Significance of Defect Severity in Technetium-99m-MIBI SPECT at Rest to Assess Myocardial Viability: Comparison with Fluorine-18-FDG PET

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The pathophysiological significance of ^{99m}Tc-MIBI uptake at rest for assessing myocardial viability in patients with coronary artery disease (CAD) is still controversial. Therefore, we studied the relationship of ^{99m}Tc-MIBI uptake at rest and preserved or absent uptake of ^{18}FDG as assessed with PET in 111 consecutive patients after overnight withdrawal of their antianginal medication. **Methods:** Each ventricle was evaluated in 13 segments derived from 25 regions of interest (ROIs) in short-axis cuts and ^{18}FDG uptake was normalized to the intraindividual normal reference ROI (ROI with maximal = 100% ^{99m}Tc-MIBI uptake). Segments with a normalized ^{18}FDG uptake >70% were defined as viable while segments with a ^{18}FDG uptake <50% were defined as nonviable. **Results:** Five to 11% of segments with ^{99m}Tc-MIBI uptake at rest ≤30% of peak activity were viable and 80%–84% nonviable. Of moderate to severe ^{99m}Tc-MIBI defects at rest (31%–70% of peak), 13%–61% were viable. Segmental ^{99m}Tc-MIBI uptake and normalized ^{18}FDG uptake were linearly correlated ($r = 0.61$, $n = 1443$, $p < 0.001$). In segments revealing severely reduced ^{99m}Tc-MIBI uptake (≤50% of peak) the correlation was considerably lower ($r = 0.44$, $n = 295$, $p < 0.001$). **Conclusions:** In patients with CAD, ^{99m}Tc-MIBI uptake underestimates myocardial viability in comparison to ^{18}FDG-PET. Myocardial ^{99m}Tc-MIBI uptake therefore appears to reflect myocardial blood flow rather than myocardial viability. Patients with moderate and severe ^{99m}Tc-MIBI defects at rest may benefit from additional metabolic PET imaging prior to final therapeutic decisions.

Key Words: technetium-99m-MIBI SPECT; ^{18}FDG-PET; coronary artery disease

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Technetium-99m-labeled methoxyy-isobutyl-isonitrile (MIBI) has emerged as an excellent perfusion marker for myocardial imaging (*1–3*) to evaluate coronary artery disease (CAD). Myocardial ^{99m}Tc-MIBI uptake is based on diffusion of the tracer into the myocyte and intracellular retention. Technetium-99m-MIBI uptake therefore is affected by coronary blood flow (*4,5*) and thus delivery of the tracer to the myocyte and also by cell membrane integrity (*6*). However, the relationship between the amount of regional myocardial ^{99m}Tc-MIBI uptake and myocardial viability as assessed by metabolic PET imaging has not yet been elucidated. Our group recently demonstrated preserved glucose metabolism assessed with ^{18}FDG-PET in a significant number of patients with CAD in myocardial areas presenting resting perfusion defects in ^{99m}Tc-MIBI-SPECT (*7*). These results indicated that ^{99m}Tc-MIBI-SPECT at rest underestimates the extent of viable tissue in coronary disease. In addition, the frequency of preserved ^{18}FDG uptake appeared to be related to ^{99m}Tc-MIBI defect severity at rest (*7*). To evaluate more precisely the relationship between the severity of a ^{99m}Tc-MIBI defect at rest and the frequency of myocardial scar or preserved myocardial viability according to PET criteria, this study in 111 patients with CAD was performed.

MATERIALS AND METHODS

Patients

The 111 patients (98 male, 13 female, mean age 57.9 ± 8.8 yr, range: 33–73 yr) included in this study had angiographically proven CAD and resting wall motion abnormalities on cineventriculography. Patients underwent angiography because of recurrent or worsening stable angina despite medical therapy. In this study, patients with recent myocardial infarction (<4 wk prior to investigation), left bundle branch block or unstable angina were not included. Ninety-four patients had a history of old myocardial infarction (54 anterior wall infarctions, 51 posterior or posterolateral wall infarctions, 11 anterior and posterior wall infarctions). Eleven patients with anterior wall infarction and 13 patients with posterior wall infarction had received thrombolytic therapy. Global ejection fraction was 47% ± 11% and angina pectoris was 2.4 ± 1.1 CCS (*8*) (according to the Canadian Cardiovascular Society grading system for angina pectoris of effort in class I, II,

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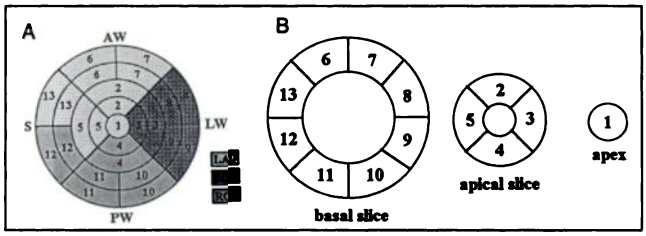

FIGURE 1. (A) Polar map of the left ventricle with 25 ROIs from apex to base in the form of a target disc displays anterior wall (AW), posterior wall (PW), lateral wall (LW) and septum (S), their relationship to the 13 left ventricular segments used for comparison of tracer uptake and the supply territories of the three major epicardial vessels. (B) Relationship of these 13 segments to the three myocardial short-axis slices: apex, apical and basal slice.

III and IV). Forty-five patients had three-vessel disease, 32 patients two-vessel disease and in 34 patients with one-vessel disease showed significant stenosis (>50% stenosis). Antianginal drugs were withdrawn for at least 12 hr prior to investigation.

SPECT and PET Protocol

Image Acquisition. Both SPECT and PET imaging were performed on the same day or within 3 days of each other. The protocol used has been previously described in detail (*7*). Briefly, SPECT was performed 1 to 2 hr after injection of 260–370 MBq ^{99m}Tc-MIBI at rest. The transaxial images, acquired with a ROTA-Dual double-head gamma camera, were reconstructed using a Butterworth filter third order and a cut-off frequency of 0.5.

Attenuation-corrected static PET images were acquired 30–45 min after injection of 200–300 MBq ^{18}FDG using an ECAT 953/15 tomograph. Patients received 50 g of glucose orally 1 hr prior to injection. PET scans were reconstructed using a Hanning filter with a cut-off frequency of 0.4 and a defined zoom factor.

Data Analysis. Compared to former analyses, newer software resulted in identical pixel sizes for SPECT and PET images. After transformation of PET slices into the SPECT file structure, both datasets were comparatively evaluated in the same dedicated computer system for SPECT data analysis. An ROI-based method previously described was used for quantitative evaluation (*7*). Using 25 ROIs in short-axis cuts (Fig. 1A), the ROI with maximal ^{99m}Tc-MIBI uptake, corresponding to the region with the intraindividually "best" perfusion, was used as the "normal" reference region. Technetium-99m-MIBI uptake was expressed as the percent uptake of this reference region and ^{18}FDG uptake was normalized to this reference region. Thirteen segments were derived from 25 ROIs (Fig. 1A). Segment one (apex) consisted of one ROI; the other 12 segments consisted of two ROIs (Fig. 1A). Technetium-99m-MIBI and ^{18}FDG uptake from both ROIs were averaged for segmental comparison. Thus, 13 segments in three myocardial slices were compared (Fig. 1B): one segment in slice 1 (apex), four segments in the apical slice and eight segments in the basal slice (Fig. 1B). Segments were categorized according to their relative ^{99m}Tc-MIBI uptake and differentiated into PET viable (corresponding ^{18}FDG uptake >70%), PET nonviable (^{18}FDG uptake <50%) or "intermediate" segments (^{18}FDG uptake 50%–70%).

Wall Motion Analysis. Regional wall motion (RWM) was measured from biplane 30° RAO/60° LAO ventriculograms using the centerline method (*9*). Wall motion is measured along 100 chords drawn perpendicular to a centerline constructed midway between end-diastolic and end-systolic contours and is normalized for heart size. Abnormality in motion is expressed in standard deviations from the mean of normal subjects. Negative values indicate reduced contractility (*9*). RWM was assessed in five areas: anterior, apical and posterior in RAO views, septal and posterolateral in LAO views. In each area, RWM was calculated in the contiguous chords that had the most depressed function and covered 50% of the entire area. Thus, the worst contracting 50% chord segment in each area was used for comparison with SPECT/PET findings.

Statistical Analysis

Chi-square analysis was used in a contingency table to determine the dependency of preserved or absent PET viability on ^{99m}Tc-MIBI defect severity. Linear regression analysis was performed to calculate the linear dependency of segmental ^{18}FDG uptake on segmental ^{99m}Tc-MIBI uptake. Regional wall motion between viable and nonviable segments was compared using the unpaired t-test. P values <0.05 were considered to represent significant differences.

RESULTS

A total of 1443 segments were evaluated. Of these, 730 segments displayed normal ^{99m}Tc-MIBI uptake (>70%) and 713 segments revealed reduced resting ^{99m}Tc-MIBI uptake (Table 1, Fig. 2). The frequency of preserved viability increased from 5% in segments with ^{99m}Tc-MIBI uptake of ≤20% of peak activity to 61% in segments with 61%–70% ^{99m}Tc-MIBI uptake, while the frequency of scar tissue declined from 80% to 9% (Table 1, Fig. 2). "Intermediate" uptake was found in 15%–37% of segments (Table 1).

Forty-seven of 57 (82%) segments revealing absent ^{99m}Tc-MIBI uptake at rest (≤30% of peak) showed ^{18}FDG uptake <50%. The predictive value for scar tissue is therefore greater than 80% if ^{99m}Tc-MIBI uptake does not exceed 30% of peak activity.

Regression analysis revealed a moderate linear correlation between segmental ^{18}FDG and ^{99m}Tc-MIBI uptake (Fig. 3A), with a correlation coefficient of 0.61 ($n = 1443$, $p < 0.001$).

Two hundred ninety-five of 1433 (20.6%) segments revealed severely reduced resting ^{99m}Tc-MIBI uptake (≤50% of peak activity). The correlation coefficient for these segments was 0.44 ($n = 295$, $p < 0.001$) (Fig. 3B).

Thirty-three patients (29.7%) had at least 1 viable segment with severely reduced ^{99m}Tc-MIBI uptake (≤50% of peak activity). In 14 patients (12.6%), two or more viable segments with severely reduced ^{99m}Tc-MIBI uptake were observed. These segments were supplied by the LAD in 16 patients, by the LCX in 6 patients and the RCA in 20 patients. Thus, in 9 patients (8.1%), the pattern of segmental ^{99m}Tc-MIBI uptake ≤50% but ^{18}FDG uptake >70% occurred in the distribution territory of two different vessels. Segments with this pattern were related to the corresponding areas from cineventriculography used for determining RWM. RWM related to these segments was −2.35 ± 0.93 ($n = 44$, range: from −4.08 to −0.58). RWM did not correlate linearly with ^{99m}Tc-MIBI uptake ($r = 0.17$, $n =$

TABLE 1
Relationship of Segmental ^{18}FDG Uptake and Perfusion Defect Severity as Assessed with ^{99m}Tc-MIBI SPECT in 111 Patients with CAD

	^{99m}Tc-MIBI uptake (% of peak activity)						
	≤20%	21%–30%	31%–40%	41%–50%	51%–60%	61%–70%	70%
Number of segments	20	37	71	167	195	223	730
PET viable (^{18}FDG uptake >70%)*	5%	11%	13%	24%	48%	61%	88%
PET nonviable (^{18}FDG uptake <50%)*	80%	84%	63%	39%	20%	9%	2%
"Intermediate" (^{18}FDG uptake 50%–70%)	15%	5%	24%	37%	32%	30%	10%

*Chi-square analysis = 21.8; $p < 0.01$.

44, p = ns) or with ^{18}FDG uptake (r = −0.12, n = 44, p = ns). RWM in nonviable segments (^{18}FDG <50%) was not significantly different (−2.63 ± 0.72, n = 134, p = ns).

DISCUSSION

Although segmental myocardial ^{99m}Tc-MIBI uptake was linearly correlated to normalized ^{18}FDG uptake in our patients, a significant number of segments revealing reduced ^{99m}Tc-MIBI uptake showed preserved ^{18}FDG uptake, suggesting maintained myocardial viability. The correlation between the two tracers was therefore lower for segments with severely reduced ^{99m}Tc-MIBI uptake (≤50% of peak activity). The predictive value of ^{99m}Tc-MIBI SPECT at rest for scar tissue is greater than 80%, if resting ^{99m}Tc-MIBI uptake approaches background (≤30% of peak activity). On the other hand, 5%–24% of segments (Table 1) were PET-viable despite severe reduction of ^{99m}Tc-MIBI uptake (≤50% of peak activity). Our study therefore indicates that myocardial viability is underestimated by ^{99m}Tc-MIBI SPECT imaging at rest (Fig. 4). However, the amount of myocardial ^{99m}Tc-MIBI uptake at rest may yield an indirect estimate of the likelihood of maintained viability. Our observations have important clinical implications for patient management. Preserved ^{18}FDG uptake in the presence of severely reduced ^{99m}Tc-MIBI uptake was observed in one-third of the patients. Fourteen (12.6%) patients even revealed two or more segments with this pattern. Maintained ^{18}FDG uptake in areas with impaired resting perfusion and contractility may indicate that these regions are potentially capable of improving wall motion after successful revascularization (*10–12*). In a considerable number of patients revealing resting perfusion defects on ^{99m}Tc-MIBI SPECT, metabolic PET imaging may therefore yield considerable diagnostic impact.

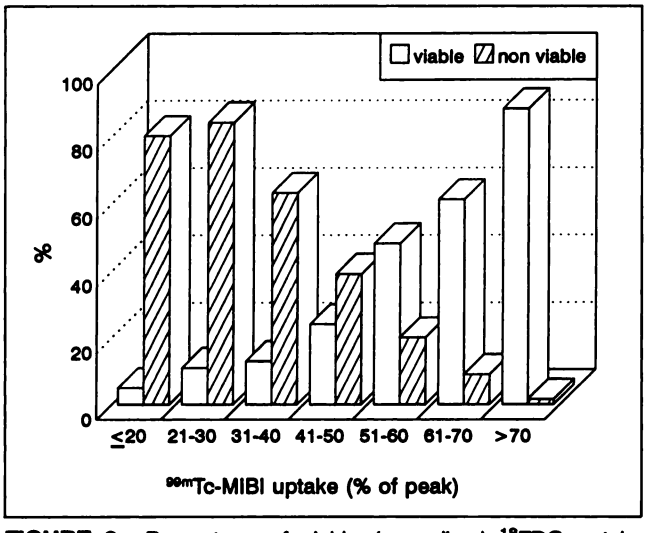

FIGURE 2. Percentage of viable (normalized ^{18}FDG uptake >70%) and nonviable (normalized ^{18}FDG uptake <50%) segments according to PET criteria in relation to ^{99m}Tc-MIBI defect severity.

Our data may not be transferred to patients with acute myocardial infarction because this subset of patients was not included in this investigation. Although absence of residual tissue metabolism in the subacute phase was associated with irreversible injury in a study by Schwaiger and colleagues (*13*), segments with preserved metabolic activity showed a variable outcome. Furthermore, ejection fraction and regional wall motion may significantly improve during the first weeks after acute myocardial infarction even in patients who were not revascularized (*14,15*) or treated with thrombolysis (*16*).

A variable number of segments revealed "intermediate" ^{18}FDG uptake. This pattern did not show a specific relationship to the amount of ^{99m}Tc-MIBI uptake. "Intermediate" ^{18}FDG uptake may represent a mixture of viable and necrotic myocardium. A histopathologic study performed by Bodenheimer and coworkers (*17*) revealed a wide range of muscle loss and fibrosis in areas with wall motion abnormalities. The percentage of muscle loss varied between <10% and >75% in their study, indicating a wide range of myocardial injury in patients with CAD.

Segments with severe ^{99m}Tc-MIBI defects revealing preserved ^{18}FDG uptake were associated with severe hypokinesis despite metabolic evidence of viability. This observation is concordant to results from other studies (*10–12,18,19*). A logarithmic relationship between hypokinesis as assessed with the centerline method and the infarct size estimated from serial creatinine kinase determinants in patients who underwent reperfusion was shown by Sheehan et al. (*9*). RWM was not significantly different in PET viable and PET nonviable segments. This finding confirms

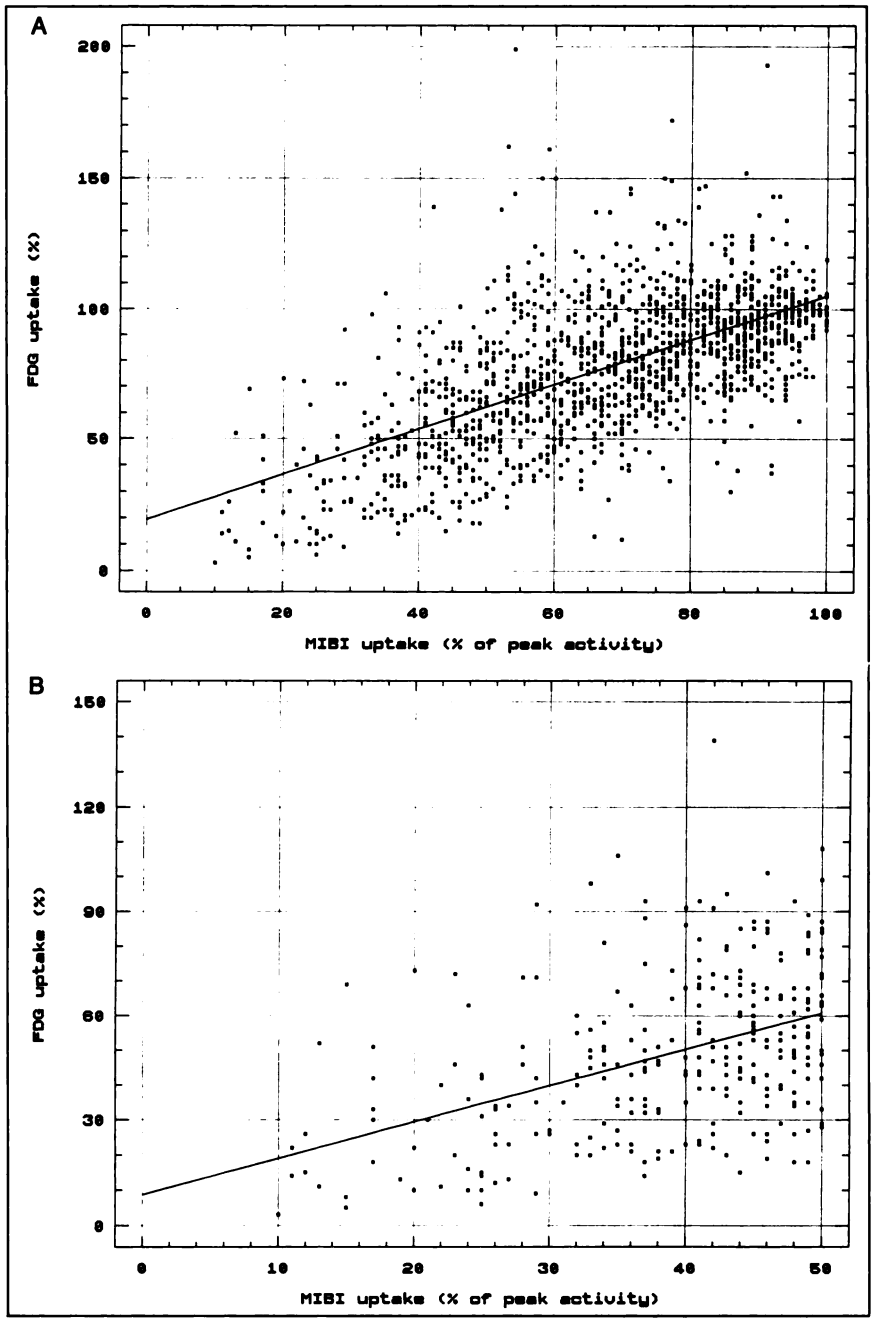

FIGURE 3. Regression analysis of segmental ^{18}FDG uptake (in percentage, normalized to the individual reference region) on segmental ^{99m}Tc-MIBI uptake (% of peak activity) for all segments (A) and for segments revealing a severe resting ^{99m}Tc-MIBI defect (≤50% of peak, B).

results by other investigators who showed that myocardial viability as assessed with ^{18}FDG-PET may not be accurately determined by wall motion analysis (*10–12*).

Our results also provide information about the determinants of myocardial ^{99m}Tc-MIBI uptake in patients with CAD in the resting state. The understanding of myocardial ^{99m}Tc-MIBI kinetics has been elucidated by experimental studies in the isolated perfused heart (*6*) and cell cultures (*20–23*). The majority of the intracellular ^{99m}Tc-MIBI pool is retained in the mitochondria (*24*).

Whereas cellular uptake has been shown to depend on blood flow (*4,5*), lipophilicity and potential dependent mechanisms (*22*), cellular retention seems to be affected mainly by transmembrane potentials (*21*). Numerous experimental studies also suggest that severely injured myocytes and necrotic tissue are unable to accumulate and retain this isonitrile (*6,25*), indicating that cell viability plays a role in tracer uptake and retention. Crane and colleagues (*24*) recently demonstrated that Ca^{2+} causes ^{99m}Tc-MIBI release from mitochondria, a phenomenon that seems to be accelerated by increased intracellular Na^+ contents. These observations are offered to explain the inability of ^{99m}Tc-MIBI retention in irreversibly injured cells (*24*). Although these data indicate that ^{99m}Tc-MIBI uptake is affected by myocardial cell viability, the importance of these findings in the clinical setting is still unclear. Animal studies have revealed the dependency of myocardial ^{99m}Tc-MIBI uptake on myocardial blood

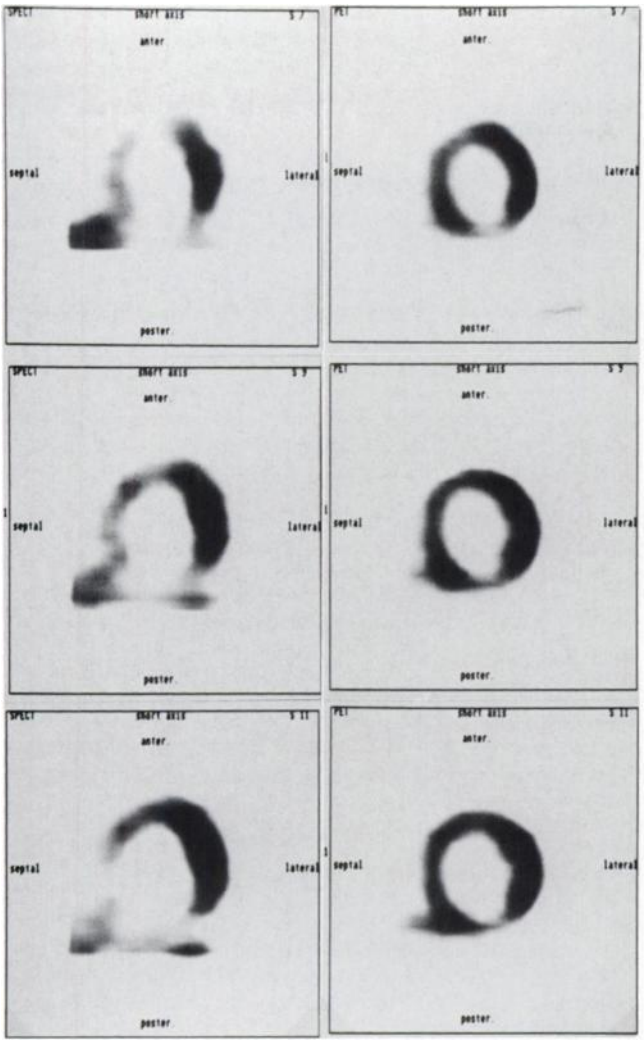

FIGURE 4. PET (right) demonstrates maintained ^{18}FDG uptake, indicating preserved myocardial viability in areas of reduced resting perfusion (anterior, septal and posterior) as assessed with ^{99m}Tc-MIBI SPECT (left). Furthermore, a small area of decreased ^{18}FDG uptake is noted in the posterior wall after previous posterior wall myocardial infarction. This patient (65-yr-old male) had three-vessel disease with occluded collateralized LAD and RCA and severe LCX stenosis on angiography.

flow (*4,5,26,27*) and thus delivery of the tracer to the myocyte.

Animal occlusion/reperfusion experiments (*25,29*) have demonstrated that ^{99m}Tc-MIBI uptake in "stunned" myocardium may indicate myocardial viability because blood flow is classically restored (*28*). However, the situation in dysfunctional myocardium resulting from chronically reduced blood flow (*18*) may be different. The fact that maintained cell viability is required for tracer accumulation and that irreversibly damaged cells are unable to retain ^{99m}Tc-MIBI (*25,30*) does not necessarily prove the inverse assumption that reduced ^{99m}Tc-MIBI uptake indicates impaired cell viability. In chronically ischemic myocardium, reduced blood flow may become the major determinant of myocardial ^{99m}Tc-MIBI uptake.

PET with ^{18}FDG as a marker of metabolic activity is widely accepted for noninvasive estimation of myocardial viability prior to revascularization in patients with severe CAD (*31*). Our study indicates a relationship between regional myocardial ^{99m}Tc-MIBI uptake and the frequency of maintained glycolytic activity in patients with CAD. Assuming that preserved ^{18}FDG uptake indicates viable myocardium despite impaired resting perfusion and contractile function, our results strongly suggest that the major determinant of myocardial ^{99m}Tc-MIBI uptake in these patients is blood flow and not cell viability. Improvement in resting ^{99m}Tc-MIBI uptake (*32,33*) and contractile function (*12,33*) after successful revascularization in regions with preoperatively maintained or enhanced ^{18}FDG uptake relative to blood flow further supports this observation.

Limitations

Technical limitations for direct comparisons of different tomographic systems with or without attenuation correction have been reported (*7*). However, myocardial SPECT imaging for evaluation of CAD is an established method despite photon attenuation. The fact that attenuation may play a role in differences of regional ^{99m}Tc-MIBI and ^{18}FDG uptake supports the need for direct comparisons with PET for interpretation of the significance of ^{99m}Tc-MIBI SPECT defect severity in regard to myocardial viability. Because PET is not widely available, it is extremely important to scrutinize the potentials and limitations of the different SPECT tracers and protocols for evaluation of myocardial viability.

We did not investigate the effect of antianginal drugs on resting ^{99m}Tc-MIBI uptake in this study. Antianginal therapy, however, may facilitate ^{99m}Tc-MIBI uptake by increasing blood flow and thus lead to an improvement in the evaluation of viability. In clinical situations where PET imaging is not available, patients should remain on their cardiac medication.

CONCLUSIONS

Our data confirm that myocardial viability is underestimated by ^{99m}Tc-MIBI SPECT at rest in comparison to ^{18}FDG-PET. On one hand, resting ^{99m}Tc-MIBI defects ≤30% of peak activity is highly predictive for scar tissue, while segments revealing normal ^{99m}Tc-MIBI uptake are usually viable. On the other hand, a significant number of segments revealing a moderate to severe ^{99m}Tc-MIBI defect at rest (31%–70% of peak) may be viable according to ^{18}FDG-PET. Patients with CAD revealing moderate to severe resting ^{99m}Tc-MIBI defects may therefore benefit from metabolic PET imaging. Further clinical studies, including larger patient populations, are needed to evaluate the fate of a resting perfusion defect as assessed with ^{99m}Tc-MIBI SPECT and contractile function after successful revascularization in relation to preoperative metabolic PET findings.

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