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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ing (and acceptance of this use) of ^{18}F-FDG."

In an attempt to explain the findings observed in nuclear studies of patients with LBBB, the relationship between septal contractility, myocardial blood flow and exercise should be considered first. The mechanisms leading to false-positive perfusion studies at exercise with ^{201}Tl are not yet entirely understood. Delayed conduction in LBBB leads to asynchronous left ventricular contraction with septal contraction occurring in late systole extending into early diastole (*9–11*). It has been hypothesized that delayed septal contraction with increased intramyocardial pressure in early diastole impairs blood flow to the septal wall as most of the myocardial blood flow occurs in the diastolic period (*11,12*). In stress-rest studies with exercise-induced tachykardia resulting in shortened diastole may, therefore, further augment septal hypoperfusion relative to other myocardial areas. Furthermore, septal asynchrony may be more severe at higher heart rates leading to pronounced relative septal hypoperfusion. A relationship between the occurrence of false-positive septal defects and the increase in heart rate that is proportional to the increase in coronary blood flow during exercise has been reported (*13*). In contrast, the specificity and the predictive value of a positive test response is significantly increased if pharmacologic vasodilatation is used instead of an exercise test (*12*). It is postulated that pharmacologic dilatation uniformly increases blood flow throughout the myocardium without inducing tachykardia-related shortening of the diastolic filling period (*12*). Vaduganathan et al. (*12*) suggested that, with use of the positive inotropic dobutamine, "the relatively lower peak heart rate achieved during dobutamine may be partly responsible for the lower incidence of false-positive defects." The experimental study by Ono et al. (*11*) further supports these theories. Pacing-induced LBBB in open-chest dogs led to a significant reduction of microsphere-determined blood flow in the septum from 1.00 ± 0.25 in the controls to 0.53 ± 0.18 ml/min/g after induction of LBBB (*11*). This reduction in septal perfusion was accompanied by impaired systolic thickening and increased septal intramyocardial pressure in the diastolic phase. Septal hypoperfusion in LBBB apparently does not go along with septal ischemia as the lactate extraction rate in this study did not show a significant change after pacing-induced LBBB (*11*). Further explanations for false-positive septal defects at stress include other underlying heart diseases like small-vessel disease, dilative cardiomyopathy or fibrodegenerative changes (*14,15*). Septal perfusion at rest may be either normal (completely reversible septal defects on ^{201}Tl stress/redistribution studies, normal stress/rest ^{99m}Tc-MIBI studies) or diminished (partially reversible or fixed ^{201}Tl defects, constant ^{99m}Tc-MIBI defects) (*12,16,17*). Although conclusive data are lacking, reduced septal blood flow at rest may be related to the same effects as delineated for stress studies and/or a thinned septal myocardium due to chronic asynchronous electric activation as suggested by Prinzen et al. (*18*). It would be interesting to relate the occurrence and severity of resting perfusion defects to the length of the R-R interval to clarify the effect of the heart rate at rest.

In contrast to nuclear perfusion studies, data on metabolic imaging in patients with LBBB are rare. Until now, 10 patients with LBBB investigated with ^{18}F-FDG PET have been reported in the literature (*4–7*). According to Yamada et al. (*7*) PET with ^{18}F-FDG revealed "defect at the septal wall" in two patients with angiographically normal coronary arteries. The other eight patients reported had documented coronary artery disease and six of these had a history of myocardial infarction. All of these eight patients showed severely reduced septal ^{18}F-FDG uptake extending into the septal parts of the anterior and posterior walls. In the six patients reported by our group (*4*), this phenomenon could not entirely be explained by a concordant reduction of septal ^{99m}Tc-MIBI uptake. The pattern of a "reversed mismatch" in the septum in patients with coronary artery disease and LBBB was not observed in a control group of patients with coronary artery disease in the absence of this conduction abnormality. These preliminary data suggested that septal ^{18}F-FDG uptake may be impaired independently of septal perfusion and/or viability. To further clarify the assumption of damaged septal ^{18}F-FDG uptake due to the conduction abnormality we subsequently investigated a patient with ^{99m}Tc-MIBI, ^{18}F-FDG and the ^{18}F-labeled fatty acid FTHA (14(R,S)-[^{18}F]-fluoro-6-thia-heptadecanoic acid). In this patient, septal ^{18}F-FDG uptake was severely decreased despite normal ^{99m}Tc-MIBI uptake in the majority of septal regions and entirely normal ^{18}F-FTHA uptake throughout the septum (*5*). Experimental and clinical data indicated metabolic trapping of ^{18}F-FTHA after mitochondrial uptake, a metabolic process associated with beta-oxidation and a correlation to oxygen consumption (*19,20*). The case report presented by Zanco et al. (*6*) further questions the usefulness of ^{18}F-FDG to assess myocardial viability in patients with LBBB. Despite preserved septal perfusion after thrombolyzed myocardial infarction and preserved septal oxidative metabolism, ^{18}F-FDG uptake in the interventricular septum remains severely impaired. Thus, with our conventional understanding of ^{18}F-FDG uptake, this finding would imply scarred septum. The initial septal ^{11}C-acetate uptake and clearance rate, however, is similar to the findings in the lateral wall suggesting maintained septal viability (*21*). One might argue that the underlying insulin-dependent diabetes mellitus in this patient might have interfered with septal ^{18}F-FDG uptake. Such a hypothesis, however, could only be supported by a regionally altered "lumped constant" as ^{18}F-FDG uptake in the lateral wall in the setting of the hyperinsulinemic-euglycemic clamp technique was good. Furthermore, none of the previously investigated patients with LBBB suffered from diabetes mellitus.

What else then may be the underlying mechanism for impaired septal ^{18}F-FDG uptake in LBBB and how can we lift the veil? Myocardial ^{18}F-FDG uptake parallels exogenous glucose utilization by the myocardium. The affinity of the glucose analog ^{18}F-FDG to transmembranous transport through the glucose transporter protein and phosporylation by hexokinase differ from glucose. The three-compartment model by Sokoloff corrects for this difference by incorporating the so-called "lumped constant". The phosphorylated ^{18}F-FDG is metabolically trapped without significant further metabolism. Impaired septal ^{18}F-FDG uptake that is not paralleled by a concordant reduction of flow to the myocardial septum must then be the result of impaired transmembranous transport and/or phosphorylation kinetics. This hypothesis either implies a regionally altered "lumped constant" by delayed conduction (not by diabetes mellitus) or alterations in the metabolic control mechanisms with a regional shift to preferred fatty acid utilization depite the application of either oral glucose load or the hyperinsulinemic-euglycemic clamp technique. The latter theory is supported by the documented preserved ^{18}F-FTHA uptake in our patient (*5*). To clarify the role of the "lumped constant" in LBBB, studies using ^{11}C-labeled glucose would be an intriguing subject for further investigations. Carbon-11-acetate rapidly enters the tricarboxylic acid cycle after activation to acetyl-CoA. The clearance

of ^{11}C-acetate from the myocardium, therefore, reflects the activity of the tricarboxylic acid cycle. Unaffected uptake of ^{18}F-FTHA and ^{11}C-acetate, as well as unaffected ^{11}C-acetate clearance in the septum relative to the lateral wall in patients with LBBB (*5,6*), nearly exclude reduced septal substrate demand as the underlying cause for the observed impairment of septal ^{18}F-FDG uptake. In their experimental study, Ono et al. (*11*) also considered reduced substrate demand unlikely for impaired septal ^{18}F-FDG uptake, "because the intramyocardial pressure in the septum was not reduced compared with the control level, suggesting that an asynchronous but reserved myocardial thickening was occurring." Their finding of reduced microsphere-determined septal blood flow in this experimental study design of pacing-induced LBBB is not in contradiction to the findings in patients with LBBB. Pacing significantly increases heart rate and, therefore, does not reflect a true resting state. Because of the relationship between septal contractility, blood flow and heart rate, reduced septal blood flow in pacing-induced LBBB is not surprising and consistent to stress/rest studies in patients. The conclusion that "reduced glucose uptake during LBBB is probably related to the reduced septal perfusion and thickening" appears tempting. However, due to the reasons mentioned above, independent mechanisms of septal blood flow and ^{18}F-FDG uptake (not necessarily glucose utilization) in LBBB may not be assessed with pacing-induced LBBB. The available metabolic data in patients, all of whom were investigated in the resting state, appear to indicate a decoupling of septal blood flow and ^{18}F-FDG uptake by the conduction abnormality itself.

Although the altered metabolic processes in delayed septal conduction remain poorly understood and only a few patients have been investigated so far, these preliminary observations suggest that ^{18}F-FDG may not serve as an accurate tracer for assessing viability in patients with LBBB. Despite the limitation of the available studies, that included only patients with severe coronary artery disease, alternate tracers such as fatty acids, acetate or ^{201}Tl after rest injection should be preferred. Further studies should aim to investigate larger patient populations, patients with angiographically-excluded coronary artery disease and use of additional metabolic tracers.

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