Should the Electrocardiogram Be Used to Guide Therapy for Patients With Left Bundle-Branch Block and Suspected Myocardial Infarction?

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The electrocardiogram (ECG) is an important clinical predictor of myocardial infarction (MI) but is of limited utility in the presence of complete left bundle-branch block (LBBB).1,2 For nearly half a century, electrocardiographers have searched for clues within the LBBB morphology that indicate acute myocardial injury. Most of the proposed criteria are insensitive and do not distinguish between acute and remote MI.3,4 Recently, Sgarbossa et al5 reported that an algorithm based on ST-segment changes had a sensitivity of 78% and a specificity of 90% for the diagnosis of MI; the authors included a small validation sample with a substantially lower sensitivity. However, these criteria were derived from a trial of thrombolytic therapy in which more than 90% of the patients with LBBB had a confirmed MI—a rate much higher than prior estimates.1 Controls were asymptomatic outpatients with LBBB and may not have been an appropriate comparison group.

The use of the Sgarbossa et al5 ECG algorithm has recently been advocated in patients presenting with suspected MI.2 However, given its imperfect sensitivity, a substantial proportion of patients with LBBB who presented with acute cardiopulmonary symptoms would have false-negative test results. These patients with MI would be denied acute reperfusion therapy if a positive test result were required for treatment.6-8 Although current guidelines recommend acute reperfusion therapy for patients with LBBB who present with acute chest pain suspicious for MI,3,6 these patients are substantially undertreated.4,9,10 Whether the proposed algorithm would improve clinical outcomes is dependent on its diagnostic test characteristics, the likelihood of MI, and the trade-off between the risks and benefits of receiving thrombolytic therapy.

See also pp 707 and 753.
To validate the performance of these criteria, we retrospectively studied a cohort of patients presenting with acute cardiopulmonary symptoms who had LBBB on their initial ECG to determine their risk of MI and the predictive value of the ECG. Using these results, we developed a decision analysis model to estimate the outcomes of treating all such patients with thrombolysis, treating none of them, or using the ECG algorithm as a screening test for thrombolysis.

**METHODS**

**Subjects**

We identified all patients older than 18 years who presented to the University of California, San Francisco (UCSF), Moffitt-Long Hospital emergency department between January 1, 1994, and December 31, 1997, with acute cardiopulmonary symptoms and a complete LBBB on their initial 12-lead ECG. We defined an LBBB as meeting all of the following criteria: (1) QRS of more than 0.12 milliseconds in the presence of normal sinus or supraventricular rhythm; (2) QS or RS complex in lead V1; (3) broad or notched R waves in leads V2 and V3 or an RS pattern; and (4) absence of a Q wave in leads V3, V4, and I.12,13 Patients with intermittent LBBB were excluded.

Patients were divided into 3 groups based on symptoms at presentation: (1) acute chest pain (chest discomfort lasting more than 20 minutes and occurring within 12 hours before presentation to the emergency department); (2) acute pulmonary edema (onset of dyspnea within 12 hours before presentation to the emergency department); and (2) acute pulmonary edema (onset of dyspnea with more than 20 minutes and occurring within 12 hours before presentation to the emergency department). These patients were required to have rales on auscultation during physical examination and bilateral infiltrates on chest radiograph;13, (3) cardiac arrest (ventricular fibrillation, ventricular tachycardia, or asystole in patients who had LBBB on conversion to a spontaneous atrial rhythm).14

We excluded patients who were not tested for elevation of myocardial enzyme levels (creatine kinase isoenzymes or troponin I) within 12 hours of their initial ECG. Entry into the study was decided by consensus of 2 authors (M.G.S. and W.L.L.) who were blinded to the ECG tracing and the outcome of the patient. Because some patients presented to the hospital more than once during the study, each presentation to medical attention was considered separately. A maximum of 3 presentations were included per patient, beginning from the time that the LBBB was first discovered. Analyses were repeated including only the first presentation within the study period. This study was approved by the UCSF Committee on Human Research.

**Measurements**

The primary predictor variables were the findings on the initial ECG. All information relevant to patient identification or outcomes was removed from the ECG tracing. The ECG features evaluated are listed in Table 1. The scoring system derived by Sgarbossa et al5 defined the ECG finding as positive (suggestive of acute MI) if it scored 3 points or higher based on 3 criteria. To control for interobserver reliability, we used only the most senior electrocardiographer (G.T.E.) at our institution. His intraobserver reliability was tested in a random sample of 20% of the overall cohort whose ECGs were analyzed twice without his knowledge; his k was 0.80 for the Sgarbossa et al5 criteria (positive vs negative findings).

Clinical characteristics of each patient, obtained by the emergency department and admitting clinicians, were identified by medical record review. These included the timing, characteristics, and symptoms of the clinical presentation; risk factors for coronary heart disease; cardiac history; and classification of the LBBB (known to be new, old, or unknown) based on prior ECGs in the hospital’s computer archives.

**Outcomes**

Given that LBBB can mask typical ECG changes of ischemia, we defined MI as having a characteristic clinical presentation (an inclusion criteria for all patients in this cohort) and an elevation of myocardial enzyme levels (serum troponin I level ≥1.5 µg/L or absolute serum creatine kinase–MB fraction ≥7 U/L that represented >3% of the total serum creatine kinase level).23-25 The outcome for each presentation was determined by consensus of 3 investigators (M.G.S., W.L.L., and A.S.G.) who were blinded to the ECG findings.

**Statistical Analysis**

Comparisons between groups for continuous variables were made using 1-way analysis of variance and the χ² test for categorical variables. Confidence intervals (CIs) for likelihood ratios were calculated. The k statistic was used to test the intraobserver correlation of our electrocardiographer. Statistical significance was defined as P<.05. The STATA statistical software package was used for all statistical analyses.31

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Table 1. Individual Electrocardiographic Predictors of Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Feature</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-segment elevation ≥1 mm in lead with concordant QRS complex*</td>
<td>5 Points</td>
<td>5</td>
</tr>
<tr>
<td>ST-segment depression ≥1 mm in leads V1, V2, or V3*</td>
<td>3 Points</td>
<td>5</td>
</tr>
<tr>
<td>ST-segment elevation ≥.5 mm in lead with discordant QRS complex*</td>
<td>2 Points</td>
<td>5</td>
</tr>
<tr>
<td>Initial (0.04-s) notching of the QRS complex in either leads II or III or in the precordial leads</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>An Rs configuration of the QRS complex in V5</td>
<td>Sign of Cabrera</td>
<td>16, 17</td>
</tr>
<tr>
<td>Notching of 0.05-s duration in the ascending limb of the S wave in V2</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>ST-segment elevation of ≥2 mm in leads with dominant upright QRS complex or ≥7 mm in leads with a dominant negative QRS complex</td>
<td></td>
<td>3, 4, 19, 20</td>
</tr>
<tr>
<td>Positive T waves in leads with a dominant upright QRS complex</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Notching of the ascending limb of the R wave in I, aVL, or V6</td>
<td>Sign of Chapman</td>
<td>22</td>
</tr>
</tbody>
</table>

*Criteria used in Sgarbossa et al5 ECG algorithm. A positive test result has at least 3 points.
Sample Size and Power
Sample size calculations were generated using conservative assumptions for the estimated sensitivity (40%) and specificity (90%) of the proposed ECG criteria and the risk of MI in patients with cardiopulmonary symptoms and LBBB. We estimated the rate of MI to be 25% in this population.1 To detect a difference between the rates of true- and false-positive test results of at least 30% (assuming 10% of patients without MI would have false-positive results), with a 2-sided a level of .05 and a power of 80%, a total sample size of 74 presentations meeting entrance criteria would be required.

Decision Analysis
We developed a decision analysis model to study the effect of our findings on clinical outcomes. We sought to determine the optimal treatment course for the average patient with LBBB presenting to medical attention with acute chest pain meeting criteria for thrombolysis9 and to establish testing and test-treatment thresholds based on the patient’s probability of having an MI.32

The decision tree (FIGURE 1) begins with a decision node delineating the 3 possible management strategies: (1) thrombolysis for all, (2) thrombolysis for none, and (3) apply ECG algorithm. The last strategy assumes that only patients with a positive test result receive thrombolysis. For patients in the thrombolysis-for-all or thrombolysis-for-none strategies, the first chance node is probability of acute MI, followed by chance nodes separating patients into the outcomes of stroke-free survival, stroke, and death. The stroke branch divides into minor and major stroke branches. The ECG algorithm strategy incorporates the sensitivity and specificity of the ECG algorithm. If the patient has an MI, then the likelihood of receiving thrombolysis equals the sensitivity of the test. Conversely, if the patient does not have an MI, the likelihood of not receiving thrombolysis equals the specificity of the test. The patient then follows the same outcome branches reflecting the probabilities of death, minor or major stroke, and stroke-free survival.

Probabilities
The probabilities used in the decision analysis and the ranges used in sensitivity analyses are shown in TABLE 2. The probability of MI for a patient with LBBB and acute chest pain and the sensitivity and specificity of the diagnostic test are based on data from the present study. Sensitivity and specificity values apply only to patients with chest pain. The clinical outcomes of patients with LBBB and MI who receive or do not receive thrombolysis are derived from the Fibrinolytic Therapy Trialists’ pooled analysis.31 The in-hospital mortality rate of patients who neither have MI nor receive thrombolysis is based on a cohort of patients with chest pain and no MI.32

The clinical outcomes of the patients with stroke were also obtained from the Fibrinolytic Therapy Trialists study. Forty percent of the patients who had a stroke died before 35 days, the time period reported in the study. Among the surviving 60%, roughly half had major disability and half had only minor sequelae.31

Utilities
The utilities in the model were chosen to bias the results against thrombolysis by weighing the negative effects of stroke heavily. We used a utility scale of 0 (death) to 1 (stroke-free survival). Major stroke

Table 2. Probabilities Incorporated Into the Decision Analysis Model

<table>
<thead>
<tr>
<th>Probability</th>
<th>Estimate</th>
<th>Range for Sensitivity Analysis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of acute myocardial infarction</td>
<td>0.28</td>
<td>0.17-0.40</td>
<td>Current study</td>
</tr>
<tr>
<td>Test sensitivity</td>
<td>0.06</td>
<td>0.01-0.27</td>
<td>Current study</td>
</tr>
<tr>
<td>Test specificity</td>
<td>0.92</td>
<td>0.90-1.0</td>
<td>Current study</td>
</tr>
<tr>
<td>Probability of death: acute myocardial infarction, no thrombolysis</td>
<td>0.236</td>
<td>0.210-0.262</td>
<td>33</td>
</tr>
<tr>
<td>Probability of death: acute myocardial infarction, with thrombolysis</td>
<td>0.186</td>
<td>0.163-0.211</td>
<td>33</td>
</tr>
<tr>
<td>Probability of death: no acute myocardial infarction, no thrombolysis</td>
<td>0.02</td>
<td>0.01-0.03</td>
<td>34</td>
</tr>
<tr>
<td>Probability of death: no acute myocardial infarction, with thrombolysis</td>
<td>0.022</td>
<td>0.009-0.031</td>
<td>33, 34</td>
</tr>
<tr>
<td>Probability of stroke with thrombolysis</td>
<td>0.016</td>
<td>0.010-0.0128</td>
<td>33</td>
</tr>
<tr>
<td>Probability of stroke, no thrombolysis</td>
<td>0.0076</td>
<td>0.0067-0.0087</td>
<td>33</td>
</tr>
</tbody>
</table>

LBBB indicates left bundle-branch block; ECG, electrocardiogram. Following the initial decision node (square) are chance nodes (circles) marking the probability of the patient reaching each possible outcome (triangles). Plus signs indicate positive test results; minus signs, negative test results.

FIGURE 1. Decision Tree Outlining Alternative Strategies for Managing a Patient With LBBB and Chest Pain
was given a utility of 0 and minor stroke was assigned a utility of 0.8.35-40

**Sensitivity Analysis**

One-way sensitivity analysis was performed using each of the ranges of probabilities in Table 2, based on the 95% CI for each variable. Two-way sensitivity analysis was performed by simultaneously varying the probability of MI and the test characteristics of the ECG algorithm. We also varied the utilities of major and minor stroke between 0 and 1. The DATA software program was used for the analyses and graphics of the decision analysis.41

**RESULTS**

**Clinical Outcomes**

We included 103 presentations of acute cardiopulmonary symptoms in 83 patients with LBBB. Thirty percent (95% CI, 21%-40%) met criteria for MI. The risk of MI was not significantly different among the 83 original presentations of each patient (31% had MI) vs 20 subsequent presentations of patients to the emergency department within the 4-year period of observation (25% had MI) (P = .58). No significant difference was seen in the proportions with MI among the 3 categories of clinical presentation (P = .21). The risk of MI was 28% (95% CI, 17%-40%) in the group with chest pain, 28% (95% CI, 13%-47%) in the group with pulmonary edema, and 56% (95% CI, 21%-86%) in the group with cardiac arrest.

**Test Characteristics of ECG Criteria**

Most of the ECG criteria were infrequently noted, leading to a low sensitivity and wide CIs around the estimated positive predictive values (Table 3). The negative predictive value for each criterion was less than 75%, similar to the pretest likelihood of not having an MI.

Using the scoring system from the study by Sgarbossa et al5 (≥3 points for a positive test result), only 3 of the ECGs met criteria for a positive test result; each of these patients had an MI. If any of the 3 ST-segment abnormalities denoted a positive test result, then the sensitivity would rise to 23% (95% CI, 10%-41%), with a specificity of 82% (95% CI, 71%-90%). These test characteristics did not change when we included only the first presentation of each patient.

The positive likelihood ratio estimates, calculated by dividing sensitivity by (1 – specificity) (Table 4), for 2 of the ST-segment criteria are undefined, given their specificity of 100%. This suggests that a positive test result would indicate a positive predictive value approximating 100%. The negative likelihood ratios for the ECG findings are all approximately 1.0. Thus, a negative test result does not decrease that patient’s probability of having an MI. Using the Sgarbossa et al5 algorithm, the positive likelihood ratio is undefined and the negative likelihood ratio is 0.9. If any 1 of the 3 ST-segment findings defined a positive test result, then the positive likelihood ratio would be 1.3 (95% CI, 0.6-2.9) and the negative likelihood ratio would be 0.9 (95% CI, 0.8-1.2). Among patients who presented with chest pain, the sensitivity of the algorithm fell to 6% and the negative likelihood ratio was 0.9 (95% CI, 0.8-1.1).

**Decision Analysis Outcomes**

For every 1000 patients who present with LBBB and chest pain, 929 would survive without major stroke if all received thrombolytic therapy (Table 5). The strategies of no thrombolysis and the ECG algorithm gave similar results: 919 patients would survive without major stroke using the Sgarbossa et al5 algorithm compared with 918 patients if none received thrombolysis. Thus, the strategy of using thrombolysis for all patients with LBBB...
and chest pain would improve stroke-
free survival by 10 patients per 1000 com-
pared with a treatment strategy based on
ECG findings. If survival is considered the
outcome, the difference between these 2
strategies increases to 12 patients. If mi-
nor and major strokes are considered
equivalent to death, the superiority of the
thrombolytic-for-all strategy remains at 10
patients per 1000 presentations.

Threshold and Sensitivity Analyses
Empirical thrombolysis is the preferred
strategy if the probability of MI is greater
than 6.5%. Thrombolysis for none is
never the optimal strategy because of the
100% specificity of this ECG diagnostic
algorithm. The Sgarbossa et al3 algo-
rithm is preferred if the probability of MI
is between 0% and 6.5%.

The thrombolysis-for-all strategy is
preferred throughout the range of the 1-
way sensitivity analyses. For example, if
the probability of thrombolytic-associated
stroke is increased to the max-
imum value of its range (1.3%), giving

<table>
<thead>
<tr>
<th>Table 5. Outcomes of Treating 1000 Patients With Left Bundle-Branch Block and Chest Pain for 3 Clinical Strategies</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Base-case analysis (quality-adjusted survival)</td>
</tr>
<tr>
<td>Survival</td>
</tr>
<tr>
<td>Survival without major stroke</td>
</tr>
<tr>
<td>Survival without any stroke</td>
</tr>
</tbody>
</table>

*ECG indicates electrocardiographic. All data presented as number of hypothetical patients.

The pretest probability of MI and the
sensitivity of the ECG algorithm had the
greater effect on the clinical outcomes of
thrombolysis for all and apply ECG
algorithm strategies. The magnitude of
difference between the 2 strategies ranged
from 5 to 16 patients per 1000 within
the range of sensitivity analyses, yet
thrombolysis for all was always the pre-
ferred decision. If the likelihood of MI
is 28% (as seen in this cohort), then the
thrombolyis-for-all strategy is preferrable
unless the diagnostic test sensitiv-
ity exceeds 85% (Figure 2).

**COMMENT**

We found that the ECG was an insensi-
tive predictor of MI in a community-
based cohort of patients with LBBB and
acute cardiopulmonary symptoms. Less
than 10% of the MIs would have been
detected using the ECG algorithm. In-
deed, the negative predictive values of all
the studied ECG criteria indicate none
can identify patients at low risk for MI.
If these algorithms were used as screen-
ing tests for reperfusion therapy, then
nearly all patients with LBBB and MI
would be denied this intervention.

Our findings have important impli-
cations for the 100 000 patients with
LBBB who have MIs in the United States
each year.10,13 These patients have the
highest mortality rate of any subset of pa-
patients with MI10,53-42-49 and have the larg-
est absolute mortality benefit from throm-
bolysis.32 Nonetheless, only 5% of these
patients receive reperfusion therapy.10

Under treatment of this high-risk syn-
drome may result from the uncertainty
of the diagnosis of MI in patients with
LBBB and the fear of needlessly causing
a complication of thrombolytic therapy,
such as intracerebral hemorrhage, in a
patient not having an MI.

Ideally, a prospective trial would evalu-
ate the clinical impact of giving thrombo-
lytic therapy to all patients with LBBB who
have symptoms consistent with MI com-
pared with using a diagnostic screening
strategy like an ECG algorithm. In the ab-
sence of such a clinical trial, we used a de-
cision analysis model to estimate the risks
and benefits of these alternative man-
agement strategies. We found that major
stroke-free survival would increase by 10
patients per 1000 presentations if throm-
bolytic therapy was consistently used in
LBBB patients with chest pain who met
criteria for reperfusion therapy. Thus,
thrombolysis would improve the outcome
of about 1000 symptomatic patients with
LBBB in the United States each year.

We did not include the option of pri-
mary angioplasty because no studies have
evaluated this strategy in LBBB pa-
ents. If primary angioplasty is avail-
able and is as effective as thrombolytic
therapy in LBBB patients, then this man-
gement strategy would have even bet-
ter outcomes because the stroke risk
would be reduced by half.50,51 We also
do not include a strategy of an alterna-
tive screening test, such as a bedside tro-
ponin assay. Although the initial sensi-
tivity for MI in patients with chest pain
has been cited as high as 66%, the nega-
tive likelihood ratio remained higher than
0.5 until 4 to 8 hours after presenta-
tion.52,53 In a population with a pretest
risk of MI of 28%, as seen in the current
study, the negative likelihood ratio of any
screening test would need to be 0.3 or
less to reduce the posttest risk of MI to
below 10% with a negative test result.
Any promising new test should be vali-
dated in the high-risk population with
LBBB prior to its adoption into wide-
spread clinical use in these patients.

A potential limitation of this study is
that our institution, which is both a com-
mmunity emergency department and a ter-
tiary referral center, may not have rep-
resentative patients. In addition, we had
only 1 reader for all the ECGs, which
could have produced measurement bias.
However, his κ statistic of 0.8 for in-
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traobserver agreement is very good. The reproducibility of this ECG algorithm in the hands of the average clinician would almost certainly decrease, further limiting the usefulness of the test.

In conclusion, we found that the ECG is a poor predictor of MI in a community-based cohort of patients with acute cardiac syndromes and LBBB. Our decision analysis demonstrates that empirical thrombolysis is likely to improve outcomes compared with a strategy of screening with the ECG. No currently available diagnostic testing strategy in these patients improves results compared with a strategy of thrombolysis for all patients. Any future screening test should demonstrate a sensitivity greater than 85% with a specificity of at least 90% to improve outcomes. Our results support the American College of Cardiology/American Heart Association recommendations that, in the absence of contraindications, acute reperfusion therapy should be used in all patients with LBBB who have clinical presentations indicative of MI.

REFERENCES


45. Gage BF, Cardinall AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fi-