Estimation of Myocardial Perfusion and Viability Using Simultaneous ^{99m}Tc-Tetrofosmin–FDG Collimated SPECT

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This study was designed to elucidate the usefulness of crosstalk correction for dual-isotope simultaneous acquisition (DISA) with ^{99m}Tc-tetrofosmin and FDG in estimating myocardial perfusion and viability. **Methods:** Eighteen patients with coronary artery disease were studied. First, SPECT was performed with a low-energy high-resolution collimator after a single injection of ^{99m}Tc-tetrofosmin (single ^{99m}Tc-tetrofosmin). Second, PET and DISA with an ultra-high-energy collimator were performed after glucose loading and an injection of FDG. DISA was designed to operate with simultaneous 3-channel acquisition, and weighted scatter correction of crosstalk from the ^{18}F photopeak to the ^{99m}Tc photopeak was performed by modification of an existing dual-window technique. The FDG SPECT images were compared with the images obtained by PET. Both crosstalk-corrected and uncorrected ^{99m}Tc-tetrofosmin images were generated and compared with the single ^{99m}Tc-tetrofosmin images. **Results:** Regional percentage uptake of FDG agreed well between DISA and PET. However, regional percentage uptake of ^{99m}Tc-tetrofosmin was generally higher on the uncorrected ^{99m}Tc-tetrofosmin images than on the single ^{99m}Tc-tetrofosmin images, especially in areas of low flow (percentage count of ^{99m}Tc-tetrofosmin ≥ 50%). The crosstalk correction contributed to improving the agreement between regional percentage uptakes and significantly improved the detectability of myocardial perfusion–metabolism mismatching. **Conclusion:** With 3-channel acquisition and weighted-scatter correction of crosstalk from the ^{18}F photopeak to the ^{99m}Tc photopeak, DISA with ^{99m}Tc-tetrofosmin and FDG is feasible for assessing regional myocardial perfusion and viability.

Key Words: FDG; SPECT; ^{99m}Tc-tetrofosmin; dual-isotope acquisition

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The identification of injured but viable myocardium in patients with previous myocardial infarction and left ventricular dysfunction has become increasingly important as a means of predicting improvement in the ventricular performance of hibernating myocardium after surgical revascularization (*1,2*). The contractility of hibernating myocardium is impaired because of chronic hypoperfusion; however, the metabolism is preserved, producing a perfusion–metabolism mismatch. Until now, perfusion–metabolism mismatching has been assessed mainly by PET, but a recent modification to SPECT enables it, with FDG, to provide clinical information equivalent to that from PET (*3–5*).

The advantage of FDG SPECT over PET is the use of dual-isotope simultaneous acquisition (DISA) by combining a ^{99m}Tc-labeled myocardial perfusion agent and FDG. The benefit lies in the shorter duration of procedures, with an identical geometric registration of the different isotope images. The reduction in patient study time decreases the risk of artifacts caused by patient motion and improves patient throughput and comfort. Quantification of DISA imaging, however, is limited by the contribution of the movement of scattered and primary photons of 1 radionuclide into the primary photopeak energy window of the other radionuclide (crosstalk). Experimental data from previous studies using simulated myocardial distributions of ^{99m}Tc and ^{18}F revealed that the downscatter contribution of ^{18}F on the ^{99m}Tc images becomes theoretically significant in severely hypoperfused areas (*6,7*). However, the efficacy of crosstalk correction for quantification of DISA has not, to our knowledge, been evaluated in clinical viability studies.

In this study, we evaluated the effects of crosstalk correction on DISA with ^{99m}Tc-tetrofosmin and FDG. We used a modified version of a previously described method of crosstalk correction based on the simultaneous use of 3 energy windows (*8,9*). This technique was applied to the quantification of myocardial tracer distribution in comparison with conventional acquired SPECT and PET.

MATERIALS AND METHODS

Eighteen patients with coronary artery disease (CAD) and a history of myocardial infarction were included in this study (14 men, 4 women; age range, 52–76 y; mean age, 64 y). We included only patients with stable CAD; patients with recent myocardial infarction (≤1 mo) were excluded. One patient had previously undergone revascularization. All patients had undergone coronary angiography and left ventriculography within 2 wk of a radionuclide study. CAD was defined as a reduction of at least 75% in the luminal diameter of at least 1 major epicardial coronary artery.

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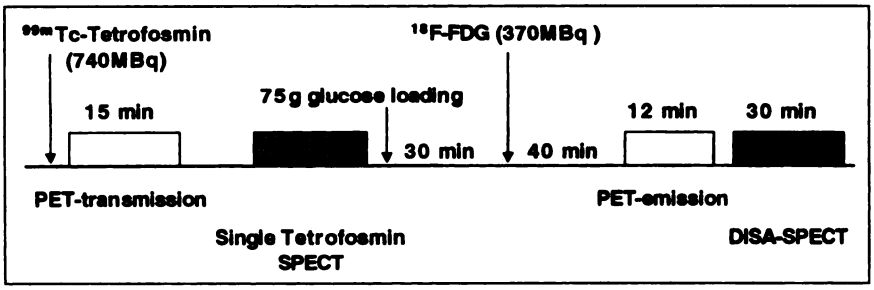

FIGURE 1. Schematic outline of imaging protocol.

Significant stenosis was present in 3 vessels in 5 patients, 2 vessels in 5 patients, and 1 vessel in 8 patients (mean, 1.8 vessels per patient). The average left ventricular ejection fraction was 35.5% ± 8.6%. We carefully excluded patients with a fasting blood glucose level greater than 100 mg/dL. All patients gave written informed consent in accord with the ethical guidelines established by the institution.

Imaging Protocol

A schematic outline of the imaging protocol is shown in Figure 1. After an overnight fast, the resting patients were injected with 740 MBq ^{99m}Tc-tetrofosmin. SPECT was performed using a dual-head system (Vertex Plus; ADAC Laboratories, Milpitas, CA) equipped with a low-energy high-resolution collimator. Thirty-two steps were acquired from each head in the photopeak energy window (140 keV ± 10%) over 360° of a 64 × 64 matrix with a pixel size of 5.1 mm. Projection data were reconstructed using 12 maximum-likelihood expectation maximization iterations and Butterworth filtering (cutoff, 0.44 cycle/cm; order, 10).

After ^{99m}Tc-tetrofosmin acquisition, the patients were given a 75-g oral dose of glucose. PET transmission was performed using a line source of ^{68}Ge and ^{68}Ga followed by intravenous administration of 370 MBq FDG; 40 min later, PET emission was conducted for 10 min. Emission data were reconstructed consecutively, with measured attenuation correction based on the transmission data. Images were reconstructed by filtered backprojection using a Hanning filter (0.5 cycle/cm), yielding 47 transverse slices having a thickness of 2.0 mm in a 128 × 128 matrix. An ECAT EXACT (Siemens Medical Systems, Inc., Hoffman Estates, IL) was used for the PET study.

Immediately after PET emission, DISA acquisition was performed in 30 steps in a 64 × 64 matrix over 180° (90 s/step) with an ultra-high-energy collimator using the same camera system for single ^{99m}Tc-tetrofosmin SPECT. The system was designed to operate with 3 independent energy windows, allowing acquisition of separate scatter images (Fig. 2). The highest photopeak was located at 511 keV ± 10% for acquisition of FDG images. For correction for the photopeak of ^{99m}Tc, a modification of an existing dual-window weighted-scatter correction technique was applied (*10*). It was based mainly on the assumption that a scintigraphic image measured in an energy window located beside the photopeak of ^{99m}Tc (140 keV ± 10%) and shifted toward higher energy values (170 keV ± 7.5%) represents the scatter component that blurs the photopeak image. The definition of this additional energy window and the scatter part under the photopeak were determined on the basis of γ energy spectra registered in the phantom experiment, and the scatter part in the photopeak window was found to be equivalent to 70% of the peak area of this scatter window for ^{99m}Tc. Accordingly, crosstalk correction was established using this percentage as the correction factor for scatter image subtraction. The weighted projection data of the higher energy window (the scatter component) was taken from the projection data of the photopeak of ^{99m}Tc. Images were reconstructed using 12 maximum-likelihood expectation maximization iterative reconstructions (Butterworth filter; 0.42 cycle/cm, order 10, for the ^{99m}Tc image; 0.38 cycle/cm, order 10, for the ^{18}F image). We generated both crosstalk-corrected and crosstalk-uncorrected perfusion images with ^{99m}Tc-tetrofosmin by DISA.

Quantitative Analysis

To compare the regional myocardial tracer distribution obtained by each of the 3 imaging procedures (single ^{99m}Tc-tetrofosmin and crosstalk-corrected and uncorrected ^{99m}Tc-tetrofosmin by DISA), a previously described method based on regions of interest was used for quantitative evaluation (*11,12*). The region of interest with maximal tracer uptake among 20 regions of interest in short-axis cuts, corresponding to the region with the best individual perfusion, was used as the normal reference region, and ^{99m}Tc-tetrofosmin uptake was expressed as percentage uptake in this reference region. FDG uptake normalized to this reference region was also compared between PET and FDG SPECT. A pattern of perfusion–metabolism mismatch was considered present when the relative ^{99m}Tc-

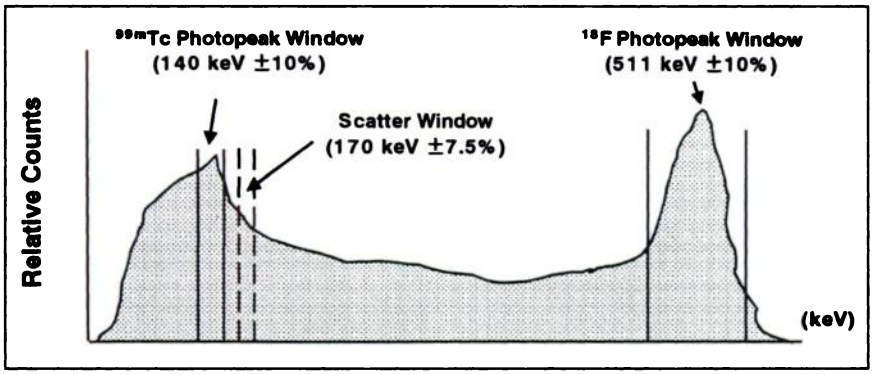

FIGURE 2. γ-Ray energy spectrum registered in patient's data during ^{99m}Tc-tetrofosmin–FDG dual-isotope acquisition. Vertical lines mark borders of the 3 energy windows.

tetrofosmin uptake was less than 70% of the maximal percentage activity and when the ratio of FDG to ^{99m}Tc-tetrofosmin exceeded 1.2 (*13*). A perfusion–metabolism match was considered present when concordance reduction (<70% of maximal activity) of ^{99m}Tc-tetrofosmin and FDG activity occurred in a given myocardial segment (*14*).

Statistical Analysis

Linear regression analysis was performed to calculate the linear dependency measurements of segmental tracer uptake in the same anatomic region in PET and DISA studies. Concordance of the regional perfusion and metabolic pattern between PET and DISA SPECT was assessed using the κ statistic and expressed as the κ score ± SD. The concordance was considered to be good for values of κ greater than 0.6, moderate for values ranging from 0.6 and 0.4, and poor for values less than 0.4. $P < 0.05$ was considered to represent significant differences (*15*).

RESULTS

Segmental Distribution in FDG and ^{99m}Tc-Tetrofosmin

In total, 360 segments were evaluated for differences in regional FDG uptake between DISA SPECT and PET, and the results showed a high linear correlation between FDG SPECT and PET ($y = 0.94x + 4.33$; $r = 0.86$; $P < 0.001$) (Fig. 3).

The overall relationships between segmental percentage uptake of single ^{99m}Tc-tetrofosmin and ^{99m}Tc-tetrofosmin for DISA with and without crosstalk correction are shown in Figure 4. The percentage uptake of both crosstalk-uncorrected and crosstalk-corrected ^{99m}Tc-tetrofosmin by DISA correlated well with that of single ^{99m}Tc-tetrofosmin ($r = 0.94$ and 0.95, respectively; $P < 0.001$), although uncorrected ^{99m}Tc-tetrofosmin by DISA tended to be slightly higher in areas of low perfusion. Because assessment of viability is of particular concern in regions with impaired myocardial flow, the data were analyzed in 97 myocardial regions with moderately to severely impaired flow (percentage uptake of single ^{99m}Tc-tetrofosmin ≤ 50%) (*16*). Regional percentage uptake of ^{99m}Tc-tetrofosmin was generally higher on the uncorrected ^{99m}Tc-tetrofosmin image by DISA than on the single ^{99m}Tc-tetrofosmin image in the low-flow areas (Fig. 5A). Crosstalk correction improved the discrepancy and agreement between single ^{99m}Tc-tetrofosmin and ^{99m}Tc-tetrofosmin by DISA (Fig. 5B). To compare the difference between crosstalk-corrected and uncorrected ^{99m}Tc-tetrofosmin images, the distance from each percentage uptake to the line of identity was calculated using vector algebra (*17*). The distance between the regional percentage uptake of uncorrected ^{99m}Tc-tetrofosmin and the line of identity was 4.30 ± 3.74; otherwise, the distance between the regional percentage uptake of the crosstalk-corrected ^{99m}Tc-tetrofosmin image and the line of identity was significantly small (3.42 ± 2.94, $P < 0.05$).

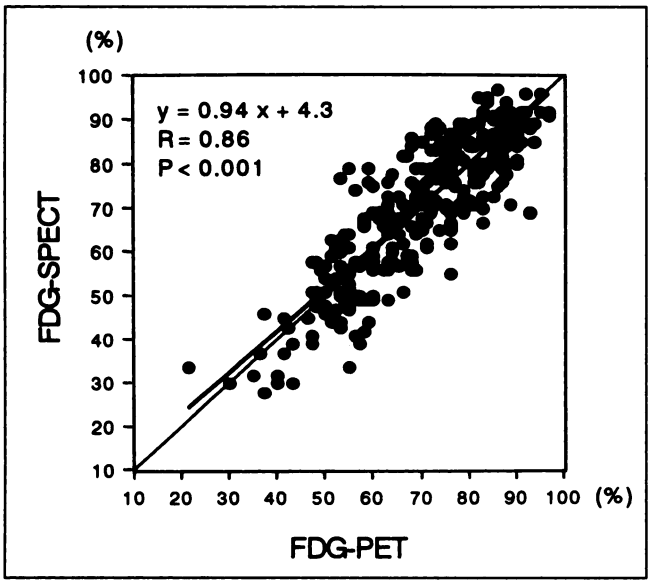

FIGURE 3. Relationship between percentage FDG uptake by DISA SPECT and PET. Linear correlation is seen between percentage uptake of FDG measured by the 2 technologies.

Detection of Perfusion–Metabolism Mismatching

For the 360 segments analyzed, the distribution of the segmental uptake pattern (matched defect and mismatched defects) was determined. The combination of PET and single ^{99m}Tc-tetrofosmin revealed 120 segments (33.3%) for mismatched defects and 97 segments (26.9%) for matched defects, whereas the combination of FDG SPECT and single ^{99m}Tc-tetrofosmin indicated 143 segments (39.7%) for mismatched defects and 74 segments (20.6%) for matched defects. A κ test suggested that the diagnostic results of PET and FDG SPECT agreed well (κ = 0.65 ± 0.05; $P < 0.05$).

To investigate the effect of crosstalk correction for the detectability of a myocardial perfusion–metabolism mismatch, a combination of FDG SPECT and single ^{99m}Tc-tetrofosmin was used as the gold standard. Table 1 compares crosstalk-corrected and uncorrected ^{99m}Tc-tetrofosmin images for viability detection. When the uncorrected ^{99m}Tc-tetrofosmin images were used, 44 segments (28.6%) of mismatched region were diagnosed as the matched region. The percentage was about twice that (13.7%) when the crosstalk-corrected ^{99m}Tc-tetrofosmin images were used. A κ test suggested that the agreement of diagnostic results was moderate when the uncorrected ^{99m}Tc-tetrofosmin images were used (κ = 0.47 ± 0.06). In contrast, the agreement of the perfusion–metabolism pattern was good when the corrected ^{99m}Tc-tetrofosmin images were used (κ = 0.67 ± 0.05). This result indicated that the crosstalk-corrected ^{99m}Tc-tetrofosmin images were better than the uncorrected ^{99m}Tc-tetrofosmin images for detecting myocardial viability.

Case Presentation

Figure 6 shows representative myocardial images using DISA and PET from a patient with 3-vessel CAD. The uncorrected ^{99m}Tc-tetrofosmin images by DISA depicted a myocardial perfusion defect in the posterolateral region but relatively preserved myocardial perfusion in the inferoposterior wall. The crosstalk-corrected images revealed less ^{99m}Tc-tetrofosmin activity in the inferoposterior wall than did the uncorrected images, suggesting an increased count

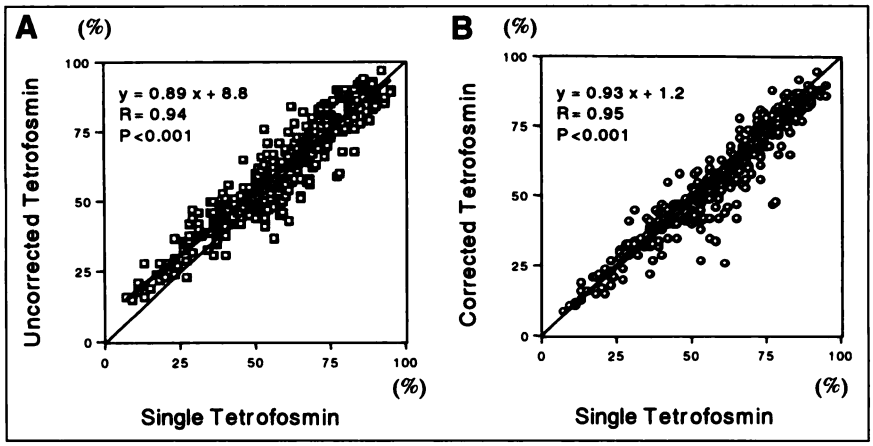

FIGURE 4. Relationship between percentage ^{99m}Tc-tetrofosmin uptake by DISA without (A) or with (B) crosstalk correction and by single acquisition. Overall linear correlation is seen between percentage uptake of ^{99m}Tc-tetrofosmin measured by the 2 technologies.

caused by crosstalk artifacts. The single ^{99m}Tc-tetrofosmin images showed defects in the inferoposterior and posterolateral walls similar to those seen on the corrected DISA images. The presence of viable myocardium in the inferoposterior wall was confirmed on FDG SPECT and PET images.

DISCUSSION

The question of whether FDG imaging with a gamma camera is an effective alternative to PET is of great interest in nuclear cardiology in terms of cost and availability (*18,19*). FDG SPECT has the advantage of being able to perform in DISA mode to simultaneously evaluate regional myocardial metabolism and perfusion. Considering the widespread availability of SPECT and the increasing interest in combinations of FDG and a ^{99m}Tc-labeled perfusion tracer in myocardial viability studies, evaluation of newer SPECT techniques using DISA for the detection of perfusion–metabolism mismatched myocardium is important.

A major finding of this study was that regional percentage uptake of FDG by DISA agrees well with uptake by PET. This finding clearly shows that the diagnostic accuracy of FDG SPECT is equivalent to that of PET. FDG SPECT has the potential limitation of lower spatial resolution and lower volume sensitivity than PET and lacks attenuation correction. Undoubtedly, SPECT images are associated with blunter myocardial wall margins and less accurate wall thicknesses than are PET images. However, reports have shown a good overall agreement between FDG SPECT and PET in consecutive studies when FDG alone was injected (*20,21*). Our results for DISA with 2 different tracers were similar to the results of the previous reports. Despite the poorer physical performance of FDG SPECT by the ultra-high-energy collimator technique, few clinically meaningful differences are apparent between the instruments in the detection of segments by FDG uptake. The attenuation of 511-keV photons in SPECT is also thought to be negligible because of the lower significance in regard to low-energy photon imaging, e.g., with ^{201}Tl and ^{99m}Tc. Thus, relative myocardial metabolic estimates by FDG SPECT are comparable with those obtained by PET.

A major problem with the DISA technique is the crosstalk between the 2 radionuclides. Because scattered radiation from the higher energy radionuclide is detected in the lower energy window, it is thought that crosstalk artifacts may unfavorably affect the quantification of regional tracer activity. Previous papers have reported crosstalk contributions of 3.7%–6.6% of the total counts from the ^{18}F photopeak to the ^{99m}Tc window for patients with normal global perfusion and metabolism (*6,7*). The possibility of errors in quantification increased in patients with ischemic

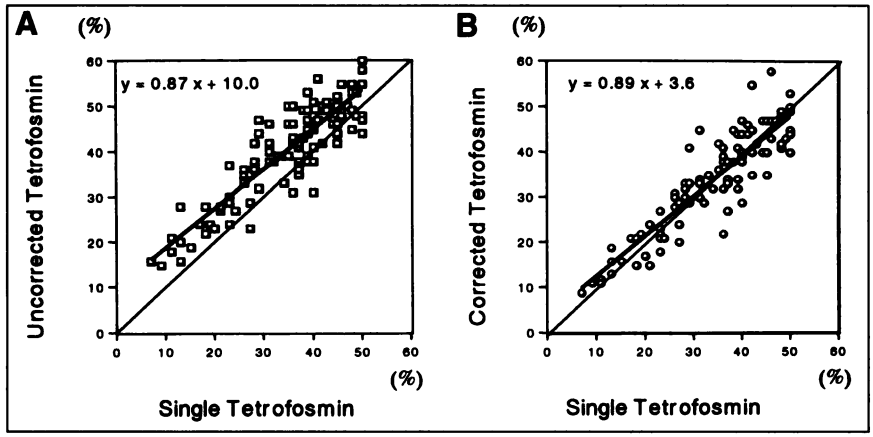

FIGURE 5. Comparison of percentage peak activity values obtained for ^{99m}Tc-tetrofosmin by DISA without (A) and with (B) crosstalk correction and for single ^{99m}Tc-tetrofosmin SPECT in region that showed severely to moderately impaired myocardial flow (percentage peak activity of single ^{99m}Tc-tetrofosmin SPECT ≤ 50%). Crosstalk correction improved agreement with single ^{99m}Tc-tetrofosmin SPECT values.

TABLE 1
Comparison of Segmental Perfusion–Metabolism Pattern Between Single ^{99m}Tc-Tetrofosmin, Uncorrected ^{99m}Tc-Tetrofosmin, and Corrected ^{99m}Tc-Tetrofosmin SPECT

	Match		Mismatch	
Single TF	Uncorrected TF	Corrected TF	Uncorrected TF	Corrected TF
Match (n = 64)	53	54	11	10
Mismatch (n = 153)	44	21	109	132

TF = ^{99m}Tc-tetrofosmin.
Data are number of segments.

heart disease manifested by decreased perfusion and increased metabolism. In this study, higher quantitative values were obtained by uncorrected ^{99m}Tc-tetrofosmin by DISA than by single ^{99m}Tc-tetrofosmin, especially in segments with low perfusion. This finding indicates that crosstalk from the ^{18}F photopeak is not negligible in regions of low ^{99m}Tc-tetrofosmin uptake and that uncorrected images are inadequate to assess myocardial perfusion accurately.

To solve this problem, we used a method of crosstalk correction from the ^{18}F photopeak to the ^{99m}Tc photopeak. The design of this study was similar to that of others (*6,8,9,22*). Our data indicated that crosstalk correction increases the concordance of regional myocardial perfusion between DISA and single ^{99m}Tc-tetrofosmin images, especially in low-flow areas. In contrast, Sandler et al. (*9*) showed that crosstalk may not be important for assessment of viability by the same DISA protocol. The reason for this discrepancy is unclear, but it may be caused by the difference in image analysis. Certainly, only in the visual assessment was a slight difference apparent between the scatter-corrected and uncorrected images. However, significantly higher quantitative values were obtained by uncorrected images than by single ^{99m}Tc-tetrofosmin in segments with low perfusion. ^{99m}Tc-tetrofosmin has been widely used as a perfusion marker because it is virtually redistribution free (*23*). ^{99m}Tc-tetrofosmin also has the same ideal property as ^{99m}Tc-sestamibi for use in combination with FDG because its γ radiation can easily be distinguished from FDG emission because of its lower γ-ray energy. In the previous myocardial viability study, the optimal threshold cutoff of ^{99m}Tc-tetrofosmin to predict functional recovery after revascularization was 50% of the peak activity (*16*). Thus, obtaining an accurate ^{99m}Tc-tetrofosmin count distribution is important for predicting myocardial viability, not only in conventional SPECT but also in DISA imaging. Because the scatter window data are acquired simultaneously using the additional energy window, and because the postprocessing steps of subtraction do not require a long time, this crosstalk correction for DISA is thought to be practical and reliable in clinical use.

We directly compared crosstalk-corrected and uncorrected ^{99m}Tc-tetrofosmin with DISA activity using single ^{99m}Tc-tetrofosmin as the reference standard; regional wall motion and functional outcome data after revascularization were not obtained. Concerning this subject, several studies have showed that preserved metabolic activity measured by FDG SPECT is an accurate marker of tissue viability and a predictor of functional recovery after revascularization (*5,24*). The purpose of this study was to investigate the usefulness of crosstalk correction on DISA with ^{99m}Tc-tetrofosmin and FDG. Further prospective studies of patients undergoing revascularization are required to determine the clinical significance of crosstalk-corrected ^{99m}Tc-tetrofosmin with DISA.

Another limitation of this study was the assessment of myocardial viability using a conventional oral glucose-loading protocol. This technique tended to underestimate myocardial viability, especially in patients with diabetes mellitus. We excluded patients with diabetes mellitus and obtained good-quality FDG scans. However, excluding patients with abnormal glucose tolerance and insulin resistance prospectively, at the time of the imaging study, is difficult. Hyperinsulinemic glucose clamping, although labor intensive, will make better studies possible (*25,26*).

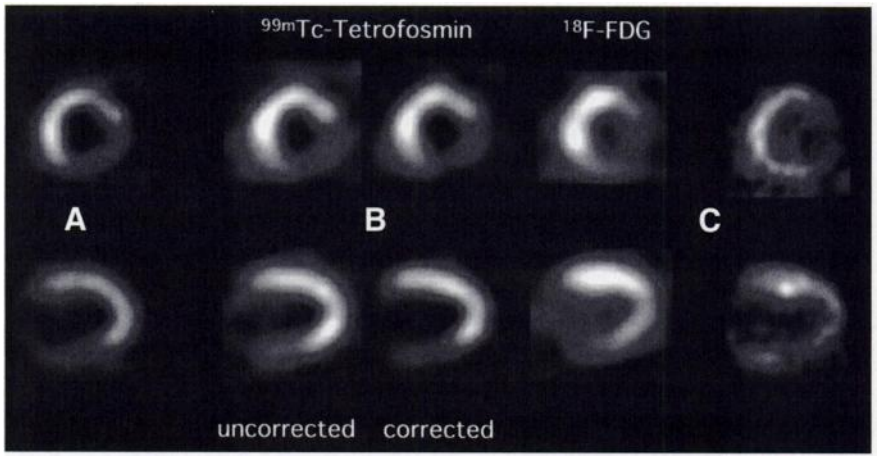

FIGURE 6. A 59-y-old man with history of severe 3-vessel disease. Single ^{99m}Tc-tetrofosmin images (A), ^{99m}Tc-tetrofosmin–FDG DISA images (B), and PET with FDG images (C).

CONCLUSION

Crosstalk-corrected DISA SPECT is a reliable technique for the quantitative assessment of myocardial perfusion–metabolism mismatching, especially in areas of low myocardial flow.

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