Prognostic Value of Vasodilator Myocardial Perfusion Imaging in Patients With Left Bundle-Branch Block

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Background—The prognostic value of tomographic myocardial perfusion imaging with dipyridamole or adenosine in patients with left bundle-branch block has not been established.

Methods and Results—The study group consisted of 245 patients with left bundle-branch block who underwent tomographic (single photon emission tomography) myocardial perfusion imaging with thallium-201 (n=173) or technetium-99m sestamibi (n=72) and either dipyridamole (n=153) or adenosine (n=92) stress. Patients were prospectively classified into two groups. Patients were classified as "high risk" if they had (1) a large severe fixed defect (n=28), (2) a large reversible defect (n=36), or (3) cardiac enlargement and either increased pulmonary uptake (thallium) or a decreased resting ejection fraction (sestamibi) (n=20). The remaining 161 patients (66% of the study group) were at "low risk." Follow-up was 99% complete at 3±1.4 years. Three-year overall survival was 57% in the high-risk group compared with 87% in the low-risk group (P<.0001). Survival free of cardiac death/nonfatal myocardial infarction/coronal transplantation was 55% in the high-risk group and 93% in the low-risk group (P<.0001). The presence of a high-risk scan had significant incremental prognostic value after adjustment for age, sex, diabetes, and previous myocardial infarction (P<.0001). Patients with a low-risk scan had an overall survival that was not significantly different from that of a US age-matched population (P=.86).

Conclusions—Tomographic myocardial perfusion imaging with adenosine or dipyridamole stress provides important prognostic information in patients with left bundle-branch block, which is incremental to clinical assessment.

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Key Words: prognosis • radioisotopes • electrocardiography

In 1909, the concept of bundle-branch block was introduced by Eppingen and Rothberger.1 Since then, several studies have examined the association between left bundle-branch block and cardiac disease. Smith et al2 and Beach et al3 suggested that acquired left bundle-branch block in asymptomatic individuals without other risk factors has a good prognosis. However, other studies have suggested that left bundle-branch block is not associated with a benign prognosis. In the Framingham Study, men who acquired left bundle-branch block were more likely to have or subsequently acquire advanced cardiovascular abnormalities than men who acquired right bundle-branch block, although the clinical correlates of the two conduction abnormalities were similar in women.4 The same study demonstrated that the 10-year cardiovascular mortality after the onset of left bundle-branch block is 50%. In patients with chronic coronary artery disease in the CASS registry,5 left bundle-branch block was a strong predictor of mortality, independent of the degree of heart failure, extent of coronary disease, and other important variables.

In patients with left bundle-branch block, treadmill exercise testing is not useful in the diagnosis of coronary artery disease.6-7 Unfortunately, the results of exercise perfusion scintigraphy with thallium-201 and technetium-99m sestamibi have also been disappointing. Specificity has been reported to be 10% to 30% for the diagnosis of coronary artery disease,8-11 primarily because of false-positive septal perfusion abnormalities. DePuey et al9 and Matzer et al10 proposed the use of abnormal perfusion in the anterior wall or the apex to improve the specificity of perfusion images, but others12 were unable to confirm any benefit with this approach.

In an attempt to improve the accuracy of perfusion imaging in patients with left bundle-branch block, several investigators have examined the use of pharmacological stress rather than exercise stress. Several studies have shown that perfusion imaging with vasodilators (dipyridamole and adenosine) is superior to exercise for detection of coronary artery disease in patients with left bundle-branch block.13-18 Pharmacological perfusion imaging has been shown to be useful for prognostic purposes in patients without left bundle-branch block.19,20 However, the prognostic value of vasodilator stress perfusion imaging with either thallium-201 or technetium-99m sestamibi and either adenosine or dipyridamole has not been studied in patients with left bundle-branch block. There are no follow-up studies examining the prognosis of patients with left bundle-branch block who underwent noninvasive stress testing of any sort. The aim of this study was to determine
whether prospectively defined "high-risk" perfusion scans were associated with subsequent cardiac events in patients with left bundle-branch block and whether such scans provide incremental value over clinical variables in predicting events.

Methods

Study Group
The patient population was selected from the single photon emission tomography (SPECT) perfusion imaging database at the Mayo Clinic. This database has been prospectively collected since 1985 and contains multiple clinical, ECG, and imaging variables. Patients were eligible for this study if they had complete left bundle-branch block at the time of stress perfusion imaging with dipyridamole or adenosine between December 1986 and December 1993. Left bundle-branch block was defined as follows: QRS duration ≥ 0.12 seconds; broad, notched, predominantly positive QRS complex in lead I and either lead V₅ or V₆; predominantly negative QRS complex in lead V₆; absence of septal Q waves in left precordial leads; and displacement of the ST segment and T wave in a direction opposite that of the major QRS direction.

Exclusion Criteria
Patients were excluded for any of the following reasons: (1) prior history of bypass surgery or coronary angioplasty, (2) paced rhythm on the ECG, (3) evidence of clinically significant valvular heart disease, or (4) hypertrophic obstructive cardiomyopathy. A total of 245 consecutive patients met these criteria.

Vasodilator Infusions
The patients received intravenous infusions of either dipyridamole (0.56 mg/kg over 4 minutes) or adenosine (140 μg · kg⁻¹ · min⁻¹ for 6 minutes) with previously described methods. The bolus quality was assessed by the time-activity curve obtained in a region of interest drawn around the superior vena cava. Images were acquired in the anterior projection with the patient in the upright position by use of the Elscint Apex 409 single-crystal gamma camera and processed on an SP4 workstation. The study was acquired in frame mode (24 frames per second) by use of a two-time zoom factor. ECG gating was used to reconstruct the representative cardiac cycle. A typical study collected ~120 000 cps during the right ventricular phase and 70 000 000 cps during the left ventricular (LV) phase. The LV ejection fraction was calculated from the background-subtracted time-activity curve.

Radionuclide Acquisitions

Thallium-201
A weight-adjusted dose of 2.5 to 3.0 mCi was injected intravenously three minutes after the completion of dipyridamole or after three minutes of adenosine infusion. Imaging was initiated five minutes after the completion of ECG monitoring. Four hours later patients received a second intravenous injection of 1.0 to 1.5 mCi thallium, and underwent repeat imaging 20 minutes later. Patients done prior to 1/1/90 had one injection of 4.0 mCi of thallium at stress without reinjection after 4 hours.

Technetium-99m Sestamibi
Patients were injected intravenously with 30 mCi at rest. First-pass images were obtained during injection, and rest perfusion images were obtained 20 to 30 minutes later. One day later, patients underwent the dipyridamole or adenosine stress test, and 15 to 20 mCi was injected intravenously 3 minutes after the completion of dipyridamole or at the start of the 4th minute of adenosine infusion. Stress perfusion images were obtained 20 to 30 minutes later.

First-Pass Rest Ejection Fraction Technique
In patients undergoing sestamibi imaging after June 1, 1993 (n=22), a first-pass resting ejection fraction was obtained. Previously described procedures were carefully followed to obtain a high-quality bolus injection through an antecubital vein. The bolus quality was assessed by the time-activity curve obtained in a region of interest drawn around the superior vena cava. Images were acquired in the anterior projection with the patient in the upright position by use of the Elscint Apex 409 single-crystal gamma camera and processed on an SP4 workstation. The study was acquired in frame mode (24 frames per second) by use of a two-time zoom factor. ECG gating was used to reconstruct the representative cardiac cycle. A typical study collected ~120 000 000 cps during the right ventricular phase and 70 000 000 cps during the left ventricular (LV) phase. The LV ejection fraction was calculated from the background-subtracted time-activity curve.

The quality of the first-pass study was assessed by use of the R-R interval and superior vena cava transit time; if the R-R interval varied by <10% and the superior vena cava transit time was <1 second, the study was considered good.

Perfusion Imaging Technique
For thallium-201 studies, an anterior planar view was obtained before SPECT imaging. SPECT images were acquired with a rotating gamma camera with an all-purpose collimator by use of a step-and-shoot approach every 6° over a 180° clockwise circular orbit beginning at a 45° right anterior oblique projection and ending at 45° left posterior. Images were reconstructed with standard backprojection algorithms and a Ramp-Hanning filter.

Scintigraphic Analysis
Stress and rest images from the short-axis, horizontal long-axis, and vertical long-axis slices were viewed side by side by two experienced observers as previously described. Uptake in each of the 14 short-axis segments was graded on a five-point scale (0=absent perfusion to 4=normal perfusion). The score in each segment was summed to obtain a global score, which had a maximum value of 56 (14×4) for a completely normal set of images. Defects in the short-axis slices were confirmed in the other two planes. Thallium lung uptake on the anterior planar image was considered increased if the counts in any part of the lungs were more than half the maximal counts in the heart.

Patient Follow-up
Follow-up was performed on all patients who fulfilled the entry criteria through a combination of a chart review and mail or telephone contact with patients or their physicians. The individual performing the follow-up was blinded to the nuclear study results. The patient's vital status was determined as of June 1, 1994, for patients studied before June 1, 1993. For patients studied after June 1, 1993, vital status was obtained as of 1 year after the date of the study, insuring a minimal follow-up of 1 year for all patients.

The following events were recorded during the follow-up: (1) cardiac death (including fatal myocardial infarction), (2) noncardiac death, (3) nonfatal myocardial infarction by history and cardiac enzymes, (4) coronary angiography, (5) cardiac transplant, and (6) coronary artery bypass graft or percutaneous transluminal coronary angioplasty. Grafting or angioplasty was considered "late" if it occurred more than 3 months after the imaging study. Hospital records and death certificates were obtained and reviewed to document accuracy of stated events. Death was determined to be cardiac or noncardiac by individuals blinded to the results of the images. Follow-up was complete in 244 patients (99.6%) at a mean of 3.0±1.4 years.

Patient Classification
Patients were classified using the following prospective criteria, which were developed on the basis of previous literature before any patient follow-up:

1. A high-risk group. This group included (a) patients with a large severe perfusion defect on the resting study (consistent with extensive infarction) defined as a resting score <46 and at least two segments with a segmental score of 2 or less on the resting images and a global reversibility score (equal to global score delayed minus global score after stress testing) ≥5. Also included were (b) patients with a large reversible defect (consistent with ischemia) defined as a post-stress testing defect score <46 and at least two segments with a segmental score of 2 or less and a global reversibility score >5. The high-risk group also included (c) patients who did not have a large post-stress testing defect but did have cardiac enlargement and either increased pulmonary uptake (for patients studied with thallium) or LV ejection fraction <45% as measured by the first-pass technique (for patients studied with sestamibi). This definition was designed to identify patients who were likely to have dilated cardiomyopathy. In patients studied with sestamibi before June 1, 1993, in whom the ejection fraction was not measured with the...
first-pass technique (n=50), an alternative measurement of ejection fraction by gated equilibrium radionuclide angiography, echocardiography, or contrast ventriculography was used.

2. A low-risk group. This group included all patients who did not belong to group 1. For example, this group included patients with (a) normal cardiac size, (b) normal pulmonary uptake (on thallium studies), or (c) normal LV ejection fraction (on sestamibi studies) and any of the following: a small mild reversible defect, a small fixed defect, or normal perfusion images.

Statistical Analysis
Baseline variables included in Cox regression analysis were as follows, (1) clinical variables, including age, sex, presence or absence of chest pain (and if present, typical or atypical angina), coronary risk factors (smoking history, family history of premature coronary artery disease, hypercholesterolemia, hypertension, and diabetes), history of myocardial infarction; (2) vasodilator variables or vasodilator-induced angina; and (3) image variables, including high-risk or low-risk scan.

Hard events were total mortality, cardiac mortality, myocardial infarction by history and cardiac enzymes, and cardiac transplantation. Late revascularization (angioplasty or bypass surgery) was a soft event.

The primary end point was total mortality, with "hard cardiac events" and "soft or hard cardiac events" as important secondary end points. Late revascularization was included as an end point in the soft or hard cardiac event analysis. Patients were censored after revascularization for the hard cardiac event analysis but not for the total mortality analysis.

Analysis was by standard survival analytic techniques: Kaplan-Meier survival curves, log-rank tests, and proportional hazards models with time to the first event as the dependent variable. To analyze the incremental value of the image results, multivariable proportional hazard analysis was done by use of first the clinical variables and then with the image variable or variables added. Post hoc comparisons were made to age- and sex-matched control subjects with use of actuarial survival data for the US population.

Observed and expected survivals were plotted together, both overall and in subgroups, and comparisons between observed and expected survival were based on a one-sample log-rank test. Categorical variables were compared among groups by use of the chi-square test for independence; continuous variables were compared among groups by use of ANOVA.

Results
Study Group
Of the 245 patients eligible for the study, 125 were men and 120 were women. The mean age of the group was 69±9 years (range, 40 to 89 years). Of the patients, 128 (74%) had current symptoms of chest pain or dyspnea, 53 (22%) had a history of previous myocardial infarction. One hundred sixty-one (66%) patients fulfilled the low-risk criteria, and 84 (34%) fulfilled the high-risk criteria—large severe fixed defect in 28 (11%), large reversible defect in 36 (15%), and dilated cardiomyopathy in 20 (8%). Detailed demographic and clinical characteristics of the patients are shown in Tables 1 and 2. The high-risk group had more men and a significantly higher incidence of insulin-requiring diabetes, smoking, and previous myocardial infarction.

Coronary Angiography
Coronary angiography was performed within 6 months of the perfusion study in 56 patients, 32 in the high-risk group and 24 in the low-risk group (Table 3). Angiography was more frequent in the high-risk group (38% versus 15%, P=.0001). Of patients in the high-risk subgroups 1a and 1b (large severe fixed defect and large reversible defect) who underwent coronary angiography, 88% had significant coronary artery disease compared with 63% of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Group (n=245), n</th>
<th>Group 1 (High Risk; n=84), n (%)</th>
<th>Group 2 (Low Risk; n=161), n (%)</th>
<th>P (Group 1 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69±9</td>
<td>70±7</td>
<td>68±10</td>
<td>.27</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>125/120</td>
<td>61/23 (73/27)</td>
<td>64/97 (40/60)</td>
<td>.001</td>
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<tr>
<td>Asymptomatic</td>
<td>63</td>
<td>23 (27)</td>
<td>40 (25)</td>
<td>.67</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>59</td>
<td>23 (27)</td>
<td>36 (22)</td>
<td>.38</td>
</tr>
<tr>
<td>Typical chest pain</td>
<td>63</td>
<td>26 (31)</td>
<td>37 (23)</td>
<td>.18</td>
</tr>
<tr>
<td>Atypical or nonanginal chest pain</td>
<td>68</td>
<td>14 (17)</td>
<td>54 (34)</td>
<td>.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>135</td>
<td>51 (61)</td>
<td>84 (62)</td>
<td>.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48</td>
<td>22 (28)</td>
<td>26 (16)</td>
<td>.06</td>
</tr>
<tr>
<td>Insulin</td>
<td>26</td>
<td>15 (18)</td>
<td>11 (7)</td>
<td>.008</td>
</tr>
<tr>
<td>No insulin</td>
<td>22</td>
<td>7 (8)</td>
<td>15 (9)</td>
<td>.8</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>91</td>
<td>28 (33)</td>
<td>63 (39)</td>
<td>.37</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>32</td>
<td>13 (15)</td>
<td>19 (12)</td>
<td>.42</td>
</tr>
<tr>
<td>Previous</td>
<td>92</td>
<td>42 (50)</td>
<td>50 (31)</td>
<td>.004</td>
</tr>
<tr>
<td>Never</td>
<td>121</td>
<td>29 (34)</td>
<td>92 (57)</td>
<td>.001</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>53</td>
<td>31 (37)</td>
<td>22 (14)</td>
<td>.001</td>
</tr>
<tr>
<td>Family history</td>
<td>71</td>
<td>30 (36)</td>
<td>41 (25)</td>
<td>.09</td>
</tr>
<tr>
<td>Adenosine-thallium</td>
<td>51</td>
<td>15 (18)</td>
<td>36 (22)</td>
<td>.41</td>
</tr>
<tr>
<td>Dipyridamole-thallium</td>
<td>122</td>
<td>41 (49)</td>
<td>81 (50)</td>
<td>.82</td>
</tr>
<tr>
<td>Dipyridamole-sestamibi</td>
<td>31</td>
<td>15 (18)</td>
<td>16 (10)</td>
<td>.08</td>
</tr>
</tbody>
</table>
who underwent coronary angiography in the low-risk group ($P=.03$). Three-vessel disease was somewhat more likely in these high-risk subgroups than in the low-risk group, but this difference did not reach significance (32% versus 8%, $P=.09$). Of the 7 patients in the high-risk subgroup 1c (cardiomyopathy) who underwent coronary angiography, 5 had significant coronary artery disease, and 2 had three-vessel disease.

### Outcome

The number of events in each group and subgroup is shown in Table 4.

There were 38 deaths (45%) in the high-risk group versus only 31 in the low-risk group (19%). This difference was even greater for cardiac deaths: 19 (23%) in the high-risk group and 6 (4%) in the low-risk group. Noncardiac deaths were common in both groups, reflecting the advanced age of the population.

### TABLE 3. Number of Patients With Various Coronary Angiographic Results Within Each Patient Subgroup

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Diseased Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0</td>
</tr>
<tr>
<td>1b</td>
<td>20</td>
</tr>
<tr>
<td>1c</td>
<td>137</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>

Three-year overall survival was 57% in the high-risk group compared with 87% in the low-risk group ($P<.0001$) (Fig 1). The total number of hard events (cardiac death or nonfatal myocardial infarction or cardiac transplant) in the high-risk group was 27 (32%) versus only 9 (6%) in the low-risk group. Three-year survival free of hard events was 55% in the high-risk group compared with 93% in the low-risk group ($P<.0001$) (Fig 2).

The total number of combined hard and soft events (cardiac death or myocardial infarction or cardiac transplant or late revascularization) in the high-risk group was 31 (37%) versus only 21 (13%) in the low-risk group. Three-year survival free of hard and soft events was 49% in the high-risk group compared with 87% in the low-risk group ($P<.0001$) (Fig 3).

With a multivariate analysis, the high-risk definition had significant incremental value compared with age, sex, diabetes, and previous myocardial infarction for the prediction of each of the three end points (Table 5).

### Secondary Analyses

Post hoc analysis was performed to compare the overall survival of our total study group to the survival of a US age-matched population. The total group had a lower overall survival than an age-matched population ($P<.0001$) (Fig 4). On the other hand, the overall survival of the low-risk group was not significantly different from that of the age-matched population ($P=.86$) (Fig 5).

Post hoc analysis was performed to compare patients in the low-risk group with a normal perfusion study to patients in the low-risk group with an abnormal perfusion study for the three
TABLE 4. Number of Events in Each Group and Subgroup

<table>
<thead>
<tr>
<th>End Point</th>
<th>1a (n=28)</th>
<th>1b (n=36)</th>
<th>1c (n=20)</th>
<th>Group 1 (High Risk; n=84), n (%)</th>
<th>Group 2 (Low Risk; n=161), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td>17</td>
<td>13</td>
<td>8</td>
<td>38 (45)</td>
<td>31 (19)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>19 (23)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>7 (8)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cardiac transplant</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Late revascularization (CABG or PTCA)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4 (5)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Hard events</td>
<td>11</td>
<td>10</td>
<td>6</td>
<td>27 (32)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Hard or soft events</td>
<td>12</td>
<td>12</td>
<td>7</td>
<td>31 (37)</td>
<td>21 (13)</td>
</tr>
<tr>
<td>Early revascularization (before 3 months)</td>
<td>3</td>
<td>10</td>
<td>2</td>
<td>15 (18)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.

end points. There was no significant difference between the two groups in overall survival or survival free of hard events.

Post hoc analysis of the three high-risk subgroups was performed. Overall survival was significantly different among the 28 patients in group 1a (large severe fixed defect, 3-year survival of 38%), the 36 patients in group 1b (large reversible defect, 3-year survival of 65%), and the 20 patients in group 1c (dilated cardiomyopathy, 3-year survival of 66%) (P=.05). There was no significant difference among the three groups for the other two end points.

A sensitivity analysis was performed for the high-risk definitions with less stringent definitions. For group 1a, the definition was changed to a resting score of <49 and a reversibility score of ≤3. For group 1b, the definition was changed to a post-stress test defect score of <49 and a global reversibility of >3. For group 1c, the ejection fraction criterion was changed to 50%. With this definition, 96 patients were high risk, but the overall results did not change (Table 6).

A sensitivity analysis was also performed with more stringent definitions for high risk. For group 1a, the definition was changed to a resting score of <43 and a reversibility score of ≤7. For group 1b, the definition was changed to a post-stress test defect score of <43 and a reversibility score of >3. For group 1c, the ejection fraction criterion was changed to 40%.

With these definitions, 70 patients were defined as high risk, but the overall results did not change (Table 6).

Because of the known impact of left bundle-branch block on septal segments, another analysis was performed, during which the five septal segments were omitted from consideration. The maximum global score then became 36 (9×4). For group 1a, the definition was changed to a resting score of <30 and a reversibility score of ≤3. For group 1b, the definition was changed to a post-stress test defect score of <30 and a reversibility score of >3. The definition for group 1c did not change. With these definitions, 80 patients were identified as high risk. Once again, the overall results did not change (Table 6).

Discussion

The current study is one of the largest reported studies on patients with left bundle-branch block and the first to examine the prognostic value of pharmacological perfusion imaging. These data document the benefit of vasodilator perfusion imaging in predicting outcome in patients with left bundle-branch block. The overall survival of our study group is significantly lower than that expected in an age-matched population, confirming that the presence of left bundle-branch block is a significant risk factor. The sensitivity analyses performed with less stringent and more stringent definitions for high risk further confirm the robustness of the findings.

Figure 1. Overall survival for the low- (solid line) and high- (dotted line) risk groups. There was a highly significant difference (P<.0001) between the two groups. The curves are truncated at 3 years because there were <10 patients followed for 4 years in the low-risk group.

Figure 2. Survival free of hard events (cardiac death, nonfatal myocardial infarction, cardiac transplantation) in the low- (solid line) and high- (dotted line) risk groups. Three-year survival free of hard events was 55% in the high-risk group and 93% in the low-risk group (P<.0001). Patients were censored at the time of revascularization.
branch block is generally associated with a worse prognosis. However, our study was unique because it used vasodilator perfusion imaging to differentiate between two groups of individuals with left bundle-branch block. The highly significant differences in all events between high- and low-risk groups suggest that this categorization is clinically useful in predicting outcome of patients with left bundle-branch block. The highly significant differences in all events between high- and low-risk groups suggest that this categorization is clinically useful in predicting outcome of patients with left bundle-branch block. The low-risk group had an overall survival that was not significantly different compared with the expected survival in an age-matched population. Most of the deaths in this group were noncardiac, reflecting the advanced age of the population. The hard cardiac event rate in the low risk group was 7% over 3 years or <2.4% per year. Such patients can be reassured from a cardiac standpoint, at least for this time period. Although some of these patients have coronary artery disease, it does not appear to be prognostically important. The overall survival and survival free of hard cardiac events were not significantly different between the low-risk group with a normal perfusion study and the low-risk group with a mildly abnormal perfusion study. Thus, our definition of low risk is more inclusive and therefore more widely applicable than a normal scan alone. The sensitivity analyses would suggest that the exact cutoffs used to define the high-risk group are not critical because most patients will be low risk regardless of the cutoffs used.

Patients with high-risk scans in the current study constituted about one third of the study group. They clearly have a very adverse prognosis with a high cardiac event rate over the next few years. Such patients would appear to merit further cardiac evaluation and additional management to try to improve their prognosis. The details of the strategy to be followed would probably vary according to the high-risk subgroup. Patients in subgroup la with a large reversible defect (the largest subgroup) would presumably undergo coronary angiography and possible revascularization with either angioplasty or bypass grafting. Patients in subgroup Ic with presumed dilated cardiomyopathies would probably merit intensive medical management, as well as consideration for cardiac transplantation if their symptoms and LV dysfunction were severe enough. Patients in subgroup Ib with a large severe perfusion defect without much reversibility would presumably also be candidates for intensive medical management of congestive heart failure and possible cardiac transplantation. The most appropriate management strategy to be followed in each high-risk subgroup will remain a matter of some clinical judgment until further studies are performed to clarify this issue.

Left bundle-branch block is often due to ischemic lesions of the left bundle. Such lesions may be due to coronary artery disease, especially disease of the left anterior descending artery. However, many patients with left bundle-branch block do not have coronary artery disease. Other causes should be considered in the evaluation of patients with left bundle-branch block, including aortic stenosis and calcification of the aortic valve.
annulus, hypertension, and idiopathic dilated cardiomyopathy. Left bundle-branch block is sometimes discovered on routine ECGs in patients without clinical evidence of heart disease.

The prognosis of patients with left bundle-branch block has long been debated. Many previous studies suggested that patients with left bundle-branch block have a similar prognosis compared with patients without left bundle-branch block. Others have suggested that the presence of left bundle-branch block is an adverse prognostic sign with incremental value compared with clinical and angiographic variables. In the Framingham Study, 55 patients with left bundle-branch block had a long-term (18-year) cardiac mortality that was significantly higher ($P<.001$) than patients without left bundle-branch block. In a cross section of the population, patients with left bundle-branch block tend to have a worse prognosis compared with others without left bundle-branch block, as demonstrated in the Framingham Study. However, in selected patients without clinical evidence of heart disease, such as the naval aviators examined by Smith et al, the mere presence of left bundle-branch block was not necessarily associated with a worse prognosis.

The contrasting difference in prognosis among different studies of patients with left bundle-branch block is most probably due to selection bias. Rodstein et al analyzed mortality figures for life insurance applicants with left bundle-branch block. In these two series, patients with left bundle-branch block who had no other evidence of major cardiovascular disease had only a slight increase in mortality compared with others without left bundle-branch block during an average 8- to 10-year follow-up period. In contrast, there was a much higher mortality for those insurance applicants with left bundle-branch block and clinical heart disease compared with those with left bundle-branch block without evidence of heart disease. Thus, the cause of left bundle-branch block is very heterogeneous, and the prognosis of patients with left bundle-branch block cannot be adequately assessed without a full clinical evaluation. Exercise perfusion imaging has been used in an attempt to detect coronary artery disease in patients with left bundle-branch block. Exercise thallium-201 imaging and technetium-99m sestamibi imaging in patients with left bundle-branch block have not proven to be useful, primarily because of increased incidence of false reversible perfusion defects, primarily in the septum. Abnormal perfusion in the anterior wall or the apex was suggested as an indicator of disease in the left anterior descending coronary artery, but this finding was not confirmed by others. We used adenosine or dipyridamole perfusion imaging because of its proven diagnostic accuracy in detecting coronary artery disease in patients with left bundle-branch block. Dipyridamole–thallium-201 SPECT perfusion imaging was first shown to be superior to exercise thallium-201 SPECT perfusion imaging by Burns et al and subsequently confirmed by others. Adenosine–thallium-201 SPECT imaging has also proved superior to exercise–thallium-201 SPECT in patients with left bundle-branch block.

Several previous studies have shown the value of dipyridamole thallium perfusion imaging in patients with LV dysfunction to distinguish ischemic from nonischemic origins. Eichhorn et al demonstrated that the stress perfusion defect was significantly smaller in patients with dilated cardiomyopathy compared with those with ischemic heart disease. Chikamori et al demonstrated that patients with dilated cardiomyopathy had a significantly lower prevalence of reversible defects compared with patients with coronary artery disease. This same study demonstrated that dipyridamole-thallium imaging had incremental diagnostic value when added to clinical and ECG variables.

This study has several limitations. Coronary angiography was not routinely done on every patient in the study group, so the relationship between the scan results and coronary anatomy cannot be fully examined. Our study group consisted of patients seeking treatment at the Mayo Clinic, a tertiary care center, and does not represent a true cross section of the population at large. To avoid such referral bias would be difficult. An ideal study would enroll patients with left bundle-branch block diagnosed with routine ECG screening on a large population. All patients would subsequently undergo vasodilator perfusion imaging plus

TABLE 6. Effect of Alternative Definitions of High-Risk Subgroups on Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Prospective</th>
<th>Less Stringent</th>
<th>More Stringent</th>
<th>Septum Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>84</td>
<td>96</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Low risk</td>
<td>161</td>
<td>149</td>
<td>175</td>
<td>165</td>
</tr>
<tr>
<td>3-y survival*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk, %</td>
<td>87</td>
<td>89</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>Low risk, %</td>
<td>57</td>
<td>57</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Adjusted $\chi^2$</td>
<td>10.9</td>
<td>11.5</td>
<td>15.1</td>
<td>14.8</td>
</tr>
<tr>
<td>3-y survival free of hard events*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk, %</td>
<td>93</td>
<td>93</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Low risk, %</td>
<td>55</td>
<td>61</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Adjusted $\chi^2$</td>
<td>18.1</td>
<td>12.0</td>
<td>14.4</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*For all four definitions, the differences in 3-year survival and 3-year survival free of hard events were highly significant ($P<.0001$).

†For all four definitions, the $\chi^2$ (adjusted for age, sex, diabetes, previous myocardial infarction, and hypercholesterolemia) in the multivariate analysis was highly significant ($P<.0001$).
coronary angiography and then be followed. The feasibility of such a perfectly designed study is problematic.

Of the 49 patients in groups 1a and 1b who underwent thallium imaging, 12 were studied before January 1, 1990, and therefore were not reinjected with thallium; these patients might have been classified differently if reinjection had been performed. Although we assessed the images for the presence of cardiac enlargement (which was required for group 1c), we did not routinely record the presence of transient ischemic dilatation, which was therefore not considered in any of the high-risk definitions.

Currently, many patients with left bundle-branch block undergo cardiac catheterization to establish the cause of this finding and their prognosis. Our results suggest the feasibility of vasodilator perfusion imaging as a noninvasive “gatekeeper” in such patients. Patients with left bundle-branch block who undergo vasodilator perfusion imaging and have low-risk results need not undergo cardiac catheterization. Such low-risk results occurred in about two thirds of our study population. In contrast, patients who belong to the high-risk group clearly merit further cardiac evaluation and appropriate management.

References

Prognostic Value of Vasodilator Myocardial Perfusion Imaging in Patients With Left Bundle-Branch Block
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