Effects of Left Bundle Branch Block on Myocardial FDG PET in Patients Without Significant Coronary Artery Stenoses

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Cardiac PET studies in patients with left bundle branch block (LBBB) are few, and the results are conflicting. In particular, even if a reduced uptake of FDG is reported, confirmation in a large group of patients and exact understanding of the underlying cause are lacking. **Methods:** We selected 29 consecutive patients who had complete LBBB and no significant stenosis on coronary angiography scheduled for FDG and ^{13}N-NH_3 PET for myocardial viability evaluation at our center. Wall motion was evaluated using 2-dimensional echocardiography. Ten volunteers without coronary stenosis or LBBB served as a control group. **Results:** All LBBB patients had a reverse mismatch in the septum, defined as reduced uptake of FDG in comparison with ^{13}N-NH_3. The mismatch extended to the anterior and inferior walls in 17 patients. The mean (±SD) septal-to-lateral ratio was 0.57 ± 0.11 for FDG (range, 0.28–0.76) and 0.99 ± 0.12 for ^{13}N-NH_3 (range, 0.75–1.18), with $P < 0.0001$. In contrast, no significant differences in uptake were seen in the control group, which had a septal-to-lateral ratio of 0.95 ± 0.13 for FDG (range, 0.78–1.15; $P < 0.01$ with respect to LBBB patients) and 0.94 ± 0.11 (range, 0.85–1.20) for ^{13}N-NH_3. **Conclusion:** Our study suggests that in LBBB patients without significant coronary stenosis, FDG uptake in the septum changes without a correlating change in perfusion. To avoid possible overestimation of necrosis, especially in the LAD territory, this phenomenon must be considered in evaluations of myocardial viability using FDG images.

Key Words: left bundle branch block; PET; FDG; ^{13}N-NH_3

J Nucl Med 2000; 41:973–977

Scintigraphic techniques appear to be significantly less accurate in patients with left bundle branch block (LBBB), especially in the septum, than in other patients with coronary artery disease (*1*). Large numbers of false-positive fixed or reversible septal defects, not correlated with significant stenoses in the left anterior descending artery territory, have been reported for stress thallium images (*2–3*). Some investigators have had slightly better results through applying pharmacologic stress (*4–5*) instead of exercise or through using sestamibi as a tracer (*6*), but the specificity of scintigraphy continues to be low, both in the evaluation of perfusion defects and in viability research. A similar situation has been seen in both humans and animals in a few studies with PET and FDG (*7–8*).

To explain this phenomenon, some investigators supposed a real decrease in the perfusion of the septum because of an increase in intramyocardial pressure in the diastolic phase (*1,8*). Other investigators reported preserved perfusion in this area and supposed a shift in the metabolic substrate for cardiac myocytes from glucose to fatty acids (*9*), confirmed by the report of a preserved oxidative metabolism (*10*). However, to our knowledge only 10 patients whose LBBB was investigated with FDG have been reported in the literature (*7–11*), and the underlying pathophysiology of this phenomenon is not well understood, particularly in patients without coronary stenosis or myocardial infarction.

In this article, we report our experience with a group of LBBB patients without coronary disease. Glucose uptake and myocardial perfusion were evaluated by PET, using FDG and ^{13}N-NH_3, respectively, as tracers, and the results were compared with those of a group of similar individuals without LBBB.

MATERIALS AND METHODS

Patients

We retrospectively enrolled 29 consecutive patients (19 men, 10 women; age range, 37–82 y; mean age ± SD, 61 ± 10 y) who had complete, persistent LBBB and no significant stenosis on coronary angiography. The patients had been referred to our center for evaluation of myocardial viability with FDG and ^{13}N-NH_3 PET (Table 1). All the patients presented with left ventricular dilatation, with an end-diastolic volume greater than 80 mL/m^2 body surface. All the enrolled patients presented with normal fasting blood glucose levels; 4 patients with diabetes were excluded from the study. A 12-lead electrocardiogram, routinely obtained immediately before PET studies in our center, confirmed the presence of LBBB in all enrolled patients. Ten individuals with left ventricular

Received May 17, 1999; revision accepted Sep. 23, 1999.

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TABLE 1
Main Characteristics of LBBB Patients and PET Results

Patient no.	Age (y)	Sex	EF	EDV	RA	LAD %	RM site	RM ext	S/LR FDG	S/LR ^{13}N-NH_3
1	68	M	33	150	—	0	Sep-ant-inf	5	0.76	0.94
2	73	M	40	136	—	0	Sep	2	0.69	1.00
3	72	F	27	158	—	0	Sep	2	0.54	1.18
4	74	M	35	132	—	0	Sep-inf	4	0.67	1.15
5	58	M	42	145	—	20	Sep-ant	4	0.61	0.85
6	61	M	32	122	—	0	Sep-inf	5	0.48	1.07
7	48	M	38	95	—	0	Sep	2	0.45	0.88
8	68	M	29	121	—	40	Sep-ant-inf	6	0.65	1.14
9	84	M	34	132	—	0	Sep-ant-inf	8	0.50	0.82
10	49	M	50	80	—	0	Sep	2	0.67	1.06
11	66	F	43	82	—	0	Sep-inf	4	0.52	1.09
12	39	F	20	230	—	20	Sep-inf	6	0.65	1.12
13	67	M	39	203	—	0	Sep	2	0.52	1.02
14	58	M	30	95	—	0	Sep-inf	4	0.50	1.07
15	66	M	32	176	—	30	Sep-ant-inf	7	0.65	1.02
16	65	F	41	152	—	0	Sep-ant	4	0.55	0.98
17	67	F	22	110	—	40	Sep-ant-inf	6	0.40	0.88
18	76	M	38	136	—	0	Sep	3	0.41	1.09
19	72	F	40	87	—	40	Sep	2	0.67	1.01
20	63	M	37	98	—	0	Sep	3	0.51	0.86
21	54	M	32	107	—	30	Sep	3	0.63	1.11
22	43	F	49	98	—	0	Sep	2	0.74	1.02
23	71	F	29	132	—	0	Sep-inf	4	0.72	1.12
24	67	M	34	90	—	20	Sep-ant-inf	6	0.52	0.87
25	64	M	27	107	—	0	Sep	3	0.68	0.88
26	72	F	41	132	—	40	Sep	2	0.58	1.11
27	67	M	35	115	—	0	Sep-ant-inf	6	0.28	0.75
28	67	F	29	100	—	0	Sep-ant	5	0.63	0.85
29	50	M	32	125	—	0	Sep-ant-inf	9	0.41	0.83
Mean ± SD	61 ± 10		35 ± 7	125 ± 35				4.17 ± 1.96	0.57 ± 0.12	0.99 ± 0.12*

*$P < 0.0001$ with respect to S/LR FDG.

EF = ejection fraction at echocardiography; EDV = end-diastolic volume at echocardiography, in mL/m^2 body surface; RA = presence of regional akinesia at echocardiography; LAD % = percentage of left anterior descending coronary artery narrowing at coronary angiography; RM = reverse mismatch; S/LR = septal-to-lateral uptake ratio; sep = septum; ant = anterior wall; inf = inferior wall.

dilatation with healthy coronary arteries but without LBBB were a control group (Table 2). No significant differences in sex, age, ejection fraction, or end-diastolic volume with respect to the LBBB group were present. All patients gave informed consent.

PET

PET was performed using an ECAT EXACT scanner (model 921), which allows simultaneous acquisition of 47 contiguous transaxial images, with a total axial field of view of 16.2 cm. The calculated resolution of our scanner was 4.8 ± 0.6 mm in the axial direction and 6.1 ± 0.2 mm in transaxial planes.

At first, a transmission scan of 15 min was obtained for attenuation correction, using retractable ^{68}Ge rod sources. For emission studies, the tracers were ^{13}N-NH_3 (dose, 10 MBq/kg) injected at rest and FDG (dose, 4 MBq/kg) injected after an oral glucose load coupled with intravenous insulin, according to the method of Lewis et al. (*12*). The emission scan started 4 min after the ^{13}N-NH_3 injection and 45 min after the FDG injection. The acquisition lasted 15 min with both tracers. Short-axis and vertical and horizontal long-axis slices with a thickness of 0.8 cm each were reconstructed using a Hanning filter (cutoff, 1.18 cycle/cm) and corrected for attenuation.

Both studies were performed on the same day, first the ^{13}N-NH_3 study and 2 h later the FDG study. To avoid artifacts from misalignment, the repositioning of the patient in the scanner was checked using a cross-shaped low-power laser beam and pen skin markers.

Two skilled observers, working in consensus, analyzed the images semiquantitatively. The left ventricle wall was divided into 4 walls (anterior, lateral, inferior, and septal), and each wall was divided into 3 segments (basal, midventricular, and distal) equal in dimension, for a total of 12 segments. After individual normalization of each set of images to the maximum count in the left ventricular wall, a 3-point semiquantitative score was applied to both FDG and ^{13}N-NH_3 images. Normal uptake (>75%) was scored 2, a moderate defect (50%–75%) was scored 1, and a severe defect (<50%) was scored 0. A reverse mismatch was considered present in the segments with an FDG score inferior to the corresponding ^{13}N-NH_3 score. Moreover, assuming the lateral wall as a reference, the septal-to-lateral counting rate density ratio of FDG and ^{13}N-NH_3 was calculated in the midventricular horizontal long-axis slice (interpolated at a thickness of 1.6 cm) with the region-of-interest technique, drawing for each patient 2 different regions extending from the base to the apex and normalizing the counts to the extension of each region.

TABLE 2
Main Characteristics of Control Patients and PET Results

Patient no.	Age (y)	Sex	EF	EDV	RA	LAD %	S/LR FDG	S/LR ^{13}N-NH_3
1	65	M	25	120	—	0	0.82	0.94
2	68	F	40	156	—	0	1.02	0.88
3	52	M	43	92	—	0	0.85	0.98
4	50	M	32	130	—	0	0.78	0.85
5	63	M	34	103	—	0	1.10	1.20
6	58	M	28	141	—	0	0.95	0.85
7	61	F	30	203	—	0	1.05	0.98
8	55	M	22	228	—	0	1.15	1.02
9	62	M	32	107	—	0	1.02	0.85
10	60	F	34	105	—	0	0.80	0.85
Mean ± SD	59 ± 6		32 ± 6	138 ± 45			0.95 ± 0.13*	0.94 ± 0.11

*$P < 0.01$ with respect to S/LR FDG in LBBB patients.

EF = ejection fraction at echocardiography; EDV = end-diastolic volume at echocardiography, in mL/m^2 body surface; RA = presence of regional akinesia at echocardiography; LAD % = percentage of left anterior descending coronary artery narrowing at coronary angiography; S/LR = septal-to-lateral uptake ratio.

Sonographic Examination

All the patients underwent resting 2-dimensional echocardiography within 15 d of the PET study. The studies were performed using state-of-art commercial instruments equipped with 2.5- and 3.5-MHz probes. The parasternal long-axis; parasternal short-axis (mid and basal ventricular); and apical 4-chamber, long-axis, and 2-chamber views were examined. Wall motion was evaluated on videotaped images by 2 skilled observers working in consensus who were unaware of the clinical condition of the patients. Left ventricular ejection fraction and end-diastolic volume, corrected for the body surface of the patients, were calculated in the 4-chamber apical view by the single-plane area-length method (*13*).

Coronary Angiography

All patients underwent coronary angiography within 60 d of PET. The left and right coronary arteries were imaged in multiple views, including craniocaudal projections. Coronary artery stenosis was considered significant if the lumen diameter was narrowed by more than 50%. The studies were evaluated by 2 observers unaware of clinical condition.

Statistical Analysis

The data are usually reported as mean ± SD. The Student *t* test was applied, when appropriate, to compare the mean values, with $P \leq 0.05$ considered significant.

RESULTS

At echocardiography, the mean ejection fraction was 35 ± 7 (range, 20–50) and the mean end-diastolic volume was 125 ± 35 mL/m^2 (range, 80–230 mL/m^2). No patient had a history of myocardial infarction or basal electrocardiographic findings suggesting previous necrosis. Echocardiography showed no segmental akinetic area.

All the LBBB patients had a relatively reduced FDG uptake in the septum, compared with ^{13}N-NH_3 uptake. Figure 1 shows images of an LBBB patient. This reverse mismatch also involved the anterior wall in 3 patients, the inferior wall in 6, and both walls in the other 8; in all the patients, matching of perfusion and FDG uptake in the other regions of the left ventricular wall was observed, and in no patient was a reverse mismatch in the lateral regions present. The mean of the extension of the reverse mismatch, considered as number of segments involved, was 4.17 ± 1.96 (range, 2–9) (Table 1).

The semiquantitative analysis, assuming the lateral wall as the reference, confirmed the reverse mismatch between glucose uptake and perfusion, with mean septal-to-lateral ratios of 0.57 ± 0.11 (range, 0.28–0.76) and 0.99 ± 0.12

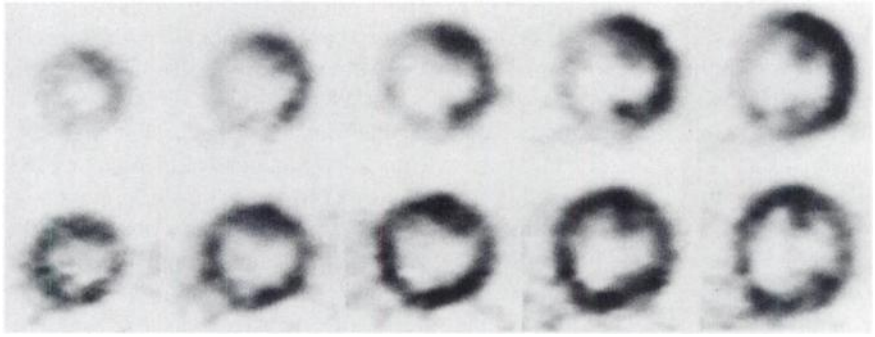

FIGURE 1. FDG (top) and ^{13}N-NH_3 (bottom) short-axis slices.

(range, 0.75–1.18), respectively. On the Student t test, the difference appeared highly significant ($P < 0.0001$).

In the control group, both tracers were distributed homogeneously in the left ventricular wall, and no patient presented with reverse mismatch. At semiquantitative analysis (Table 2), the septal-to-lateral ratio was 0.95 ± 0.13 for FDG (range, 0.78–1.15; $P < 0.01$ with respect to LBBB patients) and 0.94 ± 0.11 (range, 0.85–1.20) for ^{13}N-NH_3.

DISCUSSION

As reported in an editorial by Altehoefer (*14*), "data on metabolic imaging in patients with LBBB are rare." To our knowledge, no more then 10 LBBB patients evaluated using FDG have been reported in the literature (*7–11*), and the defect in FDG uptake in the septum that was reported for all the patients was not entirely explained by a concordant reduction in regional perfusion (*15*). To describe the pattern of decreased FDG uptake relative to myocardial blood flow, the term "reverse mismatch" has been introduced. This phenomenon has been reported in a limited number of patients with documented coronary disease and a history of myocardial infarction (*7,10*) but, to our knowledge, in only 2 patients with angiographically normal coronary arteries (*11*). Our study confirmed these data in a more significant number of LBBB patients, selected consecutively, without significant coronary stenoses, but the underlying pathophysiology of this phenomenon is not clear.

The reduced uptake of ^{201}Tl in the septum does not correlate with stenoses of coronary arteries and significantly reduces the specificity of the perfusion scan in LBBB patients (*1*). Reduced perfusion caused by the asynchrony of the wall motion presented in this conduction defect is believed to be the underlying mechanism (*1*): the septal contraction occurs during diastole, thus hampering coronary filling and reducing flow. The experience of Ono et al. (*8*) using an artificially produced block in dogs seemed to confirm this hypothesis, because an increment in intramyocardial pressure in the septum in the diastolic phase was found to be related to a comparable reduction in ^{201}Tl and FDG uptake in this area. Also, the data of Yamada et al. (*11*), obtained from 2 patients with healthy coronary arteries using ^{201}Tl for perfusion and FDG, seemed to confirm this hypothesis.

Unlike these studies, our study found that the deficit in glucose use appeared unrelated to damage of perfusion. The most probable explanation for this discrepancy is that in the uptake of ^{201}Tl, used by Ono et al. (*8*) and Yamada et al. (*11*) as a perfusion tracer, a relevant role is played by metabolic activity of the myocardial cells. In our study ^{13}N-NH_3 was used. This tracer passively diffuses into myocytes and distributes on the basis of regional perfusion. Moreover, working against the hypoperfusion hypothesis is our finding of a mismatch between glucose use and perfusion in a selected group of LBBB patients without myocardial infarction or significant coronary stenoses, especially in the left anterior descending artery, supplying the septum.

Altehoefer et al. (*9*), in a case report concerning an LBBB patient, found preserved septal uptake of long-chain fatty acid, in spite of an altered FDG uptake, thus suggesting an unaffected β-oxidation. In another patient (*10*), the oxidative metabolism was quantitatively evaluated by ^{11}C-acetate, which provides an indirect measure of myocardial oxygen consumption (*16*) independent of changes in the proportion of substrate presented to the heart (*17*). In this patient, a severe defect in FDG uptake in the septum was present, with normal perfusion and a preserved oxidative metabolism in the septum and a septal-to-lateral uptake ratio for NH_3 very similar to that for acetate. This experience tends to confirm the hypothesis of an inability to use glucose as a substrate in the septal region in the presence of LBBB. The underlying pathophysiology is difficult to understand.

Variations in FDG distribution have also been reported in healthy volunteers (*18*). However, in our opinion, the normal variability of tracer uptake could not be the explanation of the reverse mismatch reported in our LBBB patients. We are of this opinion for several reasons. First, the severity of defects in glucose use in comparison with perfusion observed in LBBB patients was definitely superior to that reported for healthy volunteers and for our reference group, and defects in glucose use were present in all the patients. Second, regional heterogeneity of FDG is usually more significant for fasting subjects than after glucose loading or clamping (*19*), the techniques used in our study. Third, in a significant number of LBBB patients the relative defect in glucose uptake also involved the inferior wall of the left ventricle, whereas in healthy volunteers mainly anteroseptal defects were reported (*19,20*). The simultaneous involvement of the inferior wall, found in a significant number of our patients, was not mentioned by other investigators using ^{201}Tl as a tracer. This discrepancy could have been caused by the possible interference in the inferior wall evaluation secondary to lack of attenuation correction of the SPECT images.

Another possible explanation for reverse mismatch in LBBB patients may be the presence of glucose intolerance. For this reason, diabetic patients were excluded from our study. All the examined patients had normal fasting glucose levels, but we cannot exclude the presence of subclinical glucose intolerance in some patients. However, this explanation appears unlikely because we achieved the metabolic shift with an insulin–glucose load technique that seems to ensure good FDG uptake even in diabetic patients (*12*).

For all PET studies, the transmission and ^{13}N-NH_3 scans were obtained first; the patients subsequently were repositioned for the FDG scan. We could therefore suppose that misalignment between the attenuation scan and the FDG images might have caused an apparent reduction in FDG uptake in the septum. However, the acquisition technique (repositioning using laser beam and skin markers) excludes this possibility, as does the lack of reverse mismatch in the control group.

In other studies (*7,9*), FDG uptake was evaluated by

normalizing the data to the perfusion images to avoid possible interference from a flow–metabolism mismatch, as occurs in hibernating myocardium. In our study, the ^{13}N-NH_3 and FDG images were individually normalized; however, we considered the presence of hibernation extremely unlikely in our population, composed only of patients without significant coronary stenoses and signs of previous myocardial infarction. Therefore, the impaired FDG uptake not linked to reduction of flow could be the result of impaired transmembranous transport or phosphorylation kinetics, as affirmed by Altehoefer (*14*). We believe the hypothesis of an interference in cellular membrane pumps, perhaps through a modification in electric potentials, appears particularly attractive, because both FDG and thallium need active pumps to enter myocardial cells.

Another interesting hypothesis, presented by Wackers in an editorial (*15*), considered histologic damage secondary to cardiomyopathy to be the cause of altered septal uptake. This hypothesis is particularly attractive in our group of patients, who can essentially be considered affected by nonischemic dilative cardiomyopathy. Evaluation, using myocardial biopsy, of the differences in histology between the patients with and without LBBB will be interesting.

A limitation of our study is that evaluation of FDG and ^{13}N-NH_3 uptake was only semiquantitative. Real quantification of glucose use and blood flow can be relevant to understanding the underlying physiopathologic mechanisms but is not important from a clinical viewpoint. Most clinical PET studies of myocardial viability rely on visual analysis of images.

CONCLUSION

Our study confirms that in LBBB patients without coronary stenoses, septal glucose use is damaged without a correlating reduction in perfusion. This phenomenon produces a reverse mismatch with perfusion, when blood flow–dependent tracers such as ^{13}N-NH_3 are used, and can make the evaluation of myocardial viability in LBBB patients problematic.

Even if the underlying mechanism of this phenomenon is not clear, it can have a clinical implication. In the search for myocardial viability, the necrotic area in LBBB patients can be overestimated using FDG. For this reason, we strongly advise the use of other metabolic PET tracers, such as ^{11}C-acetate or fatty acids, in these patients. If these are not available, perfusion, at the least, should also be evaluated.

ACKNOWLEDGMENTS

The authors thank Dr. Alberto Fini, Dr. Luciano Vettorato, and Paolo Trento for helping with the studies; Enzo Pasqualetto for helping with photography; and Neil Herbertson for revising the language of the manuscript.

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