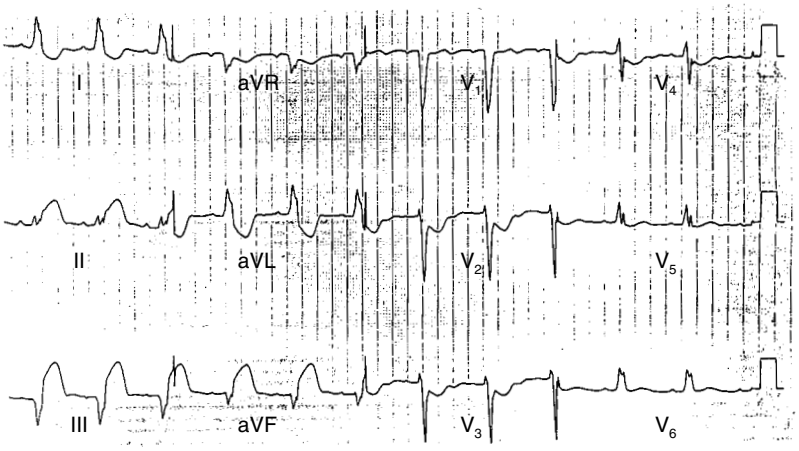

Figure 1. Electrocardiogram Meeting All Three Independent Criteria for the Diagnosis of Acute Myocardial Infarction in a Patient from the GUSTO Trial with Left Bundle-Branch Block.

The electrocardiogram shows ST-segment elevation of at least 1 mm that is concordant with the QRS complex (lead II), ST-segment depression of at least 1 mm in leads V_2 and V_3, and ST-segment elevation of at least 5 mm that is discordant with the QRS complex (leads III and aVF).

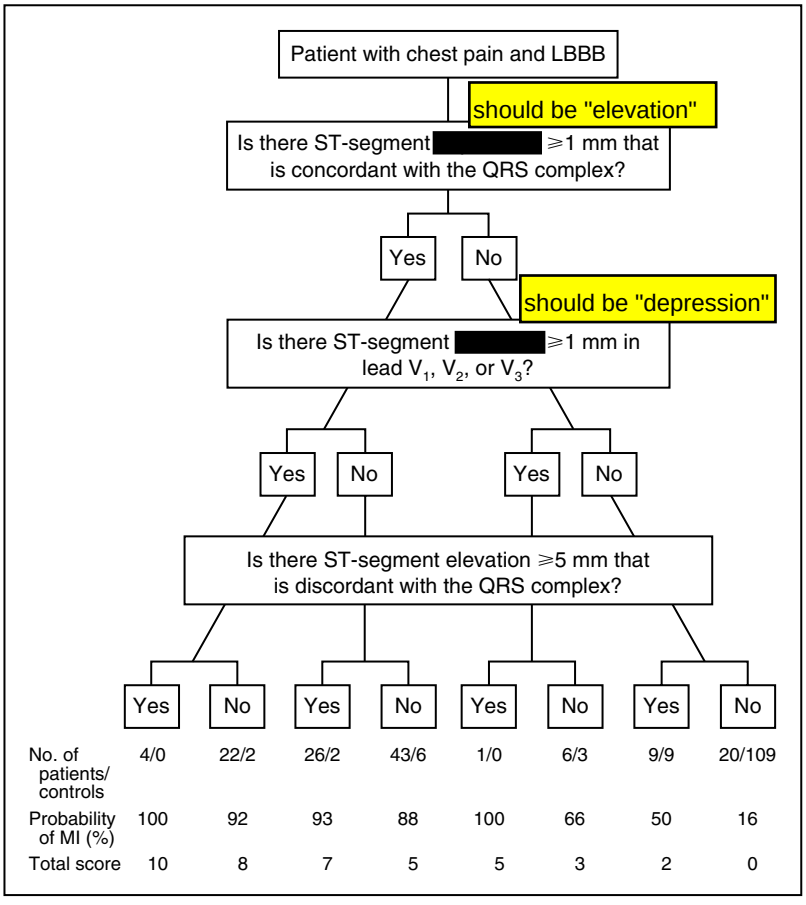

Figure 2. Flow Chart for the Prediction of Acute Myocardial Infarction in the Presence of Left Bundle-Branch Block, with the Use of All Possible Combinations of the Three Independent Electrocardiographic Criteria.

The discriminatory power of each combination of criteria for the diagnosis of acute myocardial infarction is indicated by the total score at the bottom, with higher scores indicating better discriminatory power. LBBB denotes left bundle-branch block, and MI myocardial infarction.

opposite that of the main QRS deflection.[9] In leads with a predominantly negative QRS complex, the result is an electrocardiographic pattern of ST-segment elevation with positive T waves, which is similar to the current of injury observed during acute coronary occlusion. Studies of patients with left bundle-branch block that examined serial electrocardiographic changes during either acute myocardial infarction[35-37] or occlusion of a coronary artery by an angioplasty balloon[38,39] have shown that further ST-segment elevation occurs in those leads.

Our challenge was to determine the cutoff point for the ST-segment elevation that would most effectively discriminate between patients with acute myocardial infarction and those without infarction, in the absence of information from previous or serial electrocardiographic tracings. We found that for leads with a predominantly negative QRS complex, ST-segment elevation of at least 5 mm identified patients with evolving infarction. On the other hand, ST-segment elevation in the same direction as that of the QRS complex is not expected in patients with uncomplicated left bundle-branch block. We found that any degree of ST-segment elevation in a lead with a positive QRS complex was a highly specific sign of acute myocardial infarction. Likewise, ST-segment depression in lead V_1, V_2, or V_3 should not be present in patients with uncomplicated left bundle-branch block, since the QRS complex is predominantly negative in those leads. In our study, ST-segment depression in lead V_1, V_2, or V_3 was also an independent marker of acute myocardial infarction. The mechanism for this finding is unclear; it could be a manifestation of true posterior-wall infarcts (i.e., due to occlusion of the left circumflex artery)[40] or infarcts associated with ST-segment depression (subendocardial infarcts).[41]

The presence of left bundle-branch block in patients with acute myocardial infarction is associated with an increased risk of complications and death.[42] When it is new, left bundle-branch block is correlated with the occlusion of the proximal left anteri-

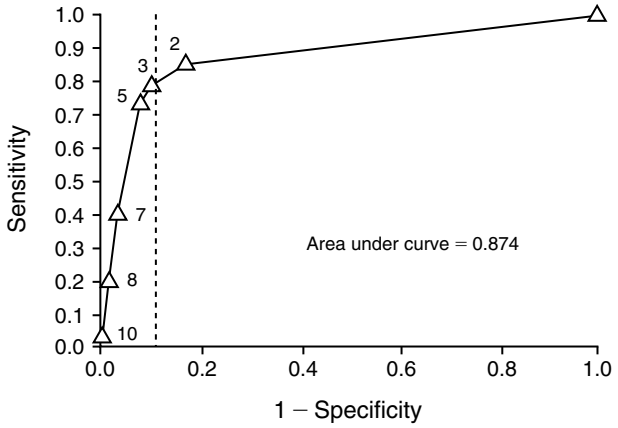

Figure 3. Receiver-Operating-Characteristic Curve for the Combined Score for the Three Independent Electrocardiographic Criteria.

The zone to the left of the broken line indicates a high probability of acute myocardial infarction. The numbers along the curve are scores.

or descending artery and a large amount of jeopardized myocardium.[43] On the other hand, a prior left bundle-branch block is a powerful marker of depressed left ventricular systolic function,[44,45] and any additional loss of myocardium is likely to result in cardiogenic shock. It is therefore not surprising that subgroup analyses in trials of thrombolytic therapy show a benefit of treatment in patients with bundle-branch block.[46] The Fibrinolytic Therapy Trialists' Collaborative Group analyzed the results of nine randomized studies and reported a dramatic 25 percent decrease in mortality at 35 days among 2032 patients with right or left bundle-branch block treated with thrombolysis.[26]

The relatively small number of patients with left bundle-branch block enrolled in these trials, however, attests to the prevailing diagnostic uncertainty. The National Registry of Myocardial Infarction has reported that patients with nondiagnostic electrocardiograms (a category that presumably included those with left bundle-branch block) were less likely to receive thrombolytic therapy than patients with diagnostic electrocardiograms.[47] In the comprehensive GUSTO-1 registry of 637 patients hospitalized for acute myocardial infarction, 219 (34 percent) did not receive thrombolytic therapy because their electrocardiograms were considered nondiagnostic. Left bundle-branch block was present in 20 of these patients and was thus responsible for 9 percent of the electrocardiogram-based exclusions (unpublished observations). In a study that did not involve thrombolytic therapy, the prevalence of left bundle-branch block among patients with acute chest pain was approximately 10 percent,[48] which is similar to the prevalence before thrombolytic therapy was available.[8]

ST-segment elevation of at least 1 mm that is concordant with the QRS complex or ST-segment depression of at least 1 mm in lead V_1, V_2, or V_3 is a specific marker of infarction, even when no other electrocardiographic change is observed. On the other hand, the sole presence of ST-segment elevation of at least 5 mm that is discordant with the QRS complex (with a score of 2) indicates a moderate-to-high probability of myocardial infarction, and further procedures should be undertaken to confirm the diagnosis.

The index score correctly classified 84 percent of the patients in the derivation sample but only 67 percent of the patients in the validation sample. A poorer performance of diagnostic criteria in the validation sample is not unexpected[49] and in our study is related to the relatively low sensitivity of the criteria. One reason for the decreased sensitivity is the difference in the two patient populations. Analysis of data from the GUSTO-1 sample (the source of the derivation sample) yielded inflated sensitivities, because the study included only patients with electrocardiographic signs of acute myocardial infarction, whereas the GUSTO-2A sample and the GUSTO-1 registry (the sources of most of the patients in the validation sample) included patients with other ischemic syndromes as well.[13]

It should be noted that the sensitivity of each individual electrocardiographic criterion in our study is also low but is similar to the sensitivity of ST-segment changes in patients with normal intraventricular conduction.[25,39] Our purpose was to improve the identification of patients with acute infarction, because they may benefit from thrombolytic therapy; to this end, a high specificity (rather than a high sensitivity) is required.[21] The high specificity of our index score in the validation sample (96 percent) may have a medicolegal benefit.[50] Electrocardiograms that are misread or considered nondiagnostic may result in a failure to diagnose infarction,[51,52] and claims of a missed infarction account for a substantial proportion of malpractice claims involving emergency departments.[51] Highly specific criteria may help physicians rapidly diagnose and treat acute infarction in patients with left bundle-branch block.

There are several potential limitations of our study. We did not attempt to distinguish between previous and newly developed left bundle-branch block, since this information was not available in the GUSTO-1 study. The absence of such a distinction is probably typical of clinical practice, since patients rarely present to the emergency department with their previous elec-

Table 5. Predictive Value of Criteria with an Index Score of at Least 3 in the Derivation and Validation Samples.

Criteria with Score ≥3	Derivation Sample (N = 262)	Validation Sample (N = 45)
Sensitivity (%)	78	36
Specificity (%)	90	96
Likelihood ratio for positive result	7.8	9.0
Likelihood ratio for negative result	0.2	0.7
Positive predictive value (%)	89	88
Negative predictive value (%)	80	61
Misclassification rate (%)	16	33

trocardiograms. It should nonetheless be noted that the effects of the conduction defect on repolarization are not expected to vary over time; our proposed ST-segment criteria probably apply to both old and new left bundle-branch block.[40,41]

Because the GUSTO-1 sample did not include a large group of patients with chest pain, left bundle-branch block, and normal creatine kinase MB values, we used controls without evidence of acute coronary events. This could have resulted in an increased specificity of the electrocardiographic signs of infarction.[13]

The high interobserver agreement with respect to our ST-segment measurements may be due to the fact that all the investigators who evaluated the electrocardiograms are cardiologists. The interpretive accuracy may be poorer among general practitioners, emergency department physicians, or paramedics.[25] Our criteria, however, rely on the identification of signs that can be interpreted by computerized electrocardiographic algorithms,[31] and it should be feasible to incorporate the signs into these algorithms, ensuring an accurate interpretation even in the nonhospital setting.

Although the diagnostic criteria were tested in patients presenting to the emergency room with both left bundle-branch block and chest pain, our validation sample may not have been sufficiently large. The criteria derived from our model should be validated prospectively in a larger cohort, and the effect of the criteria on patient care should also be examined. Meanwhile, the systematic use of these highly specific electrocardiographic signs of acute myocardial infarction in patients with chest pain and left bundle-branch block should facilitate timely intervention, particularly with thrombolytic therapy.

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