Effect of Methodology on Mismatch

TO THE EDITOR: We read with interest the article by Dobbeleir et al. (*1*) dealing with the influence of scatter on the presence and extent of mismatching between ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) and ^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) in myocardial scintigraphy. With the increase of clinical data on fatty acid imaging, there is a growing need to address basic, methodologic issues. This is especially important when conflicting results are found, such as the observation of the BMIPP-perfusion mismatch (or discordance), i.e., lower BMIPP uptake relative to perfusion, versus reversed mismatch, i.e., higher BMIPP uptake relative to perfusion.

We believe that Dobbeleir et al. conducted an important study on methodologic parameters affecting the presence and extent of mismatching between ^{99m}Tc-MIBI perfusion and BMIPP myocardial activity. Different methods of data processing were compared, especially the effect of scatter correction. In their introduction it was suggested that scatter of the high-energy photons of ^{123}I (440–625 keV) in the collimator septa contributes to an increased background level. This, however, is hardly the case: The backscatter peaks of these photons lie in the energy range of 162–181 keV. Therefore, only a small fraction of scattered high-energy photons will be present in the photopeak window (143–175 keV) used for imaging. In the Materials and Methods section, it became clear that the authors were referring to scattered photopeak photons: A second energy window between 116 and 142 keV was applied. The technique used for this (lower energy) photon scatter is based on the study by Gilardi et al. (*2*), in which ^{99m}Tc is used. Dobbeleir et al. applied the dual-window technique, which was tested by Gilardi et al., but the use of this technique with a radionuclide such as ^{123}I has not been validated. The energy spectrum of ^{123}I is built up in a different way than that of ^{99m}Tc because of the decay type of the former. Hence, a conflict with a basic assumption arises, as stated by Gilardi et al., "The unwarranted assumption that the scatter distribution within a secondary energy window is a good estimate of the true scatter." How do Dobbeleir et al. account for the difference in energy spectrum?

Furthermore, only 10 patients were studied, of whom only 6 underwent revascularization. In 2 patients, a negative BMIPP uptake in the myocardium was found because of overcorrection of the background activity. In addition, clinical outcome had been used as the standard for quantifying the correction methods, whereas the assessment of true tissue counts in an animal model, comparing true activity distribution with distribution of activity acquired by SPECT, might be the optimal validation of the correction method.

Dobbeleir et al. suggested that increased ^{123}I background activity can partly or completely disguise the reduction in fatty acid uptake or even result in increased uptake, as reported by Sloof et al. (*3*). However, many other groups have also reported increased fatty acid uptake relative to flow, particularly in animal models in which assessment of tissue activity is not hampered by background activity from surrounding tissues, indicating the validity of this observation (*4*). Furthermore, Yang et al. (*5*), in the same issue of the *Journal of Nuclear Medicine,* and Marie et al. (*6*), in the May issue of the *European Journal of Nuclear Medicine*, both reported relatively increased fatty acid uptake, albeit with different fatty acid analogs, in different models.

We would appreciate comments by Dobbeleir et al. on the following issues:

What do they consider to be the (patho-)physiologic mechanism behind the relatively decreased fatty acid uptake as a good indicator for myocardial viability? In other words, why is depressed myocardial fatty acid uptake a good predictor of myocardial viability instead of preserved fatty acid metabolism, which seems more logical from a physiologic point of view?

Other clinical data so far strongly support the suggestion that a BMIPP-perfusion mismatch (i.e., BMIPP uptake lower than perfusion) in dysfunctional myocardium is a good predictor of functional recovery after revascularization, whereas myocardial tissue with a BMIPP-perfusion match is not likely to show functional recovery (*7*). These investigations, however, did not perform scatter correction nor apply medium-energy collimators. Would Dobbeleir et al. comment on the influence of these methodologic factors on the accuracy of BMIPP-perfusion scintigraphy for myocardial viability?

REFERENCES

1. Dobbeleir AA, Hambye AE, Franken PR. Influence of methodology on the presence and extent of mismatching between ^{99m}Tc-MIBI and ^{123}I-BMIPP in myocardial viability studies. *J Nucl Med.* 1999;40:707–714.
2. Gilardi MC, Bettinardi V, Todd-Pokropek A, Milanesi L, Fazio F. Assessment and comparison of three scatter correction techniques in single photon emission computed tomography. *J Nucl Med.* 1988;29:1971–1979.
3. Sloof GW, Visser FC, Bax JJ, et al. Increased uptake of iodine-123-BMIPP in chronic ischemic myocardium: comparison with fluorine-18-FDG SPECT. *J Nucl Med.* 1998;39:255–260.
4. Miller DD, Gill JB, Livni E, et al. Fatty acid analogue accumulation: a marker of myocyte viability in ischemic-reperfused myocardium. *Circ Res.* 1988;63:681–692.
5. Yang JY, Ruiz M, Calnon DA, Watson DD, Beller GA, Glover DK. Assessment of myocardial viability using ^{123}I-labeled iodophenylpentadecanoic acid at sustained low flow or after acute infarction and reperfusion. *J Nucl Med.* 1999;40:821–828.
6. Marie PY, Menu P, Angioi M, et al. The kinetics of β-methyl-substituted labelled fatty acids in ischaemic myocardium: an analysis in man and with a blood-perfused isolated heart model. *Eur J Nucl Med.* 1999;26:474–482.
7. Yoshida S, Ito M, Mitsunami K, Kinoshita M. Improved myocardial fatty acid metabolism after coronary angioplasty in chronic coronary artery disease. *J Nucl Med.* 1998;39:933–938.

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REPLY: We thank Sloof et al. for their interest in our article (*1*). Our study was performed because we noted higher background activity in our ^{123}I-β-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) images compared with ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) for myocardial scintigraphy. This observation was visually confirmed by attentive analysis of published ^{123}I-BMIPP images in

several articles, including their own article (*2*). When quantifying background activity with both isotopes in 10 patients, we found 12% higher background activity compared with the maximum activity for ^{123}I-BMIPP images. We believed that for quantitative or semiquantitative analysis, this basic methodologic issue was important.

We completely disagree with Sloof et al. that only a small fraction of scattered high-energy photons is present in the photopeak window when low-energy collimators are used, because backscatter is not the only problem. The γ-ray spectra recorded for pure ^{123}I(p,5n) show, even in air, a continuous scatter component from the photopeak up to the high-energy photons. An important methodologic article that deals with this problem was published in 1986 by Macey et al. (*3*). They attributed this phenomenon to high-energy photon penetration through the collimator septa. These produce lead x-rays, bremsstrahlung, and secondary electrons in the collimator material close to the detector and are efficiently detected, causing summation effects. Furthermore, Macey et al. observed elevated apparent ^{123}I sensitivity values compared with ^{99m}Tc. This was confirmed by De Geeter et al. (*4*), who measured a relative sensitivity low-energy or medium-energy collimator of 0.74 for ^{99m}Tc but 1.53 for ^{123}I and also showed a nonlinear relationship between real and measured activity. In addition, we have reported a distance-dependent influence of high-energy photons (*5*). From those data, it can be concluded that the scatter component measured in the photopeak is important for ^{123}I. Furthermore, it depends not only on collimator specificities but also on individual patient-related factors such as organ distribution of the tracer in or out of the field of view and organ–detector distance.

We agree that the chosen scatter correction method for ^{123}I might not be optimal. Meanwhile, we changed to a triple-energy window correction without noticeable difference. Independent of the small number of chronic patients studied, the mean difference between ^{99m}Tc-MIBI and ^{123}I-BMIPP uptake in the infarcted area was highly significant according to the correction method applied to both tracers and varied from 0.4% for no correction to 6.4% for scatter correction and 12.8% in the case of uniform background subtraction. Applying quantitative or semiquantitative analysis between flow and fatty acid uptake, these method-dependent differences are critical for assessment of viability.

Our study was conducted partly to find out whether the methods used in the literature might influence the assessment of myocardial viability with BMIPP. The published data were obtained using different collimators (low or medium energy) and had background, scatter, or no correction applied to the reconstructed or projection images. In our study (*1*), we showed that these methodologic differences might be a source of conflicting results.

Regarding the possible influence of methodologic factors such as scatter correction on the accuracy of BMIPP-perfusion scintigraphy for viability, we can state several things. First, most groups do not mention whether they apply a correction. Second, the groups we cited and also Tamaki et al. (*6*), who performed a large study on patients with chronic myocardial infarction, used 180° acquisition instead of 360° as did we and Sloof et al. Despite possible introduction of distortions, 180° acquisition avoids increased contribution of liver counts that are strongly present in ^{123}I-BMIPP studies. In a previous study comparing 360° with 180° reconstruction with ^{99m}Tc-MIBI, the contrast ratio dropped from 9.9 with 180° to 4.7 with 360° (*7*). This will certainly be worse for ^{123}I-BMIPP. Third, most studies rely on visual analysis. When experienced observers analyze the images, they are likely to take the differences in background activity into account in the interpretation of the data.

Regarding the use of clinical outcome as a reference for validating the correction methods, we agree that animal studies are probably the optimal validation. However, clinical outcome is an accepted standard for validation of a method for viability assessment because the ultimate goals of viability studies in patients are to predict functional improvement as accurately as possible and to differentiate patients who are likely to benefit from revascularization from those who will not.

Increased fatty acid uptake has been reported with other fatty acids. With BMIPP, higher uptake than perfusion is rarely reported in patient studies and seems to be associated with unstable conditions.

Regarding the (patho-)physiologic mechanism behind the relatively decreased fatty acid uptake associated with tissue viability in coronary syndromes, it constitutes a relative decrease compared with flow and not an absence of uptake. Mismatching indicates metabolically jeopardized but viable myocardium. Ischemia is associated with a shift from β-oxidation of fatty acids to glycolysis for producing high-energy phosphates. Because glycolysis is less efficient, intracellular adenosine triphosphate (ATP) concentration decreases. Because there is a high correlation between intracellular concentration of ATP and intracellular accumulation of BMIPP, decreased ATP concentration is likely to result in decreased BMIPP activation, hence increased backdiffusion of nonmetabolized BMIPP. This phenomenon may play an important role in myocardial perfusion–metabolism mismatch on SPECT images.

In conclusion, in our study (*1*), we clarified the possible misinterpretation of image comparison between isotopes with similar energies but different energy spectra. In a similar way, care should be taken when comparing low-energy with high-energy isotopes because of huge attenuation differences. Adequate scatter and attenuation correction should be applied to avoid misinterpretation of the results.

REFERENCES

1. Dobbeleir AA, Hambÿe AE, Franken PR. Influence of methodology on the presence and extent of mismatching between ^{99m}Tc-MIBI and ^{123}I-BMIPP in myocardial viability studies. *J Nucl Med.* 1999;40:707–714.
2. Sloof GW, Visser FC, Bax JJ, et al. Increased uptake of iodine-123-BMIPP in chronic ischemic heart disease: comparison with fluorine-18-FDG SPECT. *J Nucl Med.* 1998;39:255–260.
3. Macey DJ, DeNardo GL, DeNardo SJ, Hines HH. Comparison of low- and medium-energy collimators for SPECT imaging with iodine-123-labeled antibodies. *J Nucl Med.* 1986;27:1467–1474.
4. De Geeter F, Franken PR, Defrise M, Andries H, Saelens E, Bossuyt A. Optimal collimator choice for sequential iodine-123 and technetium-99m imaging. *Eur J Nucl Med.* 1996;23:768–774.
5. Dobbeleir A, Hambÿe AS, Franken PR. Influence of high-energy photons on the spectrum of iodine-123 with low- and medium-energy collimators: consequences for imaging with ^{123}I-labelled compounds in clinical practice. *Eur J Nucl Med.* 1999;26:655–658.
6. Tamaki N, Tadamura E, Kudoh T, et al. Prognostic value of iodine-123-labelled BMIPP fatty acid analogue in patients with myocardial infarction. *Eur J Nucl Med.* 1996;23:272–279.
7. Hambÿe AS, Dobbeleir A, Stulens E, Vervaet A, Vandevivere J, Franken PR. 240 degrees: why not? *Nucl Med Commun.* 1996;17:583–690.

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