Prediction of Cardiac Events in Patients Having Left Bundle-Branch Block with/without Chest Pain Using Dipyridamole Technetium-99m-Sestamibi Myocardial Perfusion Imaging

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Key Words

Technetium-99m sestamibi • Myocardial perfusion scintigraphy • Dipyridamole • Left bundle-branch block • Coronary artery disease

Abstract

Objective: To determine the prognostic value of myocardial perfusion scintigraphy with dipyridamole stress in patients with preexisting left bundle-branch block (LBBB) with or without chest pain. **Subjects and Methods:** Seventy-six patients, mean age 53 ± 10 years, with preexisting LBBB underwent technetium-99m-sestamibi perfusion imaging with dipyridamole infusion protocol (0.56 mg/kg). Stress and rest single photon emission computed tomography (SPECT) images were interpreted by consensus of 2 experienced nuclear medicine physicians and classified as low-risk scans (normal myocardial perfusion scan, small reversible/small fixed defect) and high-risk scans (large, severe, fixed or reversible defect and dilated left ventricle cavity). The patients were followed up for 24 ± 8 months and occurrences of hard cardiac events (infarction or cardiac death) were noted. **Results:** Of the 76 patients, 52 (68%) had low-risk scans and the remaining 24 (32%) had high-risk scans. In the low-risk group, 1 (1.9%) cardiac death and 2 (3.8%) cases of nonfatal

myocardial infarction occurred, while in the high-risk group, 5 (20.8%) suffered cardiac death, and 3 (12.5%) nonfatal myocardial infarction. Overall survival rate was 98.1% in the low-risk group compared with 79.2% in the high-risk group with a significant difference of $p = 0.034$. Negative predictive value of normal myocardial perfusion scintigraphy for the occurrence of death was 100%. No significant difference in survival rate among patients with or without chest pain ($p = 0.31$) was observed. **Conclusions:** Myocardial perfusion imaging with dipyridamole provided important prognostic information in patients with LBBB; it was useful in stratifying the patients according to cardiovascular morbidity and mortality, and would thus allow the clinician to provide early treatment especially in the high-risk category.

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Introduction

The detection of myocardial ischemia in patients with preexisting left bundle-branch block (LBBB) remains a diagnostic challenge [1]. The diagnosis of myocardial ischemia in the presence of coexisting LBBB is complicated by the presence of baseline ST-T changes, that render the electrocardiogram (ECG) nondiagnostic and

treadmill exercise testing not useful in the diagnosis of coronary artery disease (CAD) [2]. The associations between LBBB and CAD have been examined in several studies [3–5], and it was shown in the Framingham Study that patients with LBBB were more likely to have or subsequently have advanced cardiovascular abnormalities than those with right bundle-branch block [5].

Myocardial perfusion scintigraphy (MPS) at stress and/or rest is often performed to detect CAD in patients with LBBB [6, 7]. However, stress scintigraphy is not specific for the frequent occurrence of septal, anterior, and apical defects in the absence of CAD. Specificity has been reported to be low primarily due to false-positive septal perfusion abnormalities [8]. But it has been shown that specificity can be improved using dipyridamole stress [9–11]. Pharmacological perfusion imaging has been shown to be useful for prognostic purposes in patients without LBBB [12]. There are only few studies examining the prognosis of patients with LBBB who underwent pharmacological stress of any sort [13, 14]. The purpose of our study was to determine the prognostic value of myocardial perfusion scintigraphy with dipyridamole stress in patients with preexisting LBBB with or without chest pain.

Subjects and Methods

Medical records from January 2002 to June 2004 were retrieved to select consecutive patients with complete LBBB with and without chest pain. The patients selected were those who had complete LBBB at the time of stress perfusion imaging with dipyridamole. LBBB was defined as follows: QRS duration >0.12 s; broad, notched, predominantly positive QRS complex in lead I and either lead V5 or V6; predominantly negative QRS complex in lead V1; 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. In addition the patients did not have obstructive lung disease and did not take coffee or theophylline products within 12–24 h. Patients with prior history of bypass surgery or coronary angioplasty, paced rhythm on the ECG, evidence of clinically significant valvular heart disease, active asthma and hypertrophic obstructive cardiomyopathy were excluded from the study.

Study Protocol

All patients underwent pharmacological stress using dipyridamole infusion (0.56 mg/kg over 4 min) followed by intravenous injection of 259 MBq (7 mCi) of technetium-99m (^{99m}Tc) sestamibi 3 min after the completion of dipyridamole infusion. Stress perfusion images were acquired 30 min later. Rest study was performed following a bolus injection of 888–968 MBq (24–28 mCi) ^{99m}Tc-sestamibi. Images were obtained 30–60 min after the injection.

Table 1. SPECT imaging variables

High-risk group
– Reversible defect involving four or more cardiac segments in one or more vascular distributions
– Extensive stress-induced hypoperfusion even in one territory
– Fixed defect involving three or more cardiac segments
– Patients with transient ischemic LV cavity dilatation from stress to rest (only visual interpretation)
Low-risk group
– Normal perfusion images with neither fixed nor reversible defect
– Small fixed defect, without additional reversible defects
– Reversible defects involving only one or two cardiac segments in a single coronary artery distribution

Single photon emission computed tomography (SPECT) study was performed with double-headed ECAM (Siemens) or Toshiba (GCA-7200A) gamma cameras, with high resolution, parallel hole collimator, using a 15% window centered on 140-keV photo peak. Acquisition was carried out in a step and shoot mode using 32 projections over a 180° noncircular orbit in a 64 × 64 matrix. Imaging time was 30 s per projection. Images were reconstructed using a filtered back-projection algorithm with no attenuation correction, with a Butterworth filter (cutoff frequency 0.4, order 8). The same acquisition time and image filters were used for both stress and rest images.

Regional myocardial perfusion was assessed using the 17-segment model recommended by the Cardiac Imaging Committee of the American Heart Association and the American Society of Nuclear Cardiology [15]. Each segment was scored using a 5-point scoring system (normal radiotracer uptake: 0; mildly reduced uptake: 1; moderately reduced tracer uptake: 2; severely reduced tracer uptake: 3; and absent radiotracer uptake: 4) [16]. Perfusion defect was considered fixed when there was no difference between rest and stress score, while reversible defect was defined as a segment with higher score on stress images. Ischemia was defined as a change of one or more grades between rest and stress images. Interpretation of tomographic images was done by consensus of 2 experienced nuclear medicine physicians unaware of other patient data. Intraobserver and interobserver variabilities for the segmental readings were 2.1 and 2.6%, respectively. Images were classified as low or high risk based on previously published criteria [17–19] as summarized in table 1.

Patient Follow-Up

Patients were followed up for an average of 24 ± 8 months (range 12–36 months, median 24 months). Follow-up for hard cardiac events (myocardial infarction, MI, or cardiac death) was initially done by telephone and further confirmed by medical records, ensuring a minimal follow-up of 1 year for all patients. The following events were recorded during follow-up: cardiac death (due to fatal MI), noncardiac death, nonfatal MI coronary angiography, and coronary artery bypass graft or coronary angioplasty.

Table 2. Baseline data

Gender	
Males/females	44/32
Age, years	53 ± 10
Risk factors	
Hypertension	9 (12)
Diabetes	5 (7)
Hypercholesterolemia	7 (9)
Smoking	11 (14)
Medical history	
Family history of CAD	12 (16)
Previous MI	2 (3)
Clinical presentation at inclusion	
Asymptomatic	25 (33)
Atypical chest pain	33 (43)
Typical angina	18 (24)
Dyspnea	3 (4)

Age is given as mean and standard deviation; other parameters are values with percentages in parentheses.

Statistical Analysis

Statistical analysis was performed with SPSS software version 10.0. Kaplan-Meier survival curves were computed for the occurrence of major events. Comparison of survival curves was performed using a single-variable log-rank test. Multivariate stepwise Cox regression analyses were computed for the determination of independent predictors of events. The most relevant variables were entered into the model, i.e., age, family history, diabetes, hypertension, hypercholesterolemia and image variables. Cochran-Mantel-Haenszel analysis was used to compare the cardiac mortality between low-risk and high-risk groups.

Results

Seventy-six patients (44 males, 32 females, mean age 53 ± 10 years, range 39–72 years) were selected. Of these, 52 (68%) had low-risk scans and the remaining 24 (32%) were in the high-risk group. Detailed demographic and clinical characteristics are given in table 2.

Of the 52 patients in the low-risk group, cardiac death was observed only in 1 (1.9%) patient with atypical chest pain, while of the 24 patients in the high-risk group cardiac death occurred in 5 (20.8%) patients (3 were asymptomatic and 2 had atypical chest pain) (table 3). Nonfatal MI occurred in 2 and 3 patients of the low- and high-risk groups, respectively.

There was no noncardiac death in the study group. Overall survival rate was 98.1% in the low-risk group compared with 79.2% in the high-risk group (fig. 1).

Fig. 1. Kaplan-Meier survival curves for the occurrence of cardiovascular deaths in low-risk (solid line) and high-risk groups (dashed line). The annual mortality rate was 0.95% in patients of the low-risk group and 10.5% in the high-risk group (odds ratio = 13.42).

Comparison of Kaplan-Meier survival curves using log-rank test showed that there was a significant difference in the survival rate of low-risk and high-risk groups ($p = 0.0338$). The annualized rates of observed cardiac mortality for the low-risk and high-risk groups were 0.95 and 10.5%, respectively. Cochran-Mantel-Haenszel statistics showed that there was a significant difference in cardiac mortality rate between low-risk and high-risk groups ($p = 0.021$) with an odds ratio of 13.42. There was a significant difference in hard event rate (cardiac deaths and nonfatal MIs): in the high-risk group it was 8 (33%) versus only 3 (6%) in the low-risk group ($p < 0.05$) (fig. 2).

In the high-risk group, 6 had typical chest pain, 8 atypical chest pain and 10 were asymptomatic. Among the low-risk group 15 were symptomatic, 12 had typical chest pain and 25 atypical chest pain. Overall survival rate was 89% in the typical chest pain subgroup compared with 88% in the asymptomatic subgroup and 96% in the atypical chest pain group (fig. 3). Comparison of Kaplan-Meier survival curves using log-rank test showed that there was no significant difference in survival rate among the chest pain subgroup ($p = 0.3064$).

Multivariate analysis using Cox regression analysis (table 4) showed that chest pain was not an independent

Fig. 2. Kaplan-Meier survival curves for the occurrence of hard events (death or MI) in low-risk (solid line) and high-risk groups (dashed line). The event rate was 6% in patients of the low-risk group and 33% in the high-risk group (odds ratio = 6.725).

Fig. 3. Kaplan-Meier survival curves for the occurrence of cardiovascular deaths in the typical chest pain group (solid line), the asymptomatic group (dashed line) and the atypical chest pain group (dotted line). Comparison of Kaplan-Meier survival curves using log-rank test showed that there is no significant difference in survival rate among the groups ($p = 0.3064$).

Table 3. Events at follow-up

Event	n (%)	Annual event rate, %/year
Death		
Low-risk group	1 (1.9)	0.95
High-risk group	5 (20.8)	10.5
Acute MI		
Low-risk group	2 (3.8)	
High-risk group	3 (12.5)	
Major event (death or MI)		
Low-risk group	3 (6)	
High-risk group	8 (33)	

predictor of cardiac death, while patient sex was a significant factor as 5 deaths occurred in males. With regard to other risk factors analyzed including age, family history, diabetes, hypertension, hypercholesterolemia, the number of patients with one or more of these coexistent risk factors was too small and therefore not useful for a valid statistical conclusion (table 5).

Table 4. Events at follow-up in the low-risk and high-risk group with/without chest pain

		Cardiac death		Total
		no	yes	
Low-risk group	Asymptomatic	15	0	15
	Typical chest pain	12	0	12
	Atypical chest pain	24	1	25
High-risk group	Asymptomatic	7	3	10
	Typical chest pain	4	2	6
	Atypical chest pain	8	0	8

Coronary angiography performed within 3 months of the perfusion study in only 36 patients (high-risk group: $n = 22$, low-risk group: $n = 14$) showed that 12 had normal coronaries while 24 had significant coronary artery stenosis in one or more coronary artery territories. The sensitivity and specificity of ^{99m}Tc -MIBI scintigraphy for detecting $>50\%$ stenosis in the LAD territory were 85.7 and

Table 5. Multivariate results

	Total (n = 76)	Events (n = 6)	No events (n = 70)	χ^2	Coefficient	p value
Sex, % men	58	83	52	5.01	0.833	<0.001
Age	53 $\pm$ 10	56 $\pm$ 6	52 $\pm$ 10	23.25	56	0.004
Hypertension	9 (12)	1 (17)	8 (11)	1.01	0.167	0.363
Diabetes	5 (7)	0	5 (7)	0.001	–	NS
Hypercholesterolemia	7 (9)	0	7 (10)	0.001	–	NS
Family history of CAD	12 (16)	2 (33)	10 (14)	–	–	NS
Previous MI	2 (3)	0	2 (3)	1.002	0.162	NS
Chest pain						
Typical	18 (24)	2 (33)	16	–	–	NS
Atypical	33 (43)	1 (17)	32	–	–	NS
Asymptomatic	25 (33)	3 (50)	2	–	–	NS
Dyspnea, high- vs. low-risk scan	3 (4)	2 (33)	1 (2)	0.001	–	NS

Age is given as mean $\pm$ SD, other parameters are values with percentages in parentheses. Event = Cardiac death; NS = not significant.

62.5%, respectively, when anterior wall, apical and/or septal hypoperfusion were taken to represent CAD in the LAD territory. For LCX and RCA the values were 92.85/87.5% and 89.2/75%, respectively.

Discussion

The ECG changes induced by LBBB render stress ECG uninterpretable by masking the ST depression of stress-induced ischemia. Thus basal and stress ECG has persistently shown low sensitivity and specificity in diagnosing CAD in this group of patients [20]. Moreover exercise MPS is also not as effective because of its high likelihood of recording artifactual, reversible septal-perfusion defects [21]. Possible explanations for the heart-rate-dependent artifact include prolonged compression of the septal perforators, reduced diastolic flow, small-vessel CAD, septal fibrosis, and wall motion artifact [22]. Hence, MPS with coronary vasodilators (dipyridamole or adenosine) is the preferred noninvasive diagnostic modality for this population because of its superior accuracy and much lower incidence of artifactual reversible perfusion defects [23].

In our study, when patients were stratified according to the presence or absence of chest pain, no significant survival benefit was observed between the two groups ($p = 0.31$). Significant difference was seen in the survival rate of LBBB patients categorized as having low risk or high risk ($p = 0.0388$) based on perfusion abnormalities

on dipyridamole MPS. This indicates that in these patients, findings on dipyridamole MPS were a better predictor of events compared to the presence or absence of chest pain.

The overall better survival rate in the low-risk versus the high-risk group of our study confirmed the results reported in previous studies [13, 14]. Nigam and Humen [14] described the prognostic role of dipyridamole MPS in LBBB patients. In their study, cardiac mortality rate with a normal or low-risk scan was 0.85% per year in contrast to a rate of 9.9% per year in patients with a high-risk scan. Our annualized cardiac mortality rates are in close agreement with those of Nigam and Humen [14]. Similarly the overall survival rate of 98.1% in the low-risk group versus 79.2% in the high-risk group in our study is comparable to results previously reported by Hisham et al. [13] (57% in the high-risk vs. 87% in the low-risk group). Another study reported that patients with abnormal myocardial perfusion scans have an increased rate of cardiac death and nonfatal infarction during follow-up [18]. The greater the extent of stress-induced hypoperfusion and reversibility, the greater is the probability of an event. In our study, patients with normal small reversible/small fixed defect had a good prognosis and prolong survival. These validated findings thus lend support to a strategy incorporating myocardial perfusion imaging as the initial test for detecting CAD and assessing prognosis in patients with LBBB with/without chest pain and suspected CAD.

This study clearly showed the importance of vasodilator perfusion imaging in predicting outcome in patients with LBBB. These highly significant differences in all events between high- and low-risk groups suggest that the categorization of patients with the help of vasodilator perfusion imaging is invaluable in the management of patients with LBBB. The majority of LBBB patients (68%) were in the low-risk group. The hard cardiac event rate in this group was 6% over 2 years. Such patients can be reassured from the cardiac standpoint at least for this time period. Although some of these patients have CAD, low-risk scan and low cardiac event rate clearly suggest that this is not prognostically significant. Our results suggest the feasibility of vasodilator perfusion imaging as a non-invasive 'gatekeeper' in such patients. Patients with LBBB and chest pain who undergo vasodilator perfusion imaging and have low-risk results need not undergo cardiac catheterization. In contrast, patients who belong to the high-risk group clearly merit further cardiac evaluation and appropriate management.

The limitations of our study include the population size and not using gated MPS that would have allowed the

combined analysis of myocardial perfusion and wall motion and might have provided better results. Coronary angiography was not routinely performed on every patient in the study group.

Conclusions

MPS with dipyridamole is an important tool for providing prognostic information and predicting future cardiac events in patients with or without chest pain and LBBB. Patients with a low-risk scan have good prognosis while those with a high-risk scan have a poor prognosis. The extent of hypoperfusion on ^{99m}Tc -sestamibi images can be factored into a decision-making process relative to selecting medical therapy or revascularization. Patients with normal and mild reversible perfusion defects judged not to be high risk can most often be treated medically, whereas patients with high-risk SPECT findings are candidates for further invasive strategies.

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