**EDITORIAL**

# Reverse Flow–Metabolism Mismatch: What Does It Mean?

The use of $^{18}$F-fluorodeoxyglucose (FDG) as a metabolic tracer in cardiology is likely to gain clinical acceptance with the availability of lower cost instrumentation that allows imaging of $^{18}$F using high-energy collimators or coincidence electronics in combination with standard SPECT equipment (*1,2*). The clinical utility of FDG imaging in cardiology for the assessment of tissue viability has been documented extensively in recent years (*3*). Beside the well-documented predictive value for functional recovery after revascularization (*3,4*), the prognostic implications of increased FDG uptake have been recognized by several investigators (*5–8*). This adds support to the use of this tracer in the identification of high-risk patients who are likely to benefit from revascularization. In addition, FDG imaging can be helpful in identifying patients with acceptable perioperative risk, even in the presence of severely depressed left ventricular function, as shown recently by our group (*9*). In view of the expected increased clinical use, the biological and methodological understanding of FDG imaging is important in the interpretation of scintigraphic patterns associated with the application of flow and metabolic tracers. Mismatch between flow and metabolism is one scintigraphic pattern that has been used as a hallmark of ischemically jeopardized myocardium. In addition, other criteria, including mild reduction of flow and metabolism (*10*), fixed relative threshold values (*11*) and quantitative estimates of glucose utilization (*12*), have been proposed as useful parameters of tissue viability.

In this issue of the *Journal of Nuclear Medicine,* Yamagishi et al. (*13*) address the scintigraphic finding of more severely reduced FDG uptake in comparison to $^{13}$N-ammonia (NH3) tissue retention. They define this pattern as "reverse mismatch" and describe its incidence in patients with recent myocardial infarction and in patients with chronic stable coronary artery disease. This pattern was seen more frequently in patients with recent myocardial infarction. More importantly, the data suggest that this scintigraphic pattern is associated with multivessel disease.

These observations are interesting and describe for the first time the relatively high incidence of reverse mismatch in patients after acute myocardial infarction (AMI). The clinical and pathophysiological significance of the findings, however, remains poorly defined. There is a large overlap of data among the four groups studied, and little data are provided to identify clinical details associated with reverse mismatch. The hypothesis of the investigators, that such a scintigraphic pattern would be of clinical utility in identifying patients with multivessel disease, remains speculative, unless the prognostic significance of such findings is defined in a larger patient cohort. Furthermore, the patient selection criteria for the study protocol are important in drawing clinical conclusions. It would be interesting to understand why patients in this study underwent PET after AMI. The left ventricular ejection fraction was only mildly reduced in this patient population, which suggests only mild left ventricular dysfunction. This patient population does not represent the widely accepted indication for tissue viability studies.

A defect in FDG uptake that is more severe than a corresponding defect in NH3 uptake has been noted in few publications (*14–16*). The frequency of a reverse flow–metabolism pattern has been reported to vary considerably from no detected case to 65% of investigated patients. This large range reflects differences in the selection criteria, which included patients after AMI or patients with chronic coronary artery disease, and in data analysis. Yamagishi et al. restricted their analysis to the infarcted region, whereas others evaluated all myocardial segments. Perrone-Filardi et al. (*14*) investigated 23 patients with coronary artery disease, who had more severely impaired left ventricular function than the patients in the study by Yamagishi et al. Perrone-Filardi et al. found that regions with moderately reduced FDG uptake occurred commonly in chronic coronary artery disease (26%). Interestingly, the reverse flow–metabolism mismatch pattern was most prevalent in the regions of the lateral wall (44%) and septum (28%), indicating considerable regional variations in that finding. Most of these regions exhibited impaired systolic function on rest and exercise-induced $^{201}$Tl abnormalities that were only partially reversible regions. The investigators concluded that such regions represent a mixture of fibrotic and reversibly ischemic myocardium. However, the pathophysiological mechanism of reduced glucose utilization despite normal perfusion remains unclear.

The regional comparison of FDG and NH3 has been performed in many studies to identify ischemically jeopardized myocardium (*17*). Most investigations have used visual interpretation of PET images for the detection of regional mismatch between FDG and NH3 uptake. Few semiquantitative ap-

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proaches have been validated in the literature. Semiquantitative comparison of NH3 and FDG data are limited by several factors. Relative NH3 retention represents regional myocardial perfusion in relation to a myocardial segment with maximal tracer retention. This segment is considered to be normally perfused, and ischemia or scar is defined on the basis of the relative decrease of the signal. On the other hand, FDG uptake represents a metabolic signal that can be affected globally by the metabolic state of the patient and regionally by alterations of substrate use. FDG uptake in the myocardium is not directly correlated to myocardial blood flow and varies in normal myocardium on the basis of overall metabolic conditions. Therefore, it is difficult to define normal FDG uptake in semiquantitative terms, because metabolic variation affects both normal and ischemically compromised myocardium.

Within the normal myocardium, there are regional differences in NH3 and FDG uptake. Gropler et al. (*18*) first described heterogeneity of FDG uptake with relatively decreased FDG uptake in the septum in comparison with the lateral wall. NH3, on the other hand, displays relative decreased retention in the lateral wall despite documented homogeneity of myocardial perfusion (Fig. 1). The mechanism for this regional variation of cardiac FDG uptake and NH3 kinetics is not clear, but it is not related to differences in regional perfusion. Quantitative measurements differentiating initial ammonia uptake and retention suggest that the metabolic trapping of NH3 in the lateral wall may differ from that in other areas of the myocardium (*19*). Yamagishi et al. (*13*) did not indicate the anatomic location of segments with reverse mismatch pattern, which, based on the normal distribution, are expected to occur even in healthy persons, especially in the interventricular septum.

An important step in the semiquantitative analysis comparing NH3 and FDG is the normalization of regional activity. It is not clear from the study by Yamagishi et al. whether "100% activity" was defined in the same location on NH3 and FDG images. Because FDG uptake can increase and decrease under various conditions, normalization is the most important issue for the relative comparison with NH3 activity (Fig. 2). Various approaches for normalization have been proposed but few have been clinically validated in comparison with visual interpretation (*20*). A large variation in scintigraphic patterns based on different ratios of regional tracer activity is expected in the case of independent normalization of NH3 and FDG images. Assuming that the myocardial segments with the highest NH3 uptake represent the areas with the highest likelihood of normal perfusion, normalization of regional FDG uptake to the area of highest NH3 uptake may be an approach to correct for variation of FDG uptake in normal myocardium. This approach would allow the definition of FDG uptake in areas of reduced perfusion in compari-

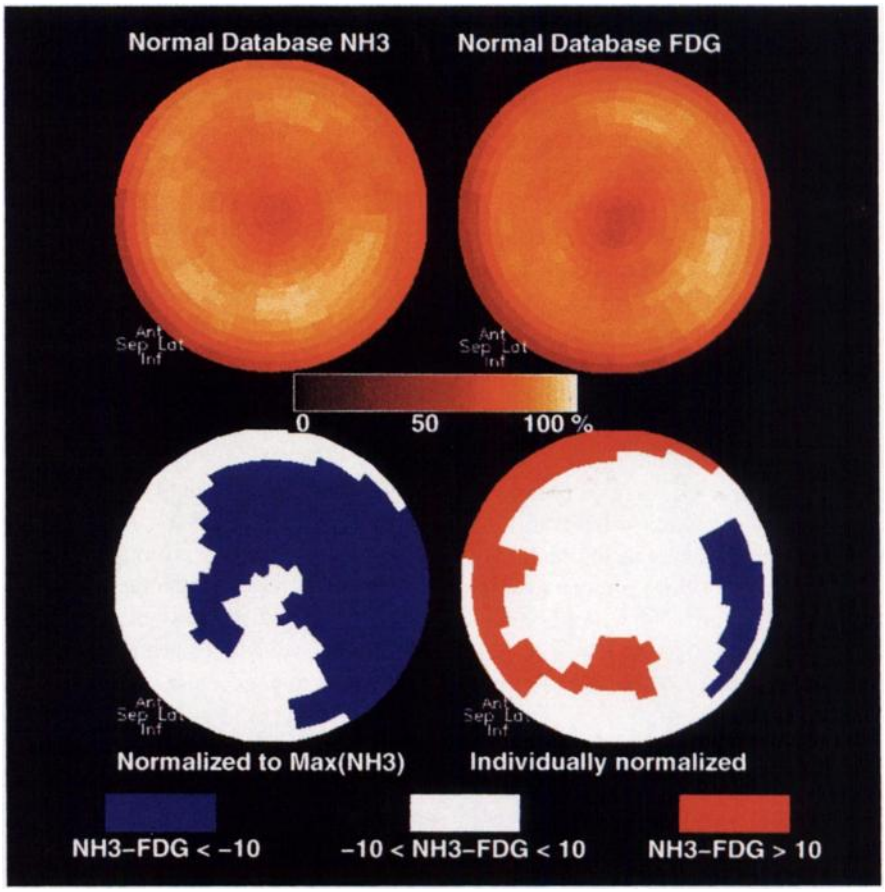


**FIGURE 1.** Top row depicts NH3 and FDG "normal" polar maps, representing mean values of relative tracer retention from 20 healthy volunteers after oral glucose load. Using these two normal databases, subtracting and segmenting with ±10% threshold yields different results depending on applied normalization. Whereas in left map normalization to maximal uptake in NH3 map is used, right map shows effect of individual normalization. Blue segments reflect extent of mismatch (NH3 − FDG < −10%) and red segments reflect reverse mismatch (NH3 − FDG > 10%). Note regional pattern representing normal mismatch between perfusion and metabolism.

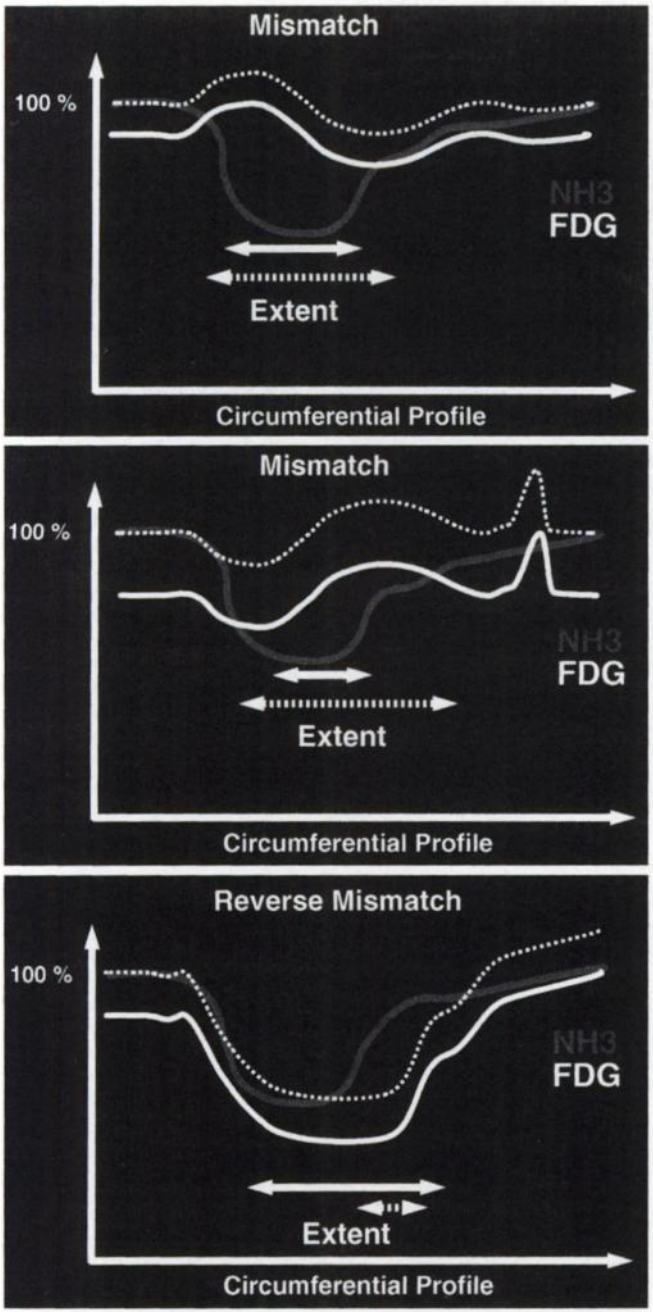


**FIGURE 2.** Effect of normalization in semiquantitative polar map analysis is shown in three different circumferential profiles. In all graphs, NH3 (gray) and FDG profile (white) with defects are shown. Dashed lines correspond to normalization to maximal NH3 uptake; solid line results from normalizing FDG data to its own maximum. When estimating extent of region that shows 10% difference between ammonia and FDG, results may differ to various degrees. (Top) Example shows relatively similar result, whereas second mismatch example (middle) and reverse mismatch (bottom) are significantly altered.

son with normal myocardium. It would be interesting to know how such a method of analysis would alter the results presented by Yamagishi et al. It is important to note that there is currently no standardized semiquantitative analysis method available that has been prospectively tested in a large patient cohort.

Metabolic standardization is of utmost importance in enhancing regional myocardial glucose utilization and, hence, FDG uptake. Yamagishi et al. used an oral glucose load, which is an accepted clinical method. However, it is associated with considerable variability in FDG uptake, especially in patients with abnormal glucose tolerance or clinically defined diabetes mellitus. The preferred methods include the use of simplified clamp procedures or infusion of acipimox (*21*). Maximizing myocardial glucose use by insulin clamp may minimize interindividual variations of FDG uptake and the influence of diabetes mellitus on FDG uptake. Insulin resistance is frequently observed in patients with coronary artery disease and may be associated with reverse mismatch because areas that are normally perfused display decreased FDG uptake as a consequence of low glucose use. Insulin resistance causes a lack of translocation of glucose transporters in response to insulin and, therefore, low glucose uptake in normal myocardium (*22*). Finally, in patients with AMI, the acute necrosis may be associated with accumulation of leukocytes, which are known to have a high glycolytic rate (*23*). Several studies indicate that the predictive value of FDG is lower in the subacute phase of myocardial infarction than in chronic coronary artery disease (*16*).

## CONCLUSION

There may be several conditions associated with reverse flow–metabolism mismatch. Thus, mismatch can be a consequence of technical factors, such as normalization of activity, but also of biological factors causing altered substrate use in normally perfused myocardium. Because of technical and biological variabilities, the clinical significance of this finding is not well defined. In addition to studies addressing the prognostic implications of reverse flow mismatch, further studies with rigid metabolic standardization are required to investigate the question of whether reverse mismatch actually represents a phenomenon related to ischemic myocardial

injury or reflects only normal biological variation.

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