Metabolic Mismatch of Septal Beta-Oxidation and Glucose Utilization in Left Bundle Branch Block Assessed with PET

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Preserved septal uptake of the new long-chain fatty acid analog [^{18}F]FTHA was found in a patient with three-vessel disease, a history of previous anterior myocardial infarction and left bundle branch block (LBBB), despite severely decreased septal [^{18}F]FDG uptake that suggested scarred tissue. Nearly absent [^{19}F]FDG uptake in the septum could not be explained by concordant reduction of septal perfusion as assessed by ^{99m}Tc-MIBI SPECT. These data may point to divergent metabolic effects of the conduction abnormality in LBBB with consecutively reduced septal exogenous glucose utilization but unaffected septal beta-oxidation.

Key Words: left bundle branch block; beta-oxidation; positron emission tomography; fluorine-18-fluorodeoxyglucose; fluorine-18-FTHA

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Noninvasive evaluation of patients with left bundle branch block (LBBB) by use of scintigraphic techniques has been problematic due to frequently observed septal abnormalities unrelated to coronary artery disease (CAD) (*1*). Although direct effects of the conduction abnormality on septal wall motion (*2*) and septal uptake of ^{201}Tl (*1*) and ^{99m}Tc-MIBI (*3,4*) have been described, little is known about the metabolic effects (*5,6*). In patients with known CAD, however, assessment of myocardial viability by metabolic techniques may have important clinical implications for patient management. Preserved glucose utilization provides important information on the potential to regain contractile function after successful revascularization (*7*). We report a patient with three-vessel disease and LBBB, who showed preserved septal [^{18}F]FTHA uptake, indicating functioning beta-oxidation but severely decreased septal [^{18}F]FDG uptake, which usually reflects irreversibly damaged myocardial tissue (*7*).

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CASE REPORT

A 65-yr-old man had a history of anterior wall myocardial infarction 16 yr prior to investigation. Coronary angiography 7 days prior to SPECT and PET imaging was performed because of recurrent exercise angina pectoris and revealed three-vessel disease with occluded right coronary artery and proximal severe stenoses of the left anterior descending artery and the posterolateral branch of the left circumflex artery. Cineventriculography showed a globally hypokinetic left ventricle with pronounced hypokinesis of the apical anterior wall. Complete constant LBBB was documented by repeated electrocardiography.

SPECT

Myocardial perfusion at rest was assessed with ^{99m}Tc-MIBI SPECT by use of a previously described protocol (*8*) on the same day as the FDG-PET study. Regional ^{99m}Tc-MIBI uptake was calculated in 25 regions of interest (ROIs) in short-axis cuts and expressed relative to the ROI with maximal (=100%) tracer uptake (Fig. 1). A gender-reference population with low likelihood for CAD was used for comparison. In addition, septal-to-lateral count ratios were calculated for two midventricular horizontal long-axis slices (1.25-cm slice thickness) for comparison with the PET images.

PET

Attenuation-corrected static PET scans were obtained with an ECAT 953/15 (Siemens-CTI, Knoxville, TN). The FDG study was performed after oral glucose load with 50 g glucose given 1 hr prior to injection of 170 MBq [^{18}F]FDG. Static scans were acquired 30 min thereafter. The next day, FTHA uptake was studied in the fasted state. Static scans were obtained from 10 to 30 min postinjection of 140 MBq [^{18}F]FTHA. Fluorine-18-FDG was prepared according to the method of Hamacher et al. (*9*) and [^{18}F]FTHA according to DeGrado (*10*). In two reconstructed (Hanning filter, cutoff frequency 0.4, slice thickness 1.25 cm) horizontal midventricular long-axis cuts (Fig. 2), the septal-to-lateral count ratios of [^{18}F]FDG and [^{18}F]FTHA were calculated with the ROI technique.

RESULTS

SPECT

Regional ^{99m}Tc-MIBI uptake is shown in Figure 1. Reduced uptake was noted in the apex, two apical anterior ROIs and the apical septal ROI (marked regions). When compared to a gender reference population, septal ^{99m}Tc-

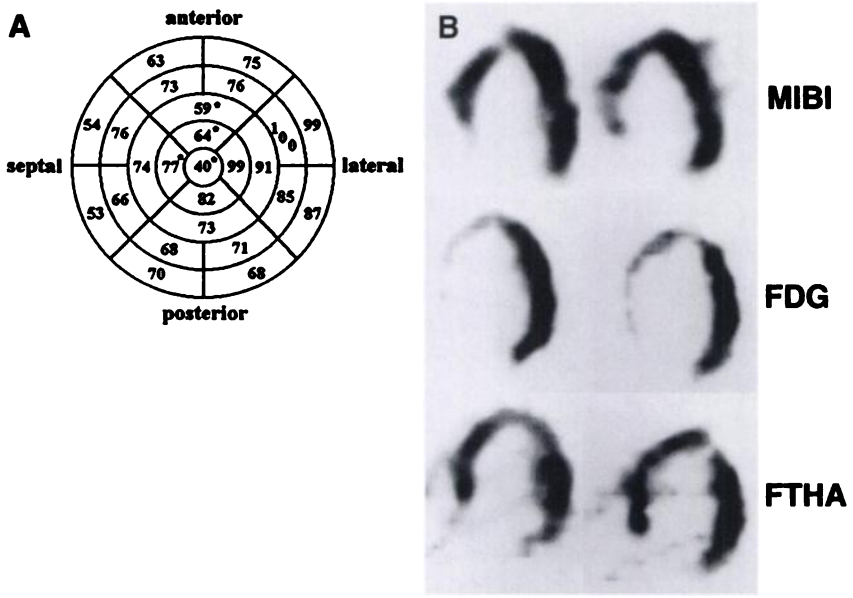

FIGURE 1. Regional ^{99m}Tc-MIBI uptake in percent peak activity in 25 ROIs in short-axis slices from apex (central ROI) to base (outer circle). When compared to a gender reference population, ^{99m}Tc-MIBI in our patient is decreased in the apex: two apical and one septal ROI (marked ROIs).

MIBI uptake was normal in five of six septal ROIs. The septal-to-lateral count ratios were >0.8 (Table 1).

Fluorine-18-FDG PET

Serum glucose levels at the time of tracer injection were 6.2 mmole/liter (normal: 3.8–6.2). Fluorine-18-FDG uptake was severely reduced in the interventricular septum (Fig. 2) and septal portions of anterior and posterior wall, whereas the lateral wall and the lateral portions of the anterior and posterior walls displayed normal tracer uptake. The septal-to-lateral count ratios were <0.6 (Table 1).

Fluorine-18-FTHA PET

The serum glucose level was between 4.3 and 4.6 mmole/l throughout the study, whereas the lactate blood level remained low (0.5 mmole/liter, normal: 0.6–2.4). Marked tracer uptake was seen in the liver. Myocardial tracer uptake was inhomogenous throughout the entire left ventricular wall and slightly decreased in the apical anterior wall after the previous infarction. The interventricular septum revealed similar uptake as the lateral wall, resulting in septal-to-lateral count ratios >0.8 (Table 1).

DISCUSSION

The conduction abnormality in LBBB has been shown experimentally to result in reduced regional myocardial blood flow as well as reduced [^{18}F]FDG uptake in the interventricular septum (*5*). This finding was interpreted to be caused by impaired systolic thickening and augmented intramyocardial pressure in the septum during LBBB (*5*). In a considerable number of patients with and without CAD, septal perfusion at rest determined by ^{99m}Tc-MIBI SPECT also was decreased (*3,4*). Experience in patients with LBBB using [^{18}F]FDG, which is accepted as an accurate marker of myocardial viability, has been limited. Our group recently demonstrated that septal [^{18}F]FDG uptake is significantly reduced in patients with CAD and LBBB as

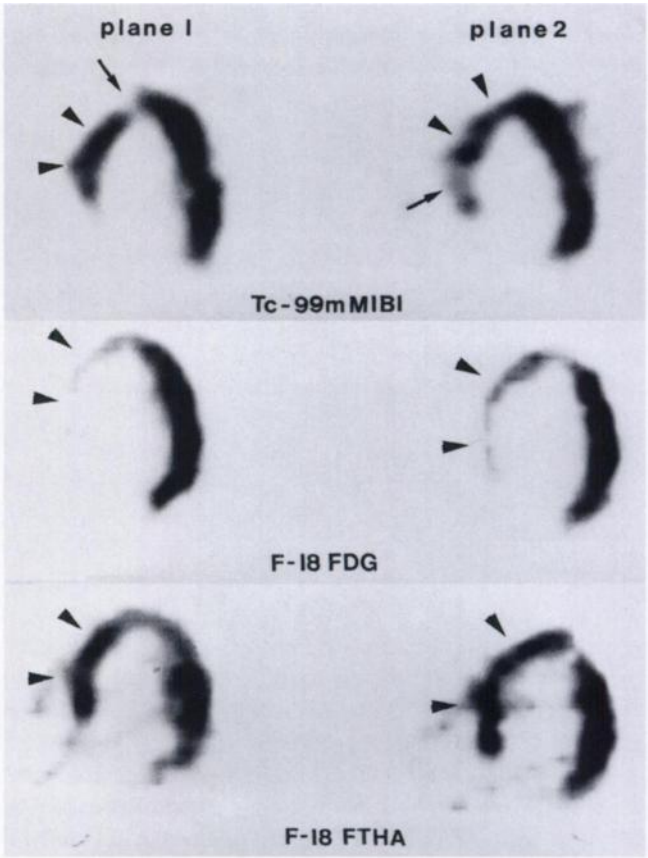

FIGURE 2. Myocardial uptake of ^{99m}Tc-MIBI, [^{18}F]FDG and [^{18}F]FTHA is displayed in two midventricular horizontal long-axis planes. Reduction of septal ^{99m}Tc-MIBI uptake is noted in only two small areas (arrows). Despite preserved ^{99m}Tc-MIBI uptake in large parts of the interventricular septum (arrowheads) and maintained septal [^{18}F]FTHA uptake (arrowheads) [^{18}F]FDG uptake is severely reduced in the entire septum (arrowheads), suggesting scarred myocardium.

TABLE 1
Septal-to-Lateral Count Ratios of Fluorine-18-FDG and Fluorine-18-FTHA Uptake in Two Midventricular Horizontal Long-axis Planes

Plane* no.	^{99m}Tc-MIBI	[^{18}F]FDG	[^{18}F]FTHA
1	0.81	0.54	1.11
2	0.84	0.47	0.90

*Planes according to Figure 2.

compared to a control group of patients with CAD but without this conduction abnormality (*6*). Our patient had an identical finding of impaired septal [^{18}F]FDG uptake. In regions of impaired contractility and resting perfusion, this finding is regarded as an accurate sign of scarred tissue (*7*).

Clinical data led to the assumption that septal [^{18}F]FDG uptake in LBBB is only of limited value for assessing septal viability (*6*). Therefore, further studies should aim at elucidating other metabolic pathways to characterize viability by a different metabolic approach. First, animal experiments indicated metabolic trapping of [^{18}F]FTHA after mitochondrial uptake (*11*). The carnitine palmitoyltransferase I inhibitor 2[5(4-chlorophenyl)-pentyl]oxirane-2-carboxylate (POCA) led to significant reduction of myocardial [^{18}F]FTHA uptake, suggesting a metabolic process associated with beta-oxidation (*11*). In humans, Patlak plots of myocardial FTHA kinetics showed a linear increase, indicating metabolic trapping (*12*). The mean uptake rate constant derived from Patlak analysis was linearly correlated to the patient's rate-pressure product as a correlate to oxygen consumption during continuous submaximal bicycle exercise (*12*). Therefore, the septal-to-lateral count ratios observed in our patient may indicate that not only mere fatty acid utilization but also septal beta-oxidation is preserved within the interventricular septum compared to the lateral wall.

Our data suggest that metabolic processes in myocytes of the interventricular septum may be observed in patients with LBBB, despite severely reduced FDG uptake. In LBBB, FTHA may indicate septal viability metabolically. Whether preserved septal FTHA uptake in this patient population reflects viability in terms of a predictive value for recovery of contractile dysfunction, however, is not certain and requires studies with a larger patient population.

Diminished septal FDG uptake in our patient could not be explained by concordant reduction of septal perfusion as assessed with ^{99m}Tc-MIBI. The septal-to-lateral count ratios were >0.8 for ^{99m}Tc-MIBI but <0.6 for [^{18}F]FDG. This finding of a reversed septal mismatch of ^{99m}Tc-MIBI and [^{18}F]FDG uptake in patients with LBBB was recently reported (*6*). This phenomenon, however, was not observed in a reference population without LBBB (*6*). In our patient, ^{99m}Tc-MIBI uptake was within normal limits in the majority of septal regions. Septal ^{99m}Tc-MIBI uptake indicates perfusion and viability because of mitochondrial uptake and tracer retention (*13*). In view of recent observations that septal ^{99m}Tc-MIBI uptake at rest is frequently reduced in LBBB, even in patients without CAD or other comprehensible organic heart diseases (*3,4*), septal ^{99m}Tc-MIBI uptake in our patient supports the interpretation that the septum is not irreversibly damaged as is suggested by FDG-PET.

The impaired septal [^{18}F]FDG uptake observed in our patient does not appear to have been caused by reduced substrate demand. Indeed, the cause of this phenomenon remains uncertain. Regionally altered transmembranous transport and phosphorylation rates for [^{18}F]FDG in relation to glucose (effect on the lumped constant) or a reduction of septal glucose uptake due to abnormal depolarization of septal myocardial cells require discussion. Changes in intracellular metabolic pathways may also lead to unresponsiveness of septal cells to increased glucose load or a shift to preferred fatty acid utilization.

CONCLUSION

Fluorine-18-FDG PET should be used with caution in patients with LBBB. FTHA, however, appears to be a promising ^{18}F-labeled compound which may be advantageous over [^{18}F]FDG in assessing septal viability in patients with CAD and LBBB. Further studies are required, however, to understand the metabolic processes associated with FTHA uptake and its clinical usefulness to FDG in predicting functional outcome after restoration of blood flow in patients with LBBB.

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