Myocardial Perfusion, Glucose Utilization and Oxidative Metabolism in a Patient with Left Bundle Branch Block, Prior Myocardial Infarction and Diabetes

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A diabetic patient affected by insulin-dependent diabetes, significant stenosis of left anterior descending (LAD) coronary, thrombolyzed myocardial infarction and complete left bundle branch block (LBBB) was examined by PET. Myocardial perfusion, glucose utilization and oxidative metabolism were evaluated by ^{13}N-ammonia, ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-acetate, respectively. Despite severe damage in ^{18}F-FDG uptake in the septum, with a septum-to-lateral ratio (S/L R) equal to 0.38, the oxidative metabolism in this area, evaluated quantitatively by dynamic acquisition, was relatively preserved (S/L R = 0.82), with a distribution similar to perfusion (S/L R = 0.87). These data reveal selective damage in glucose utilization in the septum in LBBB, unrelated to perfusion reduction and with preserved oxidative metabolism. Moreover, our experience could suggest an overestimation of the necrotic area by ^{18}F-FDG in LBBB patients.

Key Words: left bundle branch block; PET; fluorine-18-fluorodeoxyglucose; nitrogen-13-ammonia; carbon-11-acetate

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Perfusion and viability evaluation by scintigraphic techniques has always been problematic in coronary artery disease (CAD) patients affected by left bundle branch block (LBBB), in particular in the evaluation of the septum (*1*). A high number of patients presented false-positive fixed or reversible septal defects on the stress thallium imaging, not correlated with significant stenoses in the left anterior descending artery (*2,3*). Slightly better results were reported in applying pharmacological stress, dypiridamole (*4*) or adenosine (*5*), instead of exercise, or with sestamibi as the tracer (*6*). A low specificity of the scintigraphy study persists, however, both in the evaluation of perfusion defects and in the viability research. A similar situation has been referred in humans and animals in a limited number of studies with PET and ^{18}F-fluorodeoxyglucose (FDG) (*7,8*).

On the basis of this phenomenon, some authors supposed a real decrease in the perfusion of the septum, linked to an increase in intramyocardial pressure in diastolic phase (*1,8*). In contrast, other authors reported a preserved perfusion in this area, and supposed a shift in the metabolic substrate for cardiac myocites from glucose to fatty acids (*9*). However, the real mechanism causing this is not well understood. In particular, data are lacking concerning patients affected by diabetes, a metabolic disease often associated with CAD.

In this article, we report our experience concerning a diabetic patient affected by complete LBBB, stenosis of LAD and previous myocardial infarction in the anterior wall. The myocardial perfusion, glucose utilization and oxidative metabolism were evaluated by PET using ^{13}N-ammonia (NH3), ^{18}F-FDG and ^{11}C-acetate (ACE), respectively, as tracers.

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CASE REPORT

A 64-yr-old woman with a history of insulin-dependent diabetes dating back 10 yr and of an anteroseptal infarction (thrombolyzed by rTPA) occurring 2 mo before, was evaluated. The patient did not refer spontaneous or stress-related chest pain, or other symptoms referring to residual ischemia. Complete constant LBBB was documented by repeated ECG. The B-mode echocardiography, performed 15 days before the PET, revealed akinesia of the middle and apical regions of the anterior and septal walls of the left ventricle, with a telediastolic volume equal to 201 cm3 (121 cm3/m2 b.s.), the ejection fraction was 32%. At the coronary angiography, performed 20 days before PET, a critical stenosis (75%) of proximal LAD was found.

PET Studies

The PET studies were performed using a PET scanner that allows simultaneous acquisition of 47 contiguous transaxial images, with total axial field of view of 16.2 cm. The resolution of our scanner was 4.8 ± 0.6 mm in the axial direction and 6.1 ± 0.2 mm in the transaxial planes.

The first day a transmission scan was obtained for 15 min for attenuation correction, using retractable ^{68}Ge rod sources. For emission studies, the tracers were ^{13}N-NH3 (dose 10 MBq/kg) for perfusion, injected at rest, and ^{18}F-FDG (dose 4 MBq/kg) for metabolism, injected during a hyperinsulinemic euglycemic clamp (*10*). The emission scan started 4 min after the ^{13}N-NH3 injection and 45 min after the ^{18}F-FDG injection. The acquisition lasted 15 min with both tracers. Short-axis and vertical and horizontal long-axis slices, 0.8-cm thick 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 NH3 study, and 2 hr later the FDG study. To check the positioning of the patient in the scanner, a cross-shaped, low-power laser beam and pen-skin markers were applied. For image analysis, the count septum-to-lateral ratio (S/L R) of ^{13}N-NH3 and ^{18}F-FDG were calculated in the midventricular horizontal long-axis slice (interpolated at a thickness of 1.6 cm) with the region of interest (ROI) technique.

Twenty-four hours later, the patient was centered in the scanner, by laser beam, on the skin markers drawn during the first examination. Immediately after the injection of the tracer, performed in fasting condition at a dose of 15 MBq/kg, the ^{11}C-ACE emission scan was performed, by a 30-min dynamic acquisition (10 f/10 sec, 1 f/60 sec, 5 f/100 sec, 3 f/180 sec and 2 f/300 sec). From the acquired sinograms, the myocardial oxidative metabolism (MOM) was quantified in the midventricular horizontal long-axis slice, using the same two ROIs related to the septum and the lateral

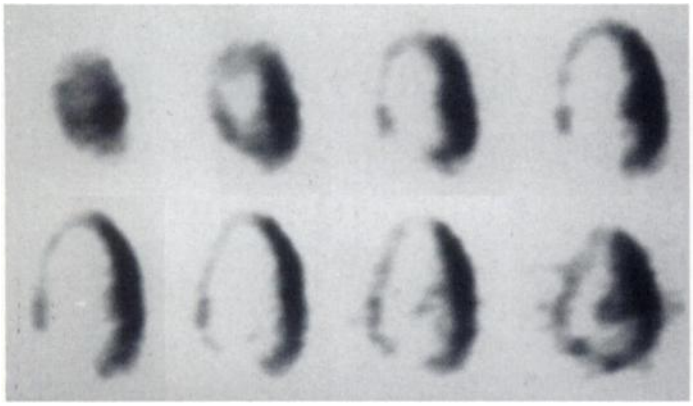

FIGURE 1. Fluorine-18-FDG horizontal long-axis slices (0.8-cm thick).

wall as in the ^{13}N-NH3 and ^{18}F-FDG studies. The MOM was calculated by determining the myocardial turnover rate constant of acetate (k mono) according to Armbrecht (*11,12*), which reflects the rate of clearance of ^{11}C activity from the myocardium and correlates closely with regional myocardial oxygen consumption. The MOM S/L R was then calculated.

RESULTS

The horizontal long-axis slices related to the ^{13}N-NH3 and ^{18}F-FDG studies are shown in Figures 1 and 2. Visual analysis shows the perfusion to be slightly reduced in the apex and in the middle and distal regions of the septum and anterior wall. In contrast, the ^{18}F-FDG uptake defect appears more extensive and severe, with almost no uptake of the septum extending to contiguous regions of the inferior and anterior walls.

The dynamic images obtained by ^{11}C-ACE (Fig. 3) revealed, at 5 min (perfusion phase), a distribution similar to ^{13}N-NH3, followed by a symmetrical dismissal of the tracer from the septum and the lateral wall, suggesting a similar oxidative metabolism in those areas.

The semiquantitative analysis, reported in Table 1, confirms the reverse mismatch between the perfusion and the glucose utilization, with a S/L R of 0.87 and 0.38, respectively. Quantitative analysis of the ^{11}C-ACE study revealed a MOM value of 0.071 in the septum and 0.087 in the lateral wall, with a ratio of 0.82.

DISCUSSION

In the ^{201}Tl perfusion scan, the reduction of uptake in the septum, not correlated to significant stenoses of coronary arteries, is a well-known phenomenon in LBBB patients and significantly reduces the specificity of the study (*1*). At the moment its genesis is not well understood. Some authors suppose a real hypoperfusion caused by the asynchrony of the wall motion presented in this conduction defect: the septal

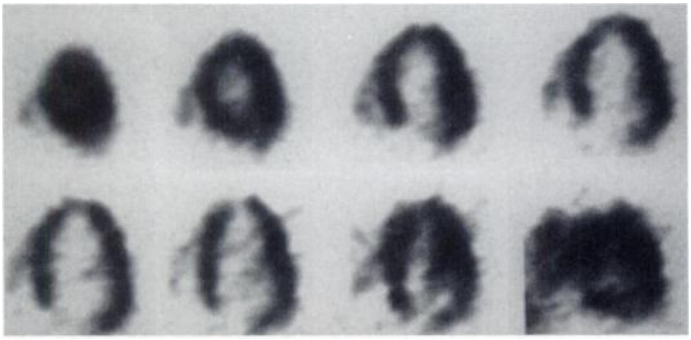

FIGURE 2. Nitrogen-13-NH3 horizontal long-axis slices (0.8-cm thick).

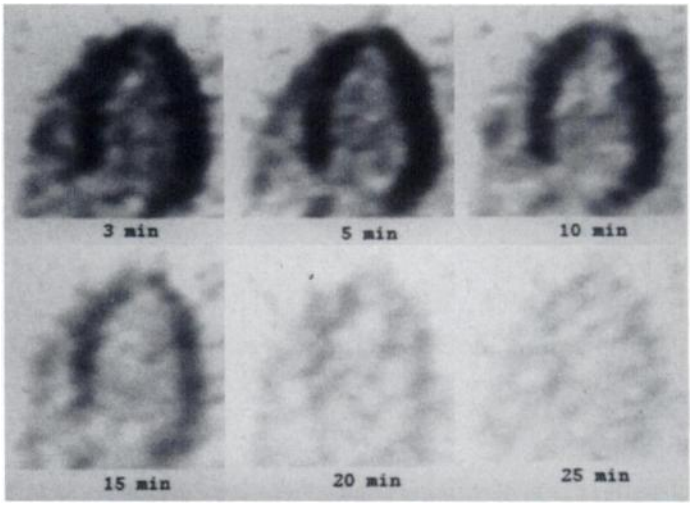

FIGURE 3. Carbon-11-ACE midventricular horizontal long-axis slices (0.8-cm thick), a dynamic sequence.

contraction occurs during the diastole, thus hampering the coronary filling and causing a flow reduction. The experimental study by Ono et al. (*8*) in dogs tends to confirm this hypothesis, as an increment in intramyocardial pressure in the septum in the diastolic phase, related to comparable reduction in ^{201}Tl and ^{18}F-FDG uptake in this area.

In the patient evaluated in our study, the differences between perfusion and glucose utilization are more striking. We could suppose different explanations for this. One might be that, in our study perfusion was evaluated by PET and ^{13}N-NH3, a tracer that passively diffuses into myocites and whose distribution is mainly influenced by regional blood flow. On the contrary, in the uptake of ^{201}Tl, used by Ono et al. (*8*), a relevant role is played by the metabolic activity of the myocardial cells.

Another explanation could be that our patient was affected by insulin-dependent diabetes. We cannot exclude an interference on ^{18}F-FDG uptake produced by this disease, although this hypothesis appears unlikely, as in our study the metabolic shift was obtained using an insulin-glucose clamp, a technique that seems to assure good ^{18}F-FDG uptake even in diabetic patients (*13*).

In LBBB, a preserved septal uptake of long-chain fatty acid was found by Altehoefer et al. (*9*), in spite of an altered FDG uptake, thus suggesting an unaffected beta-oxidation. In our study, the oxidative metabolism was quantitatively evaluated by ^{11}C-ACE. The measurement of oxidation of acetate provides an indirect measure of myocardial oxygen consumption (*14*), independent from changes in the proportion of substrate presented to the heart (*15*). Unlike glucose or fatty acid, acetate metabolizes virtually exclusively to mitochondrial oxidation. Our experience reveals a preserved MOM in the septum, with a S/L R similar to perfusion, and tends to confirm the hypothesis of an inability to utilize glucose as substrate in the septal region in the presence of LBBB. The reason is unknown, even if we could suppose an interference in neurovegetative control systems produced by the nervous damage at the basis of the LBBB.

TABLE 1
Septal-to-Lateral Ratios of Nitrogen-13-NH3 and Fluorine-18-FDG Uptake and Carbon-11-ACE Myocardial Oxidative Metabolism in Midventricular Horizontal Long-Axis Slice

^{13}N-NH3	^{18}F-FDG	^{11}C-ACE MOM
0.87	0.38	0.82

It could be interesting to study these patients by PET and recettorial tracers.

CONCLUSION

This study revealed damage in septal glucose utilization in a diabetic infarct patient affected by complete LBBB, not correlated to reduction in perfusion, and in presence of a preserved oxidative metabolism. This phenomenon could produce overestimation of the necrotic area in these patients and a reverse mismatch with perfusion when only "blood flow-dependent" tracers, such as ^{13}N-NH3, are used. Therefore, the use of ^{11}C-ACE instead of ^{18}F-FDG could be advisable in searching for myocardial viability in LBBB patients. Studies in larger populations are necessary, however, to confirm our observation.

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EDITORIAL

LBBB: Challenging Our Concept of Metabolic Heart Imaging with Fluorine-18-FDG and PET?

> Our revels now are ended: these our actors, as I foretold you, were all spirits and are melted into air, into thin air.
>
> Shakespeare, *The Tempest*

Metabolic characterization of the myocardium with PET has gained increasing clinical interest and acceptance among cardiologists with respect to accurately identifying tissue viability in patients with coronary artery disease. The ongoing development of positron emitting tracers allows in vivo imaging of different metabolic pathways, providing an estimate of cell function, metabolism and integrity. Among these tracers, ^{18}F-fluorodeoxyglucose (FDG) is the most frequently used and best investigated radiopharmaceutical in viability studies of the heart. Combined imaging of perfusion and glucose utilization with ^{18}F-FDG allows accurate identification of potentially reversible contractile dysfunction after revascularization (*1–3*). The patterns observed are generally differentiated into "perfusion-metabolism match" (concordant reduction of both blood flow and glucose utilization) or "mismatch" (reduced blood flow with preserved glucose utilization relative to perfusion). With respect to the potential recovery of contractile function after revascularization, the finding of a "match" implies a low probability for improvement of segmental contractility with an accuracy of 74% to 90% (*1,2*). Improvement of postrevascularization wall motion is predicted with a mean of about 78% of segments with a "mismatch" before revascularization (*2*). The positive predictive value of ^{18}F-FDG PET is further increased in patients with severe contractile dysfunction and in patients with documented vessel patency after revascularization (*3*). Based on investigations in more than 300 patients, PET has been recommended for assessing tissue viability (*1,2*).

With the investigation of patients with LBBB (*4–7*) at least parts of the classic scheme of metabolic imaging of the myocardium with ^{18}F-FDG has come under challenge. In this issue of *JNM*, Zanco et al. (*6*) presents PET images with various tracers in a patient with left bundle branch block (LBBB) and thrombolyzed myocardial infarction in the presence of a significant stenosis of the left anterior descending artery. Their case report shows a decreased septal ^{18}F-FDG uptake relative to septal blood flow, as assessed with ^{13}N-ammonia, and oxidative metabolism, as assessed with ^{11}C-acetate. Despite presentation of a single case report, their results are entirely consistent with recently reported findings (*4,5*). The operational term "reversed mismatch" has been introduced to describe the pattern of decreased ^{18}F-FDG uptake relative to myocardial blood flow (*4*). Burns (*8*) recently pointed out that "if LBBB poses an exception to its application, then the mechanism underlying this mismatch is essential to our understand-

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