

Can Gated-SPECT identify Coronary Artery Disease in patients with Left Bundle Branch Block (LBBB)?

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Abstract

Myocardial perfusion scintigraphy often reveals perfusion defects in septal/ anterior segments of left ventricular myocardium in patients with left bundle branch block (LBBB) even in the absence of coronary artery disease (CAD). This study investigated whether gated single photon emission computed tomography (Gated-SPECT) could identify CAD in LBBB patients. A total number of 46 LBBB patients (29 women and 17 men; mean age = 63.8±11.6 years) in two Groups, e.g., Group - 1 (n=21, CAD, with ≥70% luminal narrowing in at least one vessel), and Group-2 (n=25, normal coronary arteries), underwent Tc-99m-Sestamibi Gated-SPECT studies in conjunction with both dipyridamole pharmacological and treadmill exercise tests. Qualitative analysis of left ventricular myocardium in 17 segments scored perfusion as normal to fixed defects (0-3); motility as normal to diskynetic (0-5); and thickening as present or absent (0-1). Left ventricular ejection fraction (LVEF) was also estimated in all cases performed after tests. Qualitative analyses of myocardial perfusion, motility and thickening revealed statistically significant differences between Group-1 and Group-2 patients in the inferior segment ($p \leq 0.01$), but none in anterior, lateral and apical segment ($p > 0.05$), in both dipyridamole as well as treadmill exercise tests. However myocardial thickening was found to be significantly different in the septal segment ($p = 0.05$), in both tests. The estimated LVEF also did not reveal any significant difference between the two groups.

Results of this study revealed that septal myocardial thickening can identify CAD in LBBB patients. LBBB did not influence CAD detection in the inferior segment on Gated-SPECT.

Keywords: Gated SPECT, Myocardial perfusion scintigraphy, LBBB, Coronary artery disease

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Introduction

Myocardial perfusion scintigraphy (MPS) is widely used for diagnosis and risk stratification in coronary artery disease (CAD), and when left bundle-branch block (LBBB) is present, investigation of myocardial ischemia is mandatory. Non-invasive diagnosis of CAD is however, a clinical and methodological dilemma, because fixed or reversible septal perfusion defects, either alone or in association with perfusion defects in the anterior wall and apex has been demonstrated by MPS even in the absence of CAD (1-8). Such alterations reduce the specificity of MPS (10% to 52%), especially when performed with an exercise stress test (1,3,4-14), mainly because of the higher heart rate achieved during the exercise test, different from the 75-90% specificity when performed in conjunction with dipyridamole stress test (10,11,15).

Gated-SPECT may be a useful tool for patients with LBBB, since the concomitant assessment of several different parameters would probably yield less false positive studies resulting in more accurate diagnosis. We compared the results of gated myocardial perfusion SPECT (G-SPECT) performed with both dipyridamole pharmacological stress as well as treadmill exercise tests (ET) with the aim of identifying determinants or parameters that could differentiate between presence or absence of CAD in patients with LBBB.

Materials and Methods

Patients:

The study enrolled 46 patients (29 women, 17 men) with LBBB on rest ECG, divided into two Groups. Group I consisted of 21 patients (mean age 68.62 ± 10.45 years)

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with coronary artery disease (CAD) having $\geq 70\%$ luminal narrowing in at least one vessel, and who underwent radionuclide studies as a part of routine evaluation. Group II consisted of 25 asymptomatic patients or patients with atypical chest pain (mean age 59.76 ± 10.79 years) with abnormal MPS, but angiographically normal coronary arteries. Patients with previous myocardial infarction or coronary artery bypass graft, left ventricle ejection fraction (LVEF) lower than 50% on echocardiography (Teichholz), cardiomyopathy other than non-ischemic and complex arrhythmias were excluded. All patients underwent cardiac catheterization and myocardial gated-SPECT with both treadmill exercise test (ET) and dipyridamole pharmacologic stress test performed on two consecutive days. All patients gave informed consent to participate in the study. The protocol was approved by the scientific committee of the Heart Institute and the ethics committee of the University of Sao Paulo Medical School Hospital before the start of the study.

Myocardial gated-SPECT:

A two-day protocol was used to perform gated-SPECT studies. Rest/dipyridamole was performed on the first day. The doses of Tc-99m sestamibi used for the rest and dipyridamole studies were 10 mCi (370 MBq) and 30 mCi (1111 MBq) respectively. Rest images were acquired at fifty minutes after injection of radiotracer. For the dipyridamole stress test dipyridamole was infused intravenously (0.56 mg/Kg) over a period of four minutes. Blood pressure, heart rate and ECG were recorded at 2 and 4 minutes and at 10 minutes after the end of infusion. The maximum time to acquire images was 25 minutes after radiotracer injection. On the second day, the patients underwent treadmill exercise tests. A computerized Fukuda Denshi (Tokyo, Japan) ML 8000 Stress Test Computer System and Bruce's protocol were used (16), with 12-lead ECG simultaneously recording at rest, at the end of each stage and at every two minutes during recovery. Blood pressure was automatically measured at rest and every 90 seconds (Collin system, model STBP 780). All patients were instructed to discontinue beta-adrenergic blocker or calcium channel blocker medications for 3 days, and long-acting nitrates for 6 hours before testing. Treadmill exercise tests were discontinued whenever the maximal predicted heart rate was achieved, or some criteria for interruption developed (14). At peak exercise, Tc-99m sestamibi was injected intravenously and exercise was continued for an additional minute. Gated-SPECT images were also acquired within 25 minutes after radiotracer injection.

Image acquisition and processing:

Gated-SPECT images were acquired using a dual-head gamma camera (VERTEX PLUS MCD/AC, ADAC Laboratories) equipped with a low-energy and high-resolution collimator, setting the energy photo-peak at 140 KeV with a 15% symmetric window. Data were acquired in

sixty-four projections using a 64 x 64 matrix at a rate of 30 seconds/frame for rest and stress images, over an 180° arch from 45° right anterior oblique to 45° left posterior oblique (step/shoot acquisition mode). Images acquired at rest and at both stress tests were gated at 8 frames per cardiac cycle with an R-wave trigger. Routinely, a pre-filter for processing images was used (Butterworth order 5, cutoff 0.7 Nyquist).

Image interpretation:

After image reconstruction, transverse slices were generated every 6.09 mm along the main axis of the heart corresponding to the horizontal long axis, short axis and vertical long axis. Tomograms were divided into 17 segments corresponding to the 5 regions of the left ventricle (anterior, septal, inferior, lateral and apical). Two experienced nuclear medicine physicians qualitatively interpreted the images, as well as gated-SPECT parameters, blinded to the clinical and angiographic data of the patients. Gated-SPECT images were analyzed in a cine mode. A 4-point scoring system (0-normal, 1-mild, 2-moderate and 3-severe or fixed defect) was used for assessment of perfusion; wall motion (WM) was scored on a 6-point system (0-normal, 1-mild, 2-moderate, 3-severe hypokinesis, 4-akinesis, 5-dyskinesis) in the same regions and wall thickening (WT) was scored (0-normal, 1-absent) on the basis of visual assessment of brightening of myocardial wall in systole. LVEF was obtained at rest and after stress phases through QGS software (17).

Coronary Angiography:

Coronary angiography was performed using the technique described by Sones (18), within 180 days of gated-SPECT study, in all 46 patients. A significant coronary stenosis was defined as $\geq 70\%$ luminal diameter narrowing, in one or more of the major vessels in one angiographic projection. Patients were categorized as Group-I (G-I), if they had evidence, or Group-II (G-II) in case of no evidence of coronary stenosis.

Statistical Analysis:

Continuous variables were expressed as mean \pm SD. Treadmill exercise test (ET) and dipyridamole test data were evaluated using Student *t* test or χ^2 test for continuous and categorical variables, respectively. Fisher exact test or χ^2 test were used to compare the categorical variables in G-I and G-II, and analysis of variance (ANOVA) to compare LVEF in the groups. A *p* value of ≤ 0.05 was considered statistically significant. Calculations were made using the Statistical Analysis System software.

Results

Clinical and electrocardiographic characteristics:

Of the 46 patients with LBBB, 21 (45.6%) had CAD and 25 (54.4%) had normal coronary arteries. Mean age of patients in G-I was significantly higher than those in G-II ($68.62 \pm$

Clinical Data	Group- I	Group- II
Age (mean \pm SD)	68.6 \pm 10.4	59.8 \pm 10.8
Male	12 (57.1%)	5 (20%)
Female	9 (42.9%)	20 (80%)
Systemic Hypertension	19 (90.5%)	21 (84%)
Dyslipidemia	14 (66.6%)	11 (44%)
Diabetes Mellitus	13 (61.9%)	5 (20%)
Smokers	3 (14.2%)	3 (12%)
Coronary Angiography		
- One-vessel disease	6 (28.6%)	-
- Two-vessel disease	9 (42.8%)	-
- Three-vessel disease	6 (28.6%)	-

Group-I – patients with coronary artery disease

Group-II – patients without coronary artery disease

SD - Standard deviation.

Table 1. Clinical and angiographic data of patients.

10.45 vs. 59.76 \pm 10.79 years respectively, $p < 0.0001$). Patients in G-I were predominantly male (57%), while those in G-II were predominantly female (80%). Distribution of the risk factors for CAD and coronary angiographic data are displayed in Table 1.

Exercise test:

All the patients achieved at least 85% of the maximal predicted heart rate. Exercise-induced angina was more frequent in G-I (28.6%) than in G-II (4%), $p < 0.001$. Time of tolerance to exercise and maximal heart rates were observed to be significantly greater in G-II than in G-I (355 \pm 100 sec vs. 430 \pm 106 sec, $p = 0.01$; and 135.6 \pm 17.1 vs. 145.9 \pm 18.1, $p = 0.05$), and there was no statistically significant difference in maximal blood pressure between the two groups (192.4 \pm 24.1/86.5 \pm 16.5 vs. 182.7 \pm 21.3/88.1 \pm 12.0 mmHg, $p = 0.86$).

Perfusion scintigraphy and gated-SPECT:

Mean interval from the time of radiotracer injection to acquisition of images was 17.3 \pm 3.1 min in case of treadmill exercise test, and 17.6 \pm 5.1 min in case of dipyridamole infusion. According to the results of MPS, there were no statistically significant differences between G-I and G-II in the anterior, septal, lateral and apical segments, both with treadmill exercise ($p = 0.58, 0.65, 0.08$ and 0.08 , respectively) and dipyridamole pharmacologic stress studies ($p = 0.42, 0.75, 0.12$ and 0.08 , respectively). Only the inferior segments revealed statistically significant differences in scintigraphic parameters between Groups I and II ($p = 0.0001$), for both stress tests (Table 2).

Wall motion (WM) – WM results matched the results of perfusion for those segments. Except for the inferior segment ($p = 0.01$), WM also did not discriminate between patients with or without CAD in the presence of LBBB, for both stress tests (Table 2).

Wall thickening (WT) – WT results were the same on both stress tests (Table 2). There were no statistically significant

differences between Groups I and II in the anterior, lateral and apical segments ($p = 0.31, 1.00$ and 0.31 , respectively). However, in the septal segment WT was found to be the best gated-SPECT variable in discriminating between patients with and without CAD in the presence of LBBB ($p = 0.05$). Sensitivity and specificity of myocardial perfusion, wall motion and thickening according to the coronary artery territory are given in Table 3.

Left ventricular ejection fraction – LVEF was 46% \pm 16%, 42% \pm 16% and 47% \pm 18% in Group-I and 49% \pm 12%, 48% \pm 13% and 52% \pm 13% in Group-II at rest, after treadmill exercise and dipyridamole stress respectively. These results were similar in both groups, without statistically significant difference ($p = 0.28$). However, there was a significant reduction of LVEF, steeper in Group-I after treadmill exercise stress when compared with rest, and a significant LVEF increase after dipyridamole stress ($p = 0.02$).

Discussion

In spite of the low prevalence of LBBB in the general population (19), several studies have reported its frequent association with heart disease. In the Framingham study, CAD was found in 40% of patients with LBBB, associated with a fourfold higher risk of cardiovascular mortality (9). Dynamic alterations of cardiac cycle produced by LBBB are known. These are: 1. Asynchrony of contraction in the ventricles, with the left ventricle contracting on an average 85 ms after the beginning of contraction in the right ventricle; 2. Reduction of left ventricle (LV) diastolic time; 3. Abnormal septal motility, because its depolarization only happens at the end of LV systole, causing compression of septal arteries at the beginning of LV diastole, when the coronary perfusion occurs; 4. Abnormal septal ejection fraction, because its abnormal motility causes loss of septal contribution to the global LVEF and reduced values even in the absence of heart disease (3,4,15,20). Such functional alterations also reflect upon noninvasive diagnostic

	Anterior			Septal			Inferior			Lateral			Apical		
	G-I	G-II	p	G-I	G-II	p	G-I	G-II	p	G-I	G-II	p	G-I	G-II	p
Perfusion															
- Exercise test	8 (38.1%)	5 (20%)	0.58	13 (61.9%)	18 (72%)	0.65	11 (52.4%)	-	0.0001*	4 (19%)	1 (4%)	0.08	4 (19%)	1 (4%)	0.08
- Dipyridamole	8 (38.1%)	4 (16%)	0.42	12 (57.1%)	15 (60%)	0.75	11 (52.4%)	-	0.0001*	4 (19%)	1 (4%)	0.12	4 (19%)	1 (4%)	0.08
Wall Motion															
Exercise test	4 (19%)	3 (12%)	0.19	14 (66.7%)	16 (64%)	0.83	6 (28.6%)	2 (8%)	0.01*	2 (9.5%)	1 (4%)	0.43	6 (28.6%)	3 (12%)	0.15
- Dipyridamole	4 (19%)	1 (4%)	0.12	13 (61.9%)	13 (52%)	0.93	6 (28.6%)	2 (8%)	0.01*	2 (9.5%)	1 (4%)	0.43	6 (28.6%)	2 (8%)	0.07
Wall Thickening															
- Exercise / dipyridamole	3 (14.3%)	1 (4%)	0.31	7 (33.3%)	2 (8%)	0.05*	5 (23.8%)	-	0.01*	-	1 (4%)	1.00	3 (14.3%)	1 (4%)	0.31

G-I (Group-1) – patients with coronary artery disease; G-II (Group-2) – patients without coronary artery disease; * $p \leq 0.05$

Table 2. Distribution of perfusion defects, abnormal wall motion and absence of thickening according to the regions obtained in the Gated-SPECT in patients with left bundle branch block, with and without coronary artery disease.

	LDA		RCA		CX	
	SEN	SPE	SEN	SPE	SEN	SPE
Perfusion						
- Exercise test	68.4%	28%	69.2%	100%	36.3%	96%
- Dipyridamole	64.7%	40%	66.6%	100%	36.3%	96%
Wall Motion						
- Exercise test	68.4%	36%	45.4%	92%	18.2%	96%
- Dipyridamole	66.6%	52%	45.4%	92%	18.2%	96%
Wall Thickening						
- Exercise / Dipyridamole	36.8%	92%	36.3%	100%	-	96%

LDA - Left Descending Coronary Artery; RCA - Right Coronary Artery; CX – Circumflex Artery;
SEN – Sensitivity; SPE – specificity.

Table 3. Sensitivity and specificity of myocardial perfusion, wall motion and thickening, according to the coronary artery territory.

methods of identifying CAD, like treadmill stress test and MPS, especially in the anterior and septal segments, observed even in patients without CAD (1,5,6,8,21). The mechanisms which are responsible for those findings may be associated with “functional ischemia”(4,5,15). The prevalence of such perfusion defects in the presence of LBBB can occur in 14% to 100% of patients (1,2,4,6,11,13,21,22,23), and may be found at rest (24). The specificity of MPS performed in conjunction with treadmill exercise test is reduced when compared with dipyridamole test, and can be explained by the small increments in chronotropism and inotropism of dipyridamole, which minimize the differences of flow and perfusion in the different LV areas. This however could not be confirmed in our study, since perfusion defects in the septal segments were also frequent in patients of Group-II. The septal segment revealed the highest prevalence of perfusion defects in those patients in case of both treadmill exercise as well as dipyridamole stress tests. Similar findings have also been reported by other investigators in the past (2-6,8,11,13).

In the present study both groups had similar perfusion results in the anterior and septal segments, which highlight the difficulty in identifying CAD in this population by MPS. The sensitivity for diagnosing CAD in left descending coronary artery (LDA) area was similar to the ones previously reported (1,5,12), however with poor specificity, even for dipyridamole test, that may have been influenced by LBBB (Table 3).

MPS was not influenced by LBBB in the inferior segment, and sensitivity and specificity were high for both stress tests to detect CAD in right coronary artery (RCA) territory. The lateral segment showed low sensitivity to detect CAD in circumflex artery (CX) territory, however with high specificity for both tests. This is a less extensive area compared with the others and perfusion defects may have a lower expression or be underestimated on a qualitative evaluation. All the patients with perfusion defects in the

apical segment, except for the one from Group-I, had perfusion defects also in the anterior and/or septal segments. Those findings demonstrate that LBBB did not interfere with the evaluation of apical perfusion, and that the abnormal activation of the LV because of LBBB is more proximal (anterior and high septum areas), sparing the apical segment, which is more distal.

Wall motion (WM) alterations of varying intensities were seen in 71.4% patients of Group-I and in 64% of Group-II, mainly observed in the anterior and septal segments. However, Wall Thickness (WT) was normal in 47.6% patients of Group-I and 88% of Group-II, which shows that WT may be more specific, since the alterations of WM can either be accentuated under stress, or they may induce new alterations in the presence of LBBB (25), especially in the septal segment, independent of the presence of CAD. WM distinguished the two groups only in the inferior segment, where all Group-II patients presented with normal motility, as it was shown on perfusion. Owing to the small number of patients with WM alterations in the lateral segment, it was not possible to distinguish the groups. WT distinguished the two groups in the septal and inferior segments. This was the only variable of the gated-SPECT that could distinguish the groups in the anterior and septal segments, identifying CAD in the presence of LBBB, same as previously reported by Germano et al. (26). These results demonstrated the great advantage of the use of gated-SPECT in the diagnosis of CAD in the presence of LBBB.

The LVEF determined by gated-SPECT bears a high concordance with other methods (27,28). It seems that the delayed LV contraction in the presence of LBBB has influence upon the sequence of mechanical events of the cardiac cycle. In our study we observed that the rest LVEF of patients in Group-I and Group-II was lower than the traditionally established standard normal value (26).

The gated-SPECT variables are generally evaluated on the stress images, and acquired about one hour after the stress. Thus, LVEF usually represents rest values. However, in

patients with stress-induced ischemia, LVEF may not represent the real baseline situation, because some degree of systolic dysfunction persists until the images are acquired. It has been already demonstrated that the time to recovery of a post-stress ischemic area may vary up to two hours (29,30). In the present study, the acquisition of images was performed precociously. LVEF, however, did not distinguish between the groups. Compared to the rest, the decrease of LVEF observed in both groups after the treadmill exercise could be either secondary to CAD, or owing to the “*functional ischemia*” observed in LBBB, to the accentuation of the LV asynchronism of contraction due to the increased heart rate, or because of sub-clinical myocardial disease. On the other hand, the post dipyridamole LVEF rise which also occurred in both groups might be explained by the decrease in end-systolic volume and the reduction of diastolic blood pressure as a consequence of arteriolar vasodilatation (31). Therefore, LBBB causes a LV dynamics disarray which is reflected upon the function, demonstrated with reduction in LVEF at rest and fall after treadmill exercise stress, as well as upon myocardial blood flow.

Study limitations and recommendations:

This study was performed with a selected population of LBBB patients, so its results may not be applicable to all such patients, because the great diversity of clinical situations in which LBBB can be present may yield different results. Since LBBB patients in this study had similar clinical characteristics, perfusion defects and alterations in functional variables on gated-SPECT in both groups were expected. Although septal perfusion defects have been described in most studies like ours in patients without CAD, we believe they are secondary to the functional ischemia caused by the alterations of ventricular dynamics. Even in face of these results, MPS associated with a pharmacological test (dipyridamole, adenosine) should be routinely used for diagnostic studies in patients with LBBB, since it provides better specificity than that observed with exercise stress (1,2,10,11). Given its proven advantages and important value, gated-SPECT should be considered for identifying CAD, because its functional variables can bring additional information to the perfusion analysis.

Conclusion

Septal myocardial perfusion abnormalities either alone or along with perfusion defects in the anterior wall and apex are detected in myocardial perfusion scintigraphy performed on patients with LBBB even in the absence of coronary artery disease, thereby reducing the specificity of the test. Gated-SPECT, with its ability to evaluate myocardial perfusion and function in a more comprehensive manner may be a useful tool in the evaluation of such patients. Evaluation of myocardial wall

thickening is perhaps the most important parameter, which could identify coronary artery disease with significant specificity and accuracy.

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