

Rate dependent left bundle branch block: the pattern of myocardial perfusion SPECT

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Abstract

We report myocardial perfusion SPECT pattern in four subsequent patients with rate dependent left bundle branch block (LBBB). Three females and one male (aged 48, 51, 63 and 67 years) were studied. None of the patients had history of typical chest pain and all suffered from atypical chest pain or dyspnea on exertion. All patients were tested for baseline and serial heart rate, blood pressure, and electrocardiogram recordings. The exercise treadmill tests (ETT) were carried out under the strict supervision of a cardiologist, a nuclear medicine physician and close availability of an expert cardio-pulmonary resuscitation team and cardiac care unit within just few seconds. Maximal stress test (at least 85% of calculated heart rate, following development of LBBB) was achieved in all four patients according to standard Bruce protocol. No adverse cardiac events were noted and all ETT stress protocols terminated completely and safely. Myocardial perfusion SPECT imaging showed no evidence of reversible perfusion defects. The only patient with past history of exercise induced LBBB showed nonreversible perfusion defects in the septal and anteroseptal regions and mild LV cavity dilatation. The limited number of patients enrolled in our study does not allow us to draw a definite conclusion. Despite the presence of false-positive defects in myocardial perfusion SPECT in patients with sustained

LBBB, such a finding is not a consistent finding in patients with rate dependent or exercised-induced LBBB, unlike that which we expected to see. Maybe it is possible to continue ETT for those patients undergoing myocardial perfusion scintigraphy and developing rate dependent LBBB.

Key words: left bundle branch block, rate-dependent, myocardial perfusion scintigraphy

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Introduction

In the setting of Left Bundle Branch Block (LBBB), abnormal septal radiotracer uptake is commonly observed, even in the absence of significant Coronary Artery Disease (CAD), decreasing the diagnostic accuracy of myocardial perfusion SPECT [1]. In fact, interpretation of myocardial perfusion SPECT images is inaccurate in the presence of fixed or reversible perfusion defects in the septal or anteroseptal regions, even with normal blood flow through the left anterior descending (LAD) artery [2, 3]: In previous studies, septal or anteroseptal perfusion defects were estimated to be observed in approximately 75% of patients with LBBB, although significant LAD stenosis was detected only in 39% [4–7]. Moreover, previous studies have emphasized the fact that abnormal regional contraction patterns (such as LBBB) could generate angiographically-negative segmental perfusion abnormalities [8].

It has been proposed that patients with exercise induced- or rate dependent- LBBB-morphology arrhythmia do not have increased risk for CAD as compared with patients without such an arrhythmia [9, 10]. The idiopathic ventricular arrhythmia probably occurs in healthy individuals and often originates from the right ventricular outflow tract (RVOT), with a cyclic adenosine monophosphate-dependent and catecholamine-sensitive mechanism [11], leading to the LBBB-morphologic, inferior-axis configuration [12], usually benign in nature and outcome. However, it should be kept in mind that exercise-induced ventricular ectopies (similar to rate dependent LBBB) are not always related to a structurally normal heart [9] and sometimes they can originate from the interventricular septum associated with septal infarctions in CAD [13].

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As to the best of our knowledge, there are few reported cases on the scintigraphic pattern of myocardial perfusion in the setting of rate dependent LBBB. As the underlying mechanisms of the rate dependent LBBB seems to be different from those of sustained LBBB, it cannot be concluded that their scintigraphic pattern should be the same. Hence, we proposed to evaluate myocardial perfusion SPECT pattern in patients with rate dependent LBBB. Such information may lead to better understanding of the underlying mechanisms of false perfusion defects in the setting of LBBB.

Methodology

As a case series over 12 months period, from September 2008 to September 2009, all patients who were referred for myocardial perfusion SPECT using the stress protocol of exercise treadmill test (ETT) and developed rate-dependent LBBB during the ETT were included in the study. Ethical approval had been obtained from the committee on ethics of the Research Institute for Nuclear Medicine, Tehran University of Medical sciences.

All patients were connected to the exercise ECG machine and tested for baseline and serial heart rate, blood pressure, and electrocardiogram (ECG) recordings. Those patients with sustained LBBB (LBBB at rest) were excluded from the study — as they were considered for Dipyridamole stress protocol- and just those with normal baseline ECG or abnormalities other than LBBB proceeded to ETT. Blood pressure was recorded at 3-min intervals and heart rate and 12-lead ECG were observed continuously in order to strictly monitor the patients. The ETT tests were carried out under the strict supervision of a cardiologist, a nuclear medicine physician and close availability of an expert cardio-pulmonary resuscitation team and cardiac care unit (CCU) accessible within just few seconds, as the study was performed in a tertiary cardiac hospital setting. The ETT was proposed to terminate with each of the following conditions: at the patient's request, any reduction in systolic blood pressure (SBP), chest pain, dyspnea and/or severe fatigue. Maximal stress test (at least 85% of calculated heart rate, following development of LBBB) was considered as the endpoint for complete ETT in all patients according to standard Bruce protocols. No clinical adverse changes and no ST segment shift before development or after resolution of the aberration occurred during the test and recovery period under strict supervision of expert team. None of the patients reported chest pain after development of rate dependent LBBB.

LBBB was defined as QRS duration ≥ 120 ms, the presence of notched R waves in the lateral precordial leads (V5 and V6) and leads I and aVL, small or absent initial r waves in the right precordial leads (V1 and V2) followed by deep S waves, absent septal q waves in left-sided leads, and a prolonged intrinsicoid deflection (> 60 ms) in V5 and V6.

A commercial Sestamibi kit (AEOI, Tehran, Iran) was used and the labeling and quality control procedures were done according to the manufacturer's instructions. At peak exercise (at least 6 minutes after the start of the test), 925 MBq (25 mCi) ^{99m}Tc -sestamibi was injected intravenously and the patients were encouraged to exercise for two additional minutes before the termination of the test. Fifteen minutes after radiotracer injection, image acquisition was done using a rotating, single head gamma camera (Sopha DSX, Paris-FR) equipped with a low-energy high resolution parallel

hole collimator. A 20% window around the 140 keV energy peak of ^{99m}Tc -sestamibi was used. Patients were in a prone position during the image acquisition. Thirty-two azimuth images, 25 s/projection, were obtained in a circular orbit, beginning from right anterior oblique to left posterior oblique with step and shoot acquisition on a $64 \times 64 \times 16$ matrix and 38.5 cm detector mask (1.22 zoom). An expert nuclear physician used the cine display of the rotating planar projections to assess and optimize the technical quality of the images. The raw data were pre-filtered by ramp and subsequently by Butterworth filters with frequency cut-off of 0.40 and order of 9 without attenuation correction. Filtered back-projected data was reconstructed into short-axis, vertical long-axis and horizontal long-axis slices. The standard rest phase imaging was carried out in the same condition on the following day, 60 min after intravenous injection of 925MBq (25mCi) ^{99m}Tc -sestamibi.

Two nuclear medicine physicians (seven and eight years of experience with reading myocardial perfusion scintigraphy) blinded to other clinical data interpreted SPECT data considering the presence or absence of myocardial perfusion abnormality and final diagnoses was reached by consensus.

Cases

Out of 647 consecutive patients, four patients (0.62%) developed rate-dependent LBBB. The incidence of 0.62% found for our population of 647 patients agrees with that reported by Riera et al., 0.21% of 9318 patients, using a chi-squared analysis of proportions ($p: 0.10$). The patients had a detailed history recorded elaborated as follows:

Patient 1

A 48-year-old woman with normal baseline ECG, suffering from atypical chest pain and exertional dyspnea, and a recent inconclusive ETT. The baseline blood pressure was 140/100 mmHg and the baseline HR was 87. Two minutes and fifteen seconds following the initiation of the ETT (stage I at the heart rate of 169) the normal ECG pattern changed to LBBB (Figure 1). The radiotracer was injected at the 6th minute of the ETT. LBBB pattern changed to normal sinus rhythm two minutes and twenty seconds after the end of the ETT. The SPECT images showed no myocardial perfusion abnormality and were interpreted as normal myocardial perfusion SPECT (Figure 2).

Patient 2

A 63 year-old woman was referred to our center for a diagnostic myocardial perfusion SPECT. The baseline characteristics showed a positive family history for cardiovascular disease and atypical chest pain. The baseline blood pressure was 120/70 mmHg and the baseline HR was 72. LBBB pattern appeared at 2.50 (stage I at the heart rate of 117). The ECG changes that had occurred during exercise testing returned to the resting level in the recovery phase. The myocardial SPECT scintigraphy was visually interpreted as normal by two blinded nuclear medicine physicians.

Patient 3

A 67 years old man with the history of dyspnea on exertion, cigarette smoking and hypertension, without any complaint of chest pain, presented for further workup. There was also a past history of myocardial perfusion scanning with exercise protocol

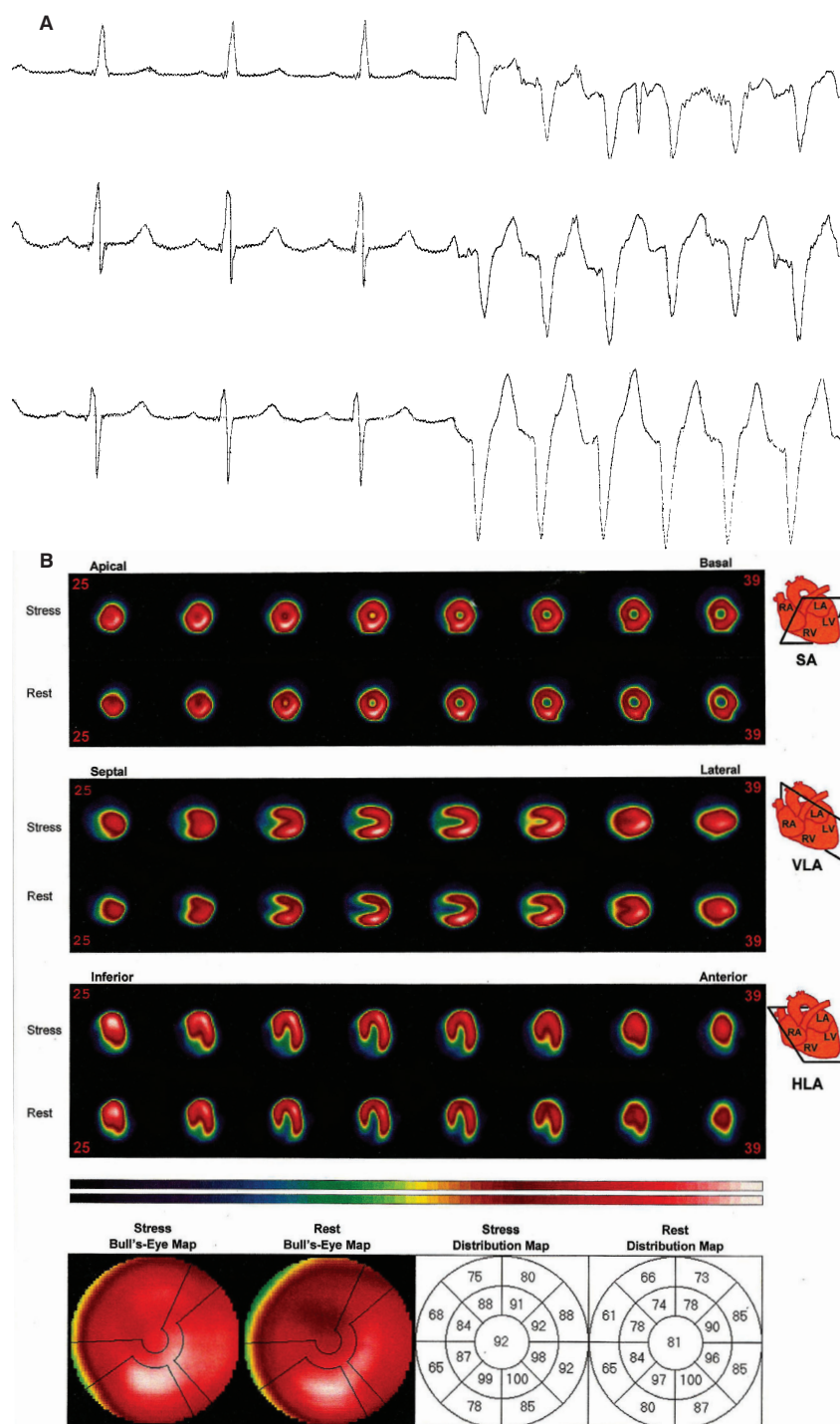


Figure 1A. Alteration of the patient's electrocardiogram from baseline Normal sinus rhythm to LBBB pattern. **B.** Myocardial Perfusion SPECT of a patient (number 1) with rate-dependent LBBB

almost two years ago. In the previous treadmill test, characteristic pattern of exercise-induced LBBB (superimposed on the baseline normal sinus rhythm) was observed at the stage II.

Due to continued complaints during the past two years, the patient was referred to repeat myocardial perfusion scintigraphy. The resting ECG showed incomplete LBBB with QRS duration of almost 100 ms, and the baseline blood pressure was 160/100 mm Hg. LBBB pattern appeared at the first stage (almost one minute and fifteen seconds after initiation of the ETT with the heart rate

of 99). No clinical adverse changes occurred during the test and recovery period under strict supervision of expert team. LBBB pattern changed to incomplete LBBB three minutes and thirty five seconds after the end of the ETT.

The scan showed no reversible myocardial perfusion abnormality, although mild decreased activity was found in the septal/anteroseptal walls on both phases. Mild LV cavity dilatation was also observed. The findings were compatible with those of the previous scintigraphic assessment.

Patient 4

A 51-year-old woman who suffered from atypical chest pain and a recent inconclusive ETT was referred to our center for a diagnostic myocardial perfusion SPECT. The baseline blood pressure was 130/80 mmHg and baseline HR was 80. Two minutes and fifty seconds following the commencement of the exercise test (stage I at the heart rate of 125) the normal ECG pattern changed to LBBB. The ECG changes that had occurred during the exercise testing returned to the baseline normal sinus rhythm at the recovery. No myocardial perfusion abnormality was seen in visual interpretation by the blind readers.

Rate dependent LBBB and CAD

Although in our study the number of patients is too low to reach a definite and statistically logical conclusion, rate dependent LBBB in our four cases was not associated with scintigraphic evidences of ischemia. Consistent with our findings, Vasey et al. sought to determine the relation between exercise-induced, acceleration-dependent LBBB and the presence of CAD. They concluded that patients with atypical chest pain in whom rate-dependent LBBB develops on the treadmill are significantly less likely to have CAD than patients who present with classic angina; They emphasized that the onset of LBBB at a heart rate of 125 beats/min or higher is highly correlated with the presence of normal coronary arteries [14].

In contrast to the data obtained from our small sample, in 2001 Bozkurt et al. presented a 53-year-old woman who developed intermittent rate-dependent asymptotically LBBB during myocardial perfusion scintigraphy using 201-Thallium chloride. Scintigraphic findings demonstrated septal-anteroseptal ischemia; however, again the coronary arteriogram was reported to be normal. The authors concluded that scintigraphic findings may be related to microcirculatory ischemia, as the cause of rate-dependent LBBB, which cannot be detected angiographically [15]. Along these lines Aoki et al. showed three out of five patients with exercise-induced LBBB had reversible perfusion defects on myocardial scintigraphy. Similar to the previous reports, in one of these three patients, however, coronary angiography demonstrated no significant stenosis. Based on these facts, they asserted myocardial scintigraphy in patients with exercise induced LBBB can be inaccurate to determine CAD [16]. Also La Canna et al. based on their experience on 33 patients showed that exercise myocardial perfusion scintigraphy has a high prevalence (64%) of reversible perfusion defects in patients with rate dependent LBBB without any evidence of CAD at angiography or coronary spasm at ergonovine test. Moreover, follow-up showed a relatively low rate of major cardiac events in these patients [17].

One of the largest sample of patients studied on this topic is reported by Riera et al, who reviewed 9318 consecutive exercise stress studies and found a total of 20 rate dependent LBBB (prevalence rate: 0.21%) [18]. They found that eight out of 20 patients had normal coronary arteries and 12 had CAD and peak O₂ consumption. Peak myocardial O₂ consumption and heart rate when block appeared were significantly higher in those with normal coronary arteries. Although there was no death in the follow-up of patients with normal coronary arteries, there were 3 deaths and 2 acute myocardial infarctions during follow-up of patients with CAD.

Also the authors concluded that “the development of permanent left bundle-branch block is frequent”.

Regarding the controversies observed between our study findings and those previous reports (all of which suffering from small sample sizes) and also with respect to the discrepancies exist between anatomical imaging modalities (coronary angiography) and physiological imaging (myocardial perfusion imaging), further evaluation is highly warranted in order to more accurately detect influences of exercised-induced or rate-dependent LBBB on myocardial perfusion SPECT pattern.

LBBB and characteristic scintigraphic pattern

Sustained LBBB is a rather common disorder and is often related to the organic heart disease [19]. Although based on Framingham study, the presence of LBBB was associated with a three-to fourfold increase in cumulative cardiovascular mortality [20], based on our study findings and those reviewed previously, patients with rate dependent LBBB has much more favorable prognosis and lower risk of detectable CAD.

In patients with LBBB, exercise perfusion scintigraphy is limited because of frequent occurrence of false-positive perfusion defects [21–23]. Few mechanisms and hypotheses have been suggested and assumed as the explanations for the altered pattern of myocardial perfusion SPECT in the setting of LBBB:

- in 1999, Skalidis et al. evaluated 16 patients with permanent and complete LBBB who consented to have myocardial perfusion scintigraphy, coronary-flow velocity measurement and cardiac catheterization [19]. Finally, they suggested that the false-positive exercise scintigraphic perfusion defects, which are frequently observed in patients with LBBB, are associated with a reduced coronary flow reserve in the area supplied by the given coronary artery. On the other hand, they proved that reduced coronary flow reserve to adenosine (the response to which is independent of myocardial demands) showed an impairment of microvascular function, suggesting that true ischemia was the cause of the perfusion defects. Their findings were not consistent with other available reports which asserted that reduced myocardial septal blood flow is not necessarily an indication of septal ischemia, but may be caused by hypoperfusion due to autoregulation resulting from the lower demands of the septum [24] or suggested that these perfusion defects are a result of reduced wall thickening rather than actual hypoperfusion at rest [25]. Moreover, preservation of septal myocardial perfusion in patients with LBBB was shown in recent positron emission tomography studies using ¹⁵O-water and ¹³N-NH₃, which are strong markers of myocardial blood flow, as blood flow tracers [26, 27]
- it has been suggested that the defects may be related to reduced septal blood flow- as the consequence of dys-synchronous contraction of the septum- or septal microcirculatory dysfunction and it seems to be heart-rate dependent [2, 3, 28]. Other factors have been shown to influence septal tracer uptake, including reduced blood flow resulting either from decreased demand [29, 30] or from a shortened diastolic filling time [31] — early activation of the septum, leading to shortened diastole and hence reduced blood flow [32] — partial volume effects caused by septal thinning and impairment of thickening

ing noted in experimental models of LBBB with right ventricle pacing [33]; and increased septal intra-myocardial pressure during diastole, resulting in reduced flow reserve [24]. In the other words, assumptions for this phenomenon have been considered to include both technical and pathophysiological aspects [1]: Particularly, wall motion abnormalities as well as reduced ventricular wall thickness may cause false perfusion defects, just because of the partial volume effect [34, 35];

— as mentioned earlier, bundle branch block is a conduction abnormality, although seen in apparently structurally normal hearts, it is mostly acquired with fibrous or fibro-degenerative disorders affecting the septum. Rate dependent BBB is an incomplete abnormality occurring at a critical rate that may or may not proceed to permanent BBB [18]. On the other hand, permanent LBBB, as well as long standing RV apical pacing due to prolonged activation abnormality may result in mechanical and structural remodeling with or without corresponding blood flow changes. To answer the assumption regarding permanent BBB and false positive results, a second imaging modality such as echocardiography or MRI can also be used that could show the structural/morphologic features of the septal area, and correlate these cases with evidence of positivity of scintigraphy; i.e. if it is structural or functional positivity. In a recent study, Marholdt et al. compared SPECT perfusion with cardiac MR in LBBB patients. They claimed that septal hypoperfusion was related not only to septal wall motion abnormalities, but also to myocardial thickness [34]. Interestingly, nearly all segments with normal thickness were correctly identified as normal on SPECT imaging. Their results suggest that septal myocardial thinning associated with fibro-degenerative processes affecting the septum and not only segmental wall motion abnormalities might be responsible for the septal perfusion defects of patients with LBBB. Also it would be interesting to compare rate dependent aberration with similar conditions that could induce the same activation abnormality, such as RV pacing that, in contrary to the current study, has been shown to result in reversible perfusion defects “on and off pacing” in pacemaker dependent patients, i.e. functional abnormality [36].

Our study showed no significant evidence of perfusion defect even in the septum or anteroseptal regions which commonly appeared as the false positive defects in patients with sustained LBBB. It seems that our study does not endorse the theory that the decreasing flow reserve in septum and anteroseptal regions in patients with sustained LBBB may cause the false-positive defects in the myocardial perfusion SPECT, as we expect the same false perfusion defects in the setting of rate dependent LBBB. Also based on our evidence, which demonstrates normal myocardial perfusion scan in patients with rate-dependent LBBB, wall motion abnormality is not a very robust reason for explanation of these defects in myocardial perfusion SPECT, as the same wall motion abnormalities seems to be present in patients with rate dependent LBBB. Reduced blood flow resulting either from decreased demand [29, 30] or from a shortened diastolic filling time [35] — early activation of the septum, leading to shortened diastole and hence reduced blood flow, increased septal intra-myocardial pressure during diastole, resulting in reduced flow reserve [24] do not seem to be quite complete explanation for false perfusion defects. In fact,

we suggest that partial volume effects caused by septal thinning and impairment of thickening noted in experimental models of LBBB should be kept in mind as the more probable explanation, as this is the main difference between the rate dependent LBBB cases and sustained LBBB patients who had enough duration of the disease to achieve ventricular remodeling in response to LBBB. Septal myocardial thinning associated with fibro-degenerative processes affecting the septum can be the other probable explanation, as the third case in our study with prolonged duration of suffering from rate dependent LBBB had enough opportunity to develop such ventricular abnormalities (as it was evident by the nonreversible decreased activity of the septal and anteroseptal regions on the myocardial perfusion scintigram of the patient).

The limited number of patients enrolled in our study and also the previous investigations [the main reason of which is the remarkably low prevalence rate of rate-dependent LBBB (<1.0%)] does not allow us to draw a definite conclusion. Thus, further studies are warranted depending on the clinical scenario-comparing myocardial perfusion SPECT of patients with sustained (permanent) LBBB and those with exercised-induced or accelerated rate-dependent LBBB. Lack of angiographic correlation was the other main limitation of our study, as it was considered unethical to perform angiography on patients with atypical chest pain and negative myocardial perfusion scintigraphies. Lack of ECG-gated data (current state of the art imaging technique of myocardial perfusion scanning) and follow-up of the patients are the other limitation of our report. Our study population consisted of 3 patients with intermediate probability of CAD and one with low probability of CAD. It would also be interesting to show other cases with genuine chest pains and high possibility of CAD in future studies, as some authors have concluded that ETT-induced LBBB predicts a higher risk of death and major cardiac events [37]. Such an explanation was confirmed by the findings of the Moran et al [38]. They divided their patients into two groups: group A, patients with atypical chest pain or abnormal exercise electrocardiogram of which just 3/12 abnormal MPI, and group B, patients with definite or probable angina, which patients had significantly more abnormal MPI (17/25) than group A patients. Considering coronary angiography as the gold standard, Moran et al. showed that MPI has a predictive accuracy of 85% for CAD [38].

Conclusion

Despite the presence of false-positive defects in myocardial perfusion SPECT in patients with sustained LBBB, such a finding is not a consistent finding in patients with rate dependent or exercised-induced LBBB, unlike that which we expected to see. Maybe it can be possible to continue ETT as the stress protocol for those patients undergoing myocardial perfusion scintigraphy and developing rate dependent LBBB. This observation needs further investigation, also in order to evaluate the exact differences between the mechanisms of sustained LBBB and exercised-induced or rate- dependent LBBB and their influences on myocardial perfusion SPECT.

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