# Prediction of Improvement of Regional Left Ventricular Function After Revascularization Using Different Perfusion–Metabolism Criteria

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Increased myocardial uptake of $^{18}$F-fluorodeoxyglucose (FDG) in regions with perfusion defects (perfusion–FDG mismatch) has been shown to predict functional recovery after revascularization; conversely, a concordant decrease in perfusion and FDG uptake (perfusion–FDG match) represents scar tissue (varying from subendocardial to transmural scar) that will not improve in contractile function after revascularization. Several recent studies have used a mild reduction in perfusion or FDG uptake (or both) as an indicator of viable tissue. To our knowledge, this criterion has not been validated against functional outcome after revascularization. This study aimed to compare the predictive value for functional recovery of these different perfusion–metabolism criteria. **Methods:** Forty-two patients referred for revascularization were studied with early resting $^{201}$Tl SPECT (to evaluate perfusion) and FDG SPECT. Contractile function was evaluated before and 3–4 mo after revascularization using two-dimensional echocardiography. Angiography was not repeated. **Results:** Two hundred six dysfunctional segments were identified; functional recovery occurred in 71 segments. The 206 dysfunctional segments were divided into five groups: group I, segments (n = 37) with normal perfusion; group II, segments (n = 69) with a mild reduction in perfusion (≥60% of normal $^{201}$Tl uptake) without increased FDG uptake (mild match); group III, segments (n = 29) with a mild reduction in perfusion and increased FDG uptake (mild mismatch); group IV, segments (n = 46) with a more severe reduction in perfusion (<60% of normal $^{201}$Tl uptake) without increased FDG uptake (severe match); and group V, segments (n = 25) with a $^{201}$Tl activity < 60% and increased FDG uptake (severe mismatch). The mean wall motion score improved significantly in groups I, III and V but not in groups II and IV. Improvement of function was observed in 76% of group I segments, in 69% of group III segments and in 68% of group V segments. In contrast, only 13% of group II segments and 7% of group IV segments improved after revascularization. **Conclusion:** The results indicate that normal perfusion and mismatch patterns (either mild or severe) are predictive of functional recovery, whereas match patterns (either mild or severe) are predictive of absence of recovery. Match patterns are likely to represent different degrees of scar tissue, ranging from subendocardial to transmural scars. To identify segments with a high likelihood of improvement of function after revascularization, integration of information on perfusion and FDG uptake appears mandatory.

**Key Words:** $^{18}$F-fluorodeoxyglucose; SPECT; myocardial viability

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Coronary revascularization may lead to improved regional and global left ventricular (LV) function in patients with coronary artery disease and LV dysfunction (*1*). Rahimtoola (*2*) popularized the concept of hibernation to explain reversal of contractile function after revascularization. The dysfunctional but viable segments are likely to improve in contractile function, whereas the scarred segments will not improve. Reversibility of regional dysfunction after revascularization can be predicted with PET in combination with $^{18}$F-fluorodeoxyglucose (FDG) (*3*). In addition, FDG uptake has been imaged successfully with SPECT (*4–8*), and it has been shown that FDG SPECT can predict improvement of ventricular function after revascularization (*6*).

In most FDG studies, the hallmark of viability has been increased FDG uptake in areas of hypoperfusion (perfusion–FDG mismatch) (*3*). Moreover, the finding of a perfusion–FDG mismatch was predictive of functional recovery after revascularization, whereas the presence of similarly decreased perfusion and FDG uptake (perfusion–FDG match) was highly predictive of absence of recovery (*3*). In other FDG PET studies, a mild reduction in both perfusion and FDG uptake was also considered to correlate with viable tissue (*9–12*); others used a cutoff level of FDG uptake (ranging from 50% to 70%) to assess myocardial viability (*13–15*). However, in all of these investigations functional outcome after revascularization was not studied. This study was designed to compare the predictive values for functional recovery of these different patterns of perfusion and metabolism. Quantitative analysis was used instead of visual analysis to allow objective interpretation of the data.

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## MATERIALS AND METHODS

### Patients and Study Protocol

Forty-two patients were prospectively studied. Inclusion criteria were patients already scheduled for revascularization, chronic coronary artery disease, regional dysfunction on two-dimensional echocardiography and no concomitant valvular disease.

Seven patients underwent percutaneous transluminal coronary angioplasty (PTCA), and 35 patients underwent coronary artery bypass grafting. All patients had coronary angiography within 3 mo before the SPECT study. Each patient underwent resting $^{201}$Tl SPECT to evaluate regional perfusion, followed by FDG SPECT during hyperinsulinemic glucose clamping. Regional wall motion was evaluated with two-dimensional echocardiography before revascularization and repeated 3–4 mo after revascularization. All patients gave informed consent to the study protocol that was approved by the ethical committees of the participating hospitals. Eight of these patients were included in a previous study (*6*).

### SPECT Studies

The SPECT studies were performed with a dual-head rotating gamma camera system (ADAC Laboratories, Milpitas, CA). The method has been described in detail previously (*5,6*). Briefly, resting perfusion was evaluated with $^{201}$Tl-chloride (111 MBq). Imaging was performed within 15 min after tracer injection. Data acquisition was performed over 360°, with a total imaging time of 16 min. Data were stored in a 64 × 64, 16-bit matrix. For FDG SPECT the camera system was equipped with 511-keV collimators (van Mullekom; Nuclear Fields, Boxmeer, The Netherlands) to detect 511-keV photons. The special characteristics of the collimators have been described (*16*). FDG was used during hyperinsulinemic euglycemic glucose clamping to optimize and standardize metabolic conditions during the study (*17*). Separate venous infusions of glucose and insulin were given; insulin infusion rate was 100 mU/kg/h and remained constant during the study. Normoglycemia was maintained by adapting the glucose infusion rate every 10 min, guided by the determination of the plasma glucose concentration. After 60 min of clamping, 185 MBq FDG were injected; 45 min later the SPECT images were obtained (*18*).

### Reconstruction and Analysis of SPECT Images

Reconstruction and analysis were performed as described previously (*5,6*). Transaxial slices were reconstructed by filtered backprojection using a Hanning filter (cutoff frequency = 0.63 cycle per cm). Slices were not corrected for attenuation. Further reconstruction yielded long- and short-axis projections perpendicular to the heart axis. Circumferential count profiles (60 radii, highest pixel activity per radius) from FDG and $^{201}$Tl short-axis slices were generated and displayed in polar maps that were divided into 13 segments as described previously (*5,6*). The segment with the highest $^{201}$Tl uptake was considered normal. The activity of this area was normalized to the mean activity of the same area of a normal database (*5*), and all other polar map data were adjusted correspondingly. The area of normal perfusion was projected on the FDG polar map, and the same normalization procedure was followed. For this purpose a normal database of FDG activities was used (*5*). Segments with a $^{201}$Tl activity < 2 SD below the normal reference value were considered abnormal. The $^{201}$Tl and FDG activities were expressed as a percentage of the corresponding normal reference values. Increased FDG uptake in $^{201}$Tl defects was defined as a ≥7% increase in FDG activity compared with the $^{201}$Tl activity (*5,6*). The cutoff value of a 7% increase in FDG uptake in perfusion defects was established using receiver operating characteristic curve analysis (*19*) and has been applied in previous studies (*5,6*).

### Definition of Viability on FDG SPECT

To assess the predictive value of the different patterns of viability, the dysfunctional segments were divided into five groups. Group I included the segments with normal perfusion (normal $^{201}$Tl uptake). Group II included the segments with a mild reduction in perfusion (≥60% of normal $^{201}$Tl uptake) without increased FDG uptake (mild match). Group III consisted of the segments with a mild reduction in perfusion and increased FDG uptake (mild mismatch). Group IV consisted of the segments with a more severe reduction in perfusion (<60% of normal $^{201}$Tl uptake) without increased FDG uptake (severe match). Finally, group V consisted of the segments with a $^{201}$Tl activity < 60% of normal and increased FDG uptake (severe mismatch).

### Segmental Wall Motion Analysis

Two-dimensional echocardiograms were recorded in four standard views of the left ventricle (parasternal long- and short-axis, apical two- and four-chamber views) using standard equipment. Off-line analysis was performed by digitizing the videotaped images in a computer system (Prevue III; Eastman Kodak, Rochester, NY) using an electrocardiograph R-wave–triggered mechanism. The stored images were displayed side by side in a cine-loop format on a quad screen; thus, the baseline and follow-up images were displayed simultaneously in one of four standard views. The left ventricle was divided into 13 segments, matching the SPECT segments. Wall motion was scored semiquantitatively by two experienced observers who were unaware of the SPECT data. Each segment was assigned a wall motion score (WMS) ranging from 0 to 3: 0 = normal (normal endocardial excursion and systolic wall thickening), 1 = hypokinetic (reduced excursion and wall thickening), 2 = akinetic (absence of excursion and wall thickening) and 3 = dyskinetic (paradoxical outward movement in systole). Note that segments with mild hypokinesia were considered normal, whereas severely hypokinetic segments were considered hypokinetic.

A segment was considered improved if systolic thickening (either hypokinetic or normokinetic) became apparent in a segment that was akinetic or dyskinetic before revascularization or if a hypokinetic segment returned to normal contraction after the intervention. Postoperative paradoxical wall motion has been described in the septal region (*20*); for this reason, special attention was given to the endocardial thickening in these regions to study improvement after revascularization.

### Matching of SPECT and Echocardiographic Data

To correlate the SPECT data and the echocardiographic data, 13 LV segments were identified on both techniques: 1 apical segment, 6 distal segments (anterior, anterolateral, posterolateral, inferior, inferoseptal, anteroseptal) and 6 basal segments (anterior, anterolateral, posterolateral, inferior, inferoseptal, anteroseptal) (Fig. 1A).

### Cardiac Catheterization

All patients had coronary arteriography and left ventriculography. Lesions with a >50% reduction in luminal cross-sectional diameter in one or more of the major coronary arteries were considered significant.

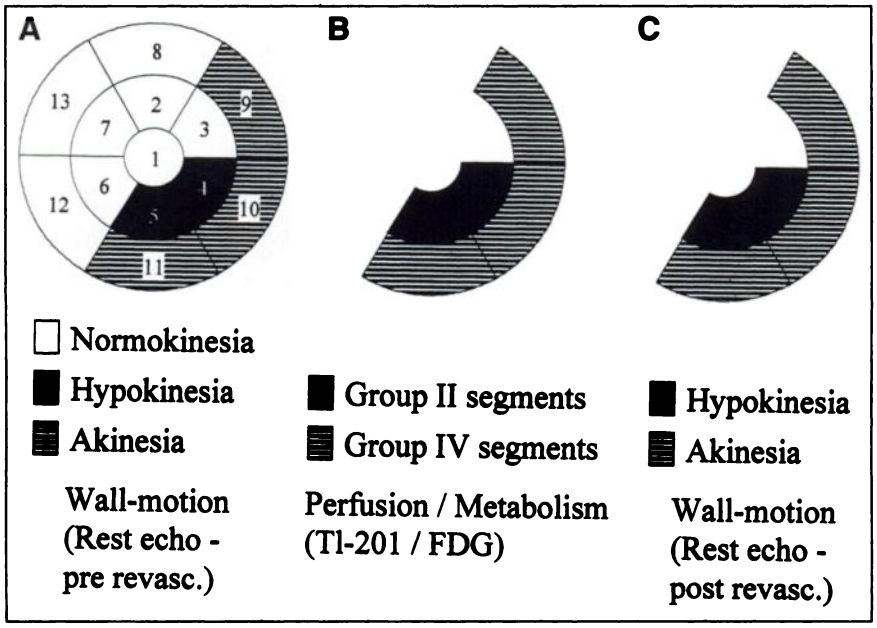


**FIGURE 1.** Schematic presentation of the 13-segment model used for echocardiography and SPECT (apex, segment 1; anterior distal, segment 2; anterolateral distal, segment 3; inferolateral distal, segment 4; inferior distal, segment 5; inferoseptal distal, segment 6; anteroseptal distal, segment 7; anterior basal, segment 8; anterolateral basal, segment 9; inferolateral basal, segment 10; inferior basal, segment 11; inferoseptal basal, segment 12; anteroseptal basal, segment 13). (A) Wall motion abnormalities at baseline (located in segments 4, 5 and 9–11) of patient with group II and group IV segments. (B) Perfusion–metabolism polar map indicates that akinetic segments 9–11 showed severe match (group IV). Hypokinetic segments 4 and 5 showed mild match (group II). (C) None of these segments improved in function after revascularization. Rest echo - pre vasc. = resting echocardiography before revascularization; FDG = $^{18}$F-fluorodeoxyglucose; Rest echo - post revasc. = resting echocardiography after revascularization.

### Assessment of Left Ventricular Ejection Fraction Before and After Revascularization

The LV ejection fraction (LVEF), before and after the revascularization, was calculated by cross-sectional echocardiography using the apical biplanar Simpson's technique (*21*). Improvement of global function after revascularization was defined as an increase of LVEF $\geq$ 5%, as used previously (*6*).

### Statistical Analysis

All results are expressed as mean ± SD. Patient data were compared using the Student *t* test for paired data. Comparison of proportions was performed using chi-square analysis. $P < 0.05$ was considered significant.

## RESULTS

### Clinical Data

Thirty-seven men and 5 women with a mean age of 60 y (range 43–76 y) were studied. Thirty-nine (93%) patients had a previous myocardial infarction. Q waves were present on the ECG in 31 patients. All patients with a previous infarction were studied more than 1 mo after the event. On average, they had 2.4 ± 0.8 stenosed vessels. The mean LVEF was 37% ± 8% (range 17%–48%; 12 patients had an LVEF of <30%). All patients were receiving cardiac medication that was continued during the SPECT study. Six patients had diabetes mellitus type II, which was well regulated with oral hypoglycemic medication; furthermore, using the clamping technique, good-quality cardiac FDG SPECT images can be obtained in this subset of patients (*22*).

### Baseline Data and Functional Outcome

Of 546 segments that were analyzed initially, 324 had normal wall motion and 222 were dysfunctional. Sixteen dysfunctional segments were not revascularized adequately (based on review of the surgical and PTCA reports) and were excluded from further analysis. These 16 segments had the following patterns on FDG SPECT: 2 with normal perfusion, 1 mild mismatch, 2 severe mismatches, 7 mild matches and 4 severe matches. None of these segments improved in function after revascularization.

The analysis was restricted to the remaining 206 dysfunctional segments. On average, the patients had 4.8 ± 3.1 dysfunctional segments.

Of the 206 dysfunctional segments, 71 improved in function, 128 remained unchanged and 7 deteriorated. Considering improvement of wall motion after revascularization as the gold standard for viability, 71 segments were classified as viable and 135 were classified as nonviable. The changes in wall motion of the individual segments are shown in Figure 2.

The segments with and without improvement after revascularization had comparable dysfunction (WMS before revascularization 1.48 ± 0.50 versus 1.52 ± 0.56; not significant [NS]).

### SPECT Data Versus Functional Outcome

According to the SPECT findings, the dysfunctional segments were grouped into five groups (Fig. 3). The mean

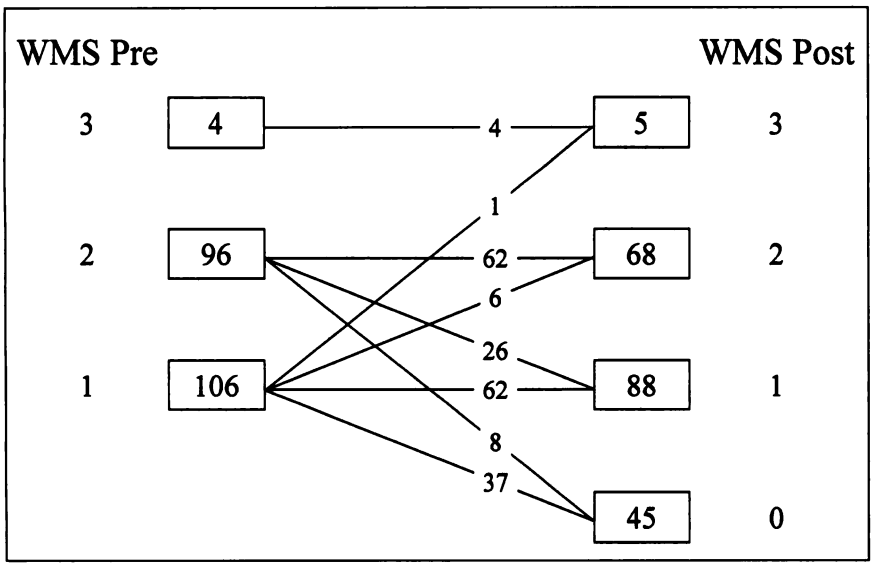


**FIGURE 2.** Changes in wall motion score before (WMS Pre) and after (WMS Post) revascularization of individual segments.

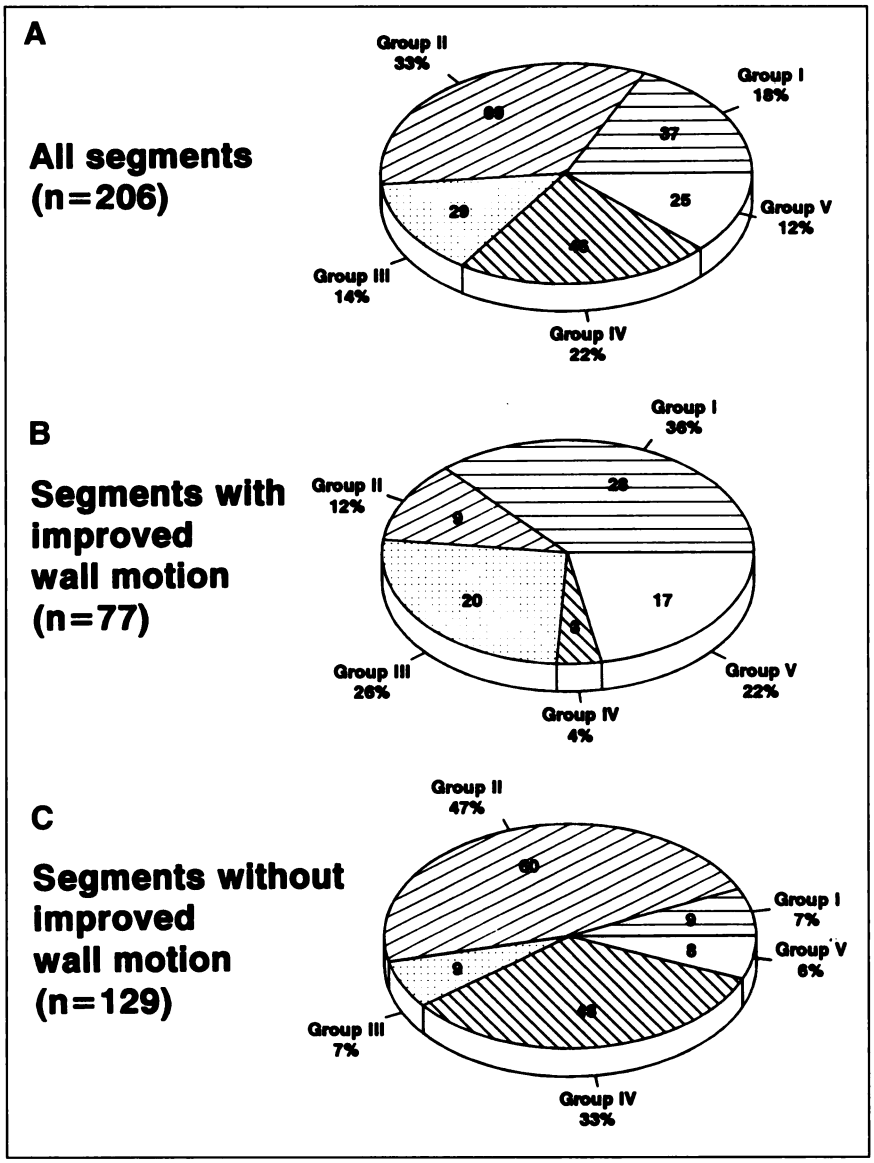


**FIGURE 3.** Frequency of different patterns. (A) Pie chart shows distribution of different SPECT patterns in 206 dysfunctional segments. Frequency of different patterns is shown in segments with (B) and without (C) recovery of wall motion after revascularization

WMS before and after revascularization of the different groups are shown in Figure 4.

*Group I: Normal Perfusion.* Thirty-seven dysfunctional segments had no perfusion defect. The mean $^{201}$Tl activity was 97.2% ± 10.1%, and the mean FDG activity was 99.7% ± 4.8% (NS versus $^{201}$Tl activity). The segments showed relative mild dysfunction (mean WMS 1.14 ± 0.34); mean WMS improved significantly after revascularization (Fig. 4).

*Group II: Mild Match.* Sixty-nine segments showed a mild reduction in $^{201}$Tl activity (mean 68.7% ± 3.7%) accompanied by a mild reduction in FDG activity (64.8% ± 9.2%). These segments showed more severe dysfunction at baseline (WMS 1.52 ± 0.55) than did the segments in group I ($P < 0.05$). After revascularization the mean WMS remained unchanged (Fig. 4). A schematic presentation of the SPECT data, baseline echo data and follow-up echo data of a patient with group II segments is provided in Figure 1.

*Group III: Mild Mismatch.* Twenty-nine segments showed a mild reduction in perfusion (mean $^{201}$Tl activity 68.6% ± 3.9%) with relatively increased FDG activity (84.1% ± 7.0%). The mean WMS (1.40 ± 0.49) was not significantly different from the mean WMS of group II. In this group, the WMS did improve significantly after revascularization (Fig. 4).

*Group IV: Severe Match.* In this group the mean $^{201}$Tl activity was 52.6% ± 9.0%. The FDG activity was 50.0% ± 9.8%. These segments showed more severe dysfunction (WMS 1.67 ± 0.51) compared with that of group I, II and III segments ($P < 0.05$). The mean WMS did not improve after revascularization (Fig. 4).

*Group V: Severe Mismatch.* The mean $^{201}$Tl and FDG activities were 51.4% ± 9.5% and 73.9% ± 16.8%, respectively. The mean WMS (1.76 ± 0.50) before revascularization was comparable with that of the group IV segments. However, the mean WMS did improve after revascularization (Fig. 4). Thus, improvement of mean WMS was observed only in groups I, III and V.

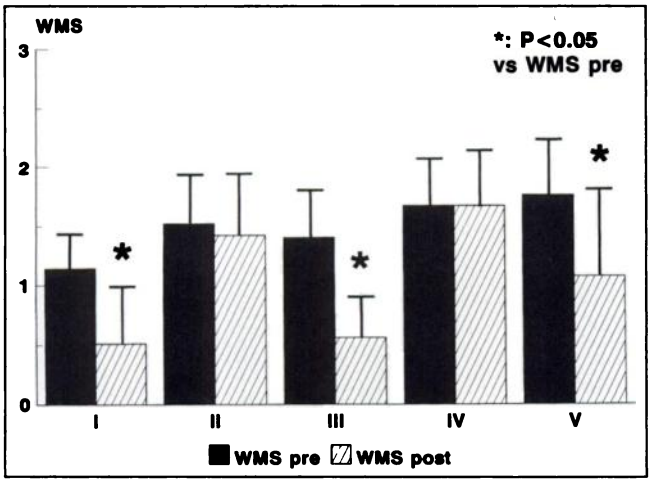


**FIGURE 4.** Mean wall motion score (WMS) before (WMS pre) and after (WMS post) revascularization of different groups. Improvement of function occurred only in groups I, III and V.

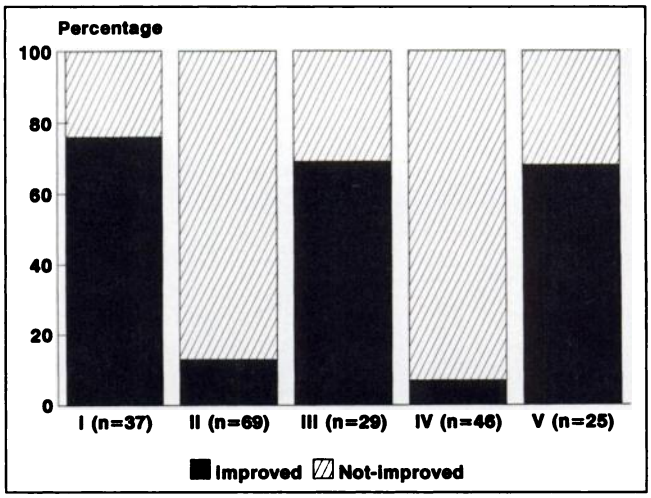


**FIGURE 5.** Percentages of segments with (Improved) and without (Not-improved) improvement in different groups. Significantly more segments showed improvement in WMS in groups I, III and V compared with that in groups II and IV.

The exact percentages of segments improving or not improving in the different groups are shown in Figure 5. Significantly more segments improved in WMS in groups I, III and V compared with groups II and IV.

Considering normal perfusion and mild and severe perfusion–FDG mismatches predictive for functional recovery, their positive values were 76%, 69% and 68%, respectively. Considering the mild and severe matches predictive for absence of recovery, their negative predictive values were 87% and 93%, respectively. When these criteria were combined, the negative and positive predictive values were 89% and 71%.

Finally, all matches and mismatches were grouped according to the $^{201}$Tl activity (Fig. 6). The highest incidence of recovery (25%) of function was observed in the matches with $^{201}$Tl and FDG activities of >70% (Fig. 6A). In the mismatches, the incidence of recovery was comparable in the different categories but was somewhat lower in the mismatches with a $^{201}$Tl activity of >70% (Fig. 6B). The somewhat lower incidence of recovery in the mismatches with a $^{201}$Tl activity of >70% is difficult to explain but may be related to the relatively small number of segments in the subgroups.

### Left Ventricular Ejection Fraction Before and After Revascularization

In the entire group, the LVEF did not increase significantly (37% ± 8% to 39% ± 7%). However, in 12 patients (29%), the LVEF increased by 5% or more. In the subgroup of 9 patients with severe LV dysfunction (LVEF < 30%), the LVEF increased significantly from 25% ± 7% to 31% ± 9% ($P < 0.05$).

## DISCUSSION

This study evaluated the use of FDG SPECT imaging to predict functional recovery in dysfunctional segments after

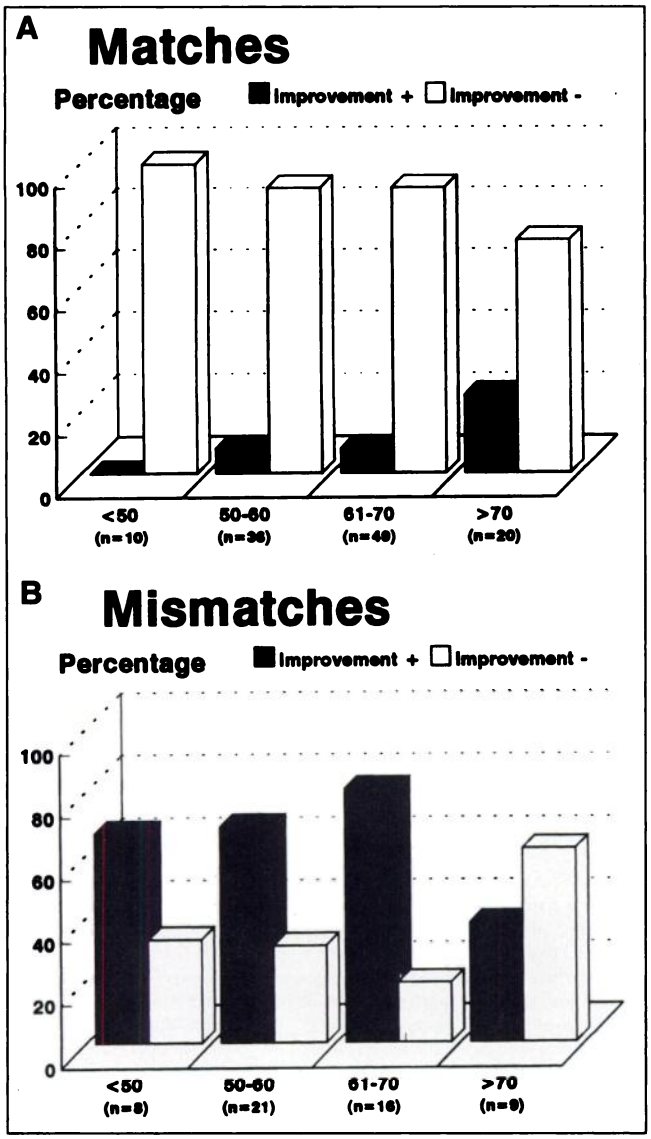


**FIGURE 6.** Incidence of recovery in segments grouped according to different $^{201}$Tl activities. (A) Segments with matches. (B) Segments with mismatches.

revascularization using different perfusion–metabolism criteria. The presence of perfusion–FDG mismatch was predictive for functional recovery after revascularization, independent of the severity of the $^{201}$Tl perfusion defect. Normal perfusion was also predictive of functional recovery. In contrast, perfusion–FDG match (both mild and severe) was predictive for absence of recovery. Probably the mild matches represent subendocardial scars, whereas the severe matches represent transmural scars.

These data indicate that the integration of perfusion and metabolism is mandatory to identify segments that are likely to improve in function after revascularization.

### Different Perfusion–FDG Patterns

In this study, five patterns of perfusion and FDG uptake were evaluated.

*Normal Perfusion.* Eighteen percent of the dysfunctional segments showed normal perfusion. Most of these segments improved in function after revascularization. Several recent studies have shown that many segments with chronic dysfunction and improvement after revascularization had nearly normal or normal perfusion before revascularization (*23–25*). Vanoverschelde et al. (*23*) have suggested that repetitive attacks of ischemia may result in chronic dysfunction, although nearly normal or normal resting perfusion is maintained. The predictive value (for improvement of function after revascularization) of normal perfusion (as assessed by SPECT) was 76%, comparable with that of the mismatch pattern, a finding not reported previously.

*Perfusion–FDG Mismatch Pattern.* Twenty-six percent of the dysfunctional segments showed a mismatch pattern. The mismatch pattern is thought to represent hibernating myocardium, which is defined as chronically reduced perfusion at rest, associated with regional dysfunction, that can be improved after successful revascularization (*2*). In this study, the mismatches were subdivided in two groups according to the severity of the perfusion defect. Most of the segments with mismatch improved in function after revascularization, in line with the literature on FDG PET (*3,26*) and previous observations with FDG SPECT (*6*).

The current data show, as indicated in Figure 6, that the severity of the underlying perfusion defect was not related to the functional fate of the segments. A study by Gewirtz et al. (*27*) showed that viability was unlikely when myocardial blood flow was severely reduced. Using PET and $^{13}$N-ammonia, they showed that regions with severely reduced blood flow rarely exhibited increased FDG uptake. In this study the incidence of increased FDG uptake was comparable in regions with mildly and severely reduced perfusion, but perfusion was measured by $^{201}$Tl SPECT. This approach does not allow absolute quantification of blood flow, and the technique does not correct for partial-volume effects (*28*). Furthermore, the number of segments with perfusion–FDG mismatch was small in this study.

*Perfusion–FDG Match.* Fifty-six percent of the dysfunctional segments showed perfusion–FDG match. Most of the segments with perfusion–FDG match did not recover in function after revascularization; these segments represent scar tissue, with varying degrees of scar formation through the myocardial wall (*29*). The scar formation involves the entire myocardial wall in transmural infarction, whereas the scar formation is restricted to the subendocardium or to localized parts of the myocardial wall in nontransmural infarction. Improvement of contractile function after revascularization is unlikely in the situation of either transmural or nontransmural infarction. In transmural infarction, both perfusion and FDG uptake will be reduced throughout the entire myocardial wall, leading to severe perfusion defects associated with severely decreased FDG uptake on SPECT and consistent with absence of recovery in contractile function after revascularization, as reported earlier (*3,6,26*) and in this study. In nontransmural infarction, with a mixture

of scar and viable tissue, the reduction in perfusion and FDG uptake will be localized to certain parts of the myocardial wall, as suggested by Perrone-Filardi et al. (*30*). However, the spatial resolution of SPECT does not allow detection of these regions, resulting in a mild reduction of both perfusion and FDG uptake throughout the entire myocardial wall. Thus, the pattern of mildly decreased perfusion and FDG uptake may represent a situation after nontransmural infarction with a mixture of fibrosis and viable myocytes, as proposed by Di Carli et al. (*29*). Revascularization of these regions will not lead to improvement of contractile function, as supported by the findings in this study. Vom Dahl et al. (*31*) reported similar findings using FDG PET and showed a poor predictive value for recovery of segments with a mild, concordant reduction in both perfusion and FDG uptake.

### Clinical Implications

The data suggest that assessment of perfusion alone appears inadequate in the prediction of functional recovery; the additional information provided by the FDG signal allowed discrimination between segments with relatively high and low likelihoods of recovery of function after revascularization. The additional information provided by the FDG uptake allowed identification of residual jeopardized yet viable tissue and differentiation from transmural and subendocardial scars. Several other studies (*32–36*) using nuclear techniques with $^{201}$Tl (*32,33*), $^{99m}$Tc-sestamibi (*34*) or $^{13}$N-ammonia (*34,35*) or contrast echocardiography (*33,36*) emphasized the suboptimal diagnostic accuracy of perfusion imaging to predict functional outcome.

In this study, we used functional outcome as the end point and gold standard to assess viability. However, the terms "viability" and "recovery of function" are not synonymous. Segments with a mild matched defect are likely to represent a subendocardial scar, and, although they do not improve in function, they contain viable tissue; similar data using $^{201}$Tl have been reported (*37–39*). The prognostic value of this pattern remains to be determined. Therefore, other end points, including long-term prognosis and prevention of LV remodeling, should be studied to assess whether the revascularization of segments with a mild reduction of perfusion and FDG uptake is clinically useful.

### Limitations

Although the same 13-segment model was used for the scintigraphic and echocardiographic studies, some misalignment may have occurred. The use of dual-isotope imaging [FDG in combination with either $^{99m}$Tc-sestamibi (*7*) or $^{99m}$Tc-tetrofosmin (*40*)] may decrease misalignment (between the perfusion and FDG images) and may also allow gated studies (to assess wall motion), thereby further reducing misalignment (between the perfusion, FDG and functional images).

Furthermore, vessel or graft patency was not determined after the procedure. Reocclusion may partially account for the failure of some viable segments to recover. To fully ascertain the adequacy of the revascularization, repeated angiography or a postrevascularization $^{201}$Tl study should have been performed.

## CONCLUSION

This study shows that segments with normal perfusion or a mismatch pattern (either mild or severe) are likely to improve in function, whereas segments with a match pattern (either mild or severe) will not improve in function after revascularization. To identify segments with a high likelihood of recovery of function after revascularization, integration of information on perfusion and FDG uptake is necessary. Additional studies with assessment of vessel or graft patency are needed to confirm these findings.

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