BMIPP Imaging to Improve the Value of Sestamibi Scintigraphy for Predicting Functional Outcome in Severe Chronic Ischemic Left Ventricular Dysfunction

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Mismatching between beta-methyl-p-iodophenyl-pentadecanoic acid (BMIPP) and perfusion accurately predicts functional outcome after acute myocardial infarction. The current investigation was aimed at evaluating the value of this method to predict the evolution of global function according to the applied treatment in patients with chronic ischemic heart disease. **Methods:** Twenty patients with infarction and chronic left ventricular dysfunction were studied (median infarction age 12 wk, range 2 wk–15 y). Radionuclide angiography, two-dimensional echocardiography and BMIPP and gated sestamibi scintigraphy were performed with the patient at rest before and >6 mo after treatment (revascularization in 13 patients and conservative therapy in 7 patients). In 7 patients, radionuclide angiography was repeated after 1 y. **Results:** On a patient basis, mismatching with BMIPP less than sestamibi was noted in 15 patients at baseline. Of these 15 patients, 11 had significant functional improvement at follow-up versus only 1 of the 5 patients with a matched decreased uptake. Hence, the combined sestamibi/BMIPP was 73% positive and 80% negative in predicting functional outcome, with a global accuracy of 75%. On a segmental basis, using an optimal threshold of uptake defined by receiver operating characteristic curve analysis, sestamibi was only 63% accurate in predicting regional outcome. Adding BMIPP improved the accuracy to 80% ($P = 0.001$). At follow-up, significant mismatching was still noted in 7 patients in the revascularized group and 1 in the medically treated group. The mismatch was associated with a further increase in ejection fraction at 1-y follow-up in only the revascularized group. **Conclusion:** In patients with chronic left ventricular dysfunction after infarction, a mismatching with BMIPP less than sestamibi reliably identifies jeopardized but viable myocardium and predicts functional recovery with an accuracy similar to that reported in the acute and subacute phases of the infarction.

Key Words: myocardial viability; BMIPP; functional recovery; chronic left ventricular dysfunction; ejection fraction

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In patients with myocardial infarction, differentiation between regions with a high and a low likelihood of functional recovery after revascularization is an important issue, especially in cases of severely compromised left ventricular function in which the restoration of flow in hypoperfused but viable myocardium dramatically improves survival and quality of life (*1*). Because of the higher morbidity and mortality associated with revascularization in these patients, accurate identification of myocardial viability before treatment is crucial to the decision to revascularize. The gold standard of the noninvasive methods aimed at evaluating the presence and extent of viable tissue is PET, particularly with ^{18}F-fluorodeoxyglucose (FDG) (*2*), although its high cost precludes widespread use and has encouraged the development of alternative techniques.

On the basis of the statement that free fatty acids are the major source of energy in well-oxygenated myocardium (*3*), imaging of cardiac metabolism with radioiodinated fatty acid analogs has been proposed as an alternative to positron tomography (*4*). The ^{123}I-15-(p-iodophenyl)-3-(R,S)-methyl-pentadecanoic acid (BMIPP) is currently considered the most suitable for imaging with SPECT because the presence of a methyl group precludes direct β-oxidation and prolongs the tissular retention time (*4*), although a significant proportion of BMIPP undergoes β-oxidation after an intermediate α-oxidation step (*5*).

In the assessment of viability, a strong association has been reported between a mismatching with BMIPP less than perfusion and jeopardized but viable myocardium on the one hand, and a matched decreased uptake of both tracers and nonviable tissue on the other hand (*6*). Compared with dobutamine stress echocardiography, the combined use of BMIPP and ^{99m}Tc-sestamibi has shown similar accuracy in predicting functional recovery after acute myocardial infarction (*6*). In the chronic phase of the disease, data are more contradictory. Recently, Sloof et al. (*7*) have suggested that a mismatching with BMIPP higher rather than lower than ^{201}Tl should be a hallmark of viability in this setting, whereas

Tamaki et al. (8) never observed this mismatching with BMIPP higher than ^{201}Tl in a group of patients with chronic myocardial infarction.

To evaluate the value of BMIPP scintigraphy for assessing viability in chronic ischemic heart disease, we studied 20 patients with myocardial infarction and chronic left ventricular dysfunction before and 6 mo to 1 y after treatment, with ^{99m}Tc-sestamibi as the perfusion tracer. This study was conducted to (a) assess the different distribution patterns of BMIPP versus sestamibi observed in chronic ischemic heart disease and the significance with regard to the evolution of global function at follow-up, (b) determine the value of sestamibi alone and in combination with BMIPP for predicting functional improvement at follow-up and (c) evaluate the influence of performing revascularization on regional perfusion and metabolic activity.

MATERIALS AND METHODS

Patient Selection

Between September 1995 and March 1997, 20 patients (17 men, 3 women; mean age ± SD, 61.5 ± 9.5 y, range 45–78 y) referred for coronary angiography because of severe angina pectoris or congestive heart failure were prospectively included in the study. Inclusion criteria were symptoms lasting >6 mo, most recent infarction >2 wk previously, severe and extended wall motion abnormalities on resting echocardiography (≥3 segments with either severe hypokinesis or akinesis), ejection fraction ≤ 45%, absence of severe arrhythmia or conduction disturbances on electrocardiography and stable angina. All patients had at least one Q-wave myocardial infarction (anterior 14, inferior/lateral 12), the most recent occurring between 2 wk and 15 y before inclusion in the study (mean 27.8 mo, median 3 mo). Mean ± SD left ventricular ejection fraction was 33.0% ± 9.8%. Stress angina (Canadian Cardiovascular Society class ≥ II) was present in 18 patients, rest angina in 4 and congestive heart failure (New York Heart Association functional class ≥ III) in 8. Two patients had a history of previous coronary artery bypass grafting (CABG), and 4 had a history of percutaneous transluminal coronary angioplasty (PTCA). On coronary angiography, a >70% stenosis of a major epicardial coronary artery or one of its main side branches was found in an average of 2.1 ± 0.7 vessels per patient.

Within the week of the procedure, resting echocardiography, radionuclide angiography, BMIPP and gated sestamibi scintigraphy were performed. These tests were followed by revascularization within the month or by optimization of the conservative therapy. The decision to revascularize was based mainly on technical feasibility (quality of the peripheral coronary arterial bed, tortuousness, location and number of lesions), although the scintigraphic findings were also included in the decision-making process.

A follow-up study performed 6 mo later included radionuclide angiography, BMIPP and gated sestamibi SPECT and echocardiography, as well as a complete electrocardiographic and clinical examination. At 1 y, a new radionuclide angiogram was obtained for 7 patients in whom >50% of the segments were still mismatched at the 6-mo follow-up.

This study was approved by the local Commission of Medical Ethics. All patients received written information and gave informed consent.

Resting Echocardiography

Two-dimensional transthoracic echocardiography was performed with a commercially available system (Sonos 2500; Hewlett-Packard, Andover, MA) equipped with a 2.5-MHz transducer. Patients were positioned in the left oblique lateral decubitus position. Left parasternal long- and short-axis and apical four- and two-chamber views were analyzed by an experienced echocardiographer to assess regional wall motion and thickening at the basal, midventricular and apical levels, with the use of a 16-segment model. For each segment, regional systolic thickening and wall motion were scored by a 4-point scale (1 = normal, 2 = moderately hypokinetic, 3 = severely hypokinetic and 4 = akinetic or dyskinetic), and a global wall motion score was calculated for each patient by summing the scores of each individual segment.

Scintigraphic Imaging Protocol

All the tests were performed within a 3-d interval. Radionuclide angiography was performed according to our standard method, for which the interobserver variability amounts to about 1% (9).

After at least 6 h of patient fasting and administration of potassium perchlorate to block thyroidal uptake of free iodine, a mean dose of 160 MBq (4.3 mCi) BMIPP was intravenously injected in resting patients, and SPECT imaging was started 30 min later, with the use of a triple-head gamma camera (Triad; Trionix Lab, Twinsburg, OH) equipped with all-purpose low-energy collimators. Ninety projections (30 per head) of 60-s duration were acquired over a 360° noncircular body-contour orbit, using a 128 × 64 matrix. Within 48 h, ^{99m}Tc-sestamibi SPECT was performed about 80 min after injection of a mean dose of 950 MBq (25.7 mCi) BMIPP at rest, using the same protocol but with 40 s per view. This acquisition was immediately followed by eight-frame gated SPECT (20 projections of 60 s each per head).

Scatter subtraction but no attenuation correction was applied.

Gated sestamibi images were processed with a Butterworth prefilter (cutoff frequency 0.35 cycles/cm, order 5) and a ramp filter–backprojection filter and used to calculate the end-diastolic and end-systolic volumes as previously reported (10).

Scatter was compensated for on the nongated images using a subtraction method with compensation κ values of 0.7 for ^{99m}Tc and 1.0 for [123]I (11). The three standard orthogonal tomograms were then obtained after filtered backprojection (Butterworth prefilter, cutoff frequency 0.75 cycles/cm for sestamibi and 0.6 cycles/cm for BMIPP, order 5 and ramp filter–backprojection filter) and appropriate reorientation of the scatter-corrected data. After reconstruction, BMIPP and sestamibi images were aligned side by side and normalized to their own maximum. For both studies, the left ventricular myocardium was divided into 16 segments matching the echocardiography (6 segments at the midventricular and at the basal levels of the short-axis images, and 4 apical segments on the midventricular vertical and horizontal long-axis tomograms). BMIPP and sestamibi uptake were graded independently by two observers.

In an initial analysis, mean uptake in each segment was expressed as percentage of the peak activity for each tracer separately according to a previously described method (11).

In addition, the uptake of both tracers was compared to classify the segments as normal, matched, mismatched or reverse mismatched (11).

Criteria of Viability

At baseline, a segment was considered viable if it was either normally perfused (namely, ≥60% of the peak sestamibi uptake)

(*12*), mismatched (sestamibi uptake < 60% and BMIPP uptake at least 10% less than sestamibi) or reverse mismatched (sestamibi uptake < 60% and BMIPP uptake at least 10% more than sestamibi). Nonviable, scarred myocardium corresponded to regions with equally decreased BMIPP and sestamibi uptake. Mismatching and reverse mismatching were considered as a whole, because of the suggested relationship between the latter and hibernation (*13*).

On a patient basis, viability was considered present if at least 50% of the dysfunctional segments showed either normal sestamibi uptake or mismatching.

At follow-up, because both the ejection fraction value and end-systolic volume are important prognostic parameters in patients with ischemic left ventricular dysfunction (*14,15*), improvement was defined as a ≥5% increase in ejection fraction (by radionuclide angiography) and a ≥10-volume-unit decrease in end-systolic volume (by gated sestamibi SPECT) compared with the baseline values.

The evolution of the regional contractility and the global wall motion score were used as independent parameters of functional outcome.

Statistical Analysis

All statistical analyses were performed with the SPSS statistical program package (SPSS, Inc., Chicago, IL). Values were expressed as median and range in cases of non-Gaussian distribution or as mean ± SD otherwise. Data between the two groups were compared by the Wilcoxon rank sum test or the Student t test, and the degree of association between two variables was measured by the Spearman rank correlation. Sensitivities and specificities were compared by the McNemar test, and differences between the proportions were calculated by the Fisher exact test or the chi-square test when appropriate. A probability value < 0.05 was considered significant. Lastly, receiver operating characteristic (ROC) curves were generated to calculate the optimal cutoff of sestamibi uptake and the number of mismatched segments predicting recovery (*16*).

RESULTS

Baseline Data

Among the 320 segments, wall motion was normal in 127 on resting echocardiography. Moderate hypokinesis was noted in 24, severe hypokinesis in 45 and akinesis/dyskinesis in 124. The mean number of segments with a wall motion score > 2 was 8.4 ± 2.6 per patient, and all were supplied by a stenotic vessel (mean stenosis in the coronary arteries supplying these segments 92% ± 11%).

With sestamibi, the number of segments with normal uptake decreased according to the severity of the contractile dysfunction, as shown in Table 1. In the segments with a wall motion score > 2, mean sestamibi uptake was significantly lower in those with a score of 4 than a score of 3 (38% ± 19% versus 52% ± 25%, P = 0.001).

Adding the BMIPP data in the regions with <60% sestamibi uptake, the ratio of nonviable (matched) to viable segments was significantly higher in those with a wall motion score of 4 than a score of 3 (P = 0.03, Table 1).

On a patient basis, scintigraphic evidence of viability was present in 15 of 20 patients.

TABLE 1
Distribution Patterns of Sestamibi and BMIPP According to Segmental Wall Motion Score

	Segmental wall motion score			
	1 (n = 127)	2 (n = 24)	3 (n = 45)	4 (n = 124)
Sestamibi ≥ 60%	116 (91%)	18 (75%)	23 (51%)	18 (14%)
Mismatching	3 (2%)	0	16 (36%)	46 (37%)
Reverse mismatching	0	0	0	11 (9%)
Matching	8 (6%)	6 (25%)	6 (13%)	49 (40%)

Wall motion score 1 = normal contractility, 2 = moderate hypokinesis, 3 = severe hypokinesis and 4 = akinesis/dyskinesis.

Mismatching = sestamibi < 60% and BMIPP at least 10% less than sestamibi; reverse mismatching = sestamibi < 60% and BMIPP at least 10% more than sestamibi; matching = sestamibi and BMIPP < 60% and equally decreased.

The patient population was divided into two groups, according to the treatment protocols. The first group consisted of the patients who underwent revascularization, and the second group consisted of patients who were conservatively treated. Baseline characteristics of both groups are reported in Table 2 and scintigraphic characteristics in Table 3.

Follow-up Data

Patient Data. Revascularization of the dysfunctional segments was performed within the month of the tests in 13 patients, 7 with CABG and 6 with PTCA. In the CABG group, 18 arteries were bypassed, of which 14 supplied myocardial regions with a wall motion score > 2. In the PTCA group, only vessels supplying severely dyscontractile segments were treated.

TABLE 2
Baseline Characteristics of Both Patient Groups

	Revascularized group (n = 13)	Medically treated group (n = 7)	P
Heart failure ≥ New York class III	5/13 patients	3/7 patients	0.85
Angina ≥ Canadian class II	12/13 patients	6/7 patients	0.64
Beta/calcium channel blockers	11/13 patients	5/7 patients	0.59
Nitrates	7/13 patients	3/7 patients	0.65
ACE inhibitors	10/13 patients	4/7 patients	0.62
Ejection fraction (%)	32.6 ± 10.2	33.5 ± 7.9	0.85
End-diastolic volume (volume units)	145 ± 54	134 ± 53	0.67
No. of abnormal segments/patient	8.2 ± 2.8	9.0 ± 2.0	0.4
Global wall motion score	38.8 ± 7.4	42.7 ± 6.4	0.25

ACE = angiotensin-converting enzyme.
Values expressed as mean ± SD.

TABLE 3
Baseline Scintigraphic Characteristics of Both Patient Groups

	Revascularized group (n = 13)	Medically treated group (n = 7)	P
Segmental sestamibi uptake	44% ± 20%	38% ± 23%	0.12
No. of segments with ≥60% sestamibi uptake	31/107	10/62	0.06
No. of segments with <60% sestamibi uptake and mismatching	57/76	16/52	<0.001
No. of viable dysfunctional segments/patient	6.9 ± 3.2	3.7 ± 3.0	0.04
No. of patients with viability	12/13	3/7	0.03

Values are expressed as mean ± SD.
Only segments with resting wall motion score > 2 are taken into account.

In the remaining 7 patients, medical therapy was optimized.

The follow-up study was completed at a mean delay of 6 mo and 3 wk after revascularization or after the first tests (range 6.0–7.5 mo). Restenosis without subsequent new infarction was documented in 1 patient 2.5 mo after PTCA and was retreated by PTCA and stenting. No other major or minor cardiac events were observed.

With the use of a ≥5% increase in ejection fraction value and a ≥10-volume-unit decrease in end-systolic volume as criteria of recovery, 12 patients improved at follow-up, 11 of whom had a mismatched pattern. A mismatching between BMIPP and sestamibi was 73% predictive of functional recovery, and a matching between both tracers was 80% predictive of no changes (75% accuracy).

A significant relationship was found between the number of mismatched segments and the changes in ejection fraction ($r = 0.7$, $P = 0.001$) and end-systolic volume ($r = -0.55$, $P = 0.015$). When the number of segments with evidence of viability versus the total number of dysfunctional segments for each individual patient was taken into account, a good relationship was noted between the ratio of viable-to-totally dysfunctional segments and the increase in ejection fraction value ($r = 0.73$, $P < 0.001$), as depicted in Figure 1. If <50% of the dysfunctional segments were viable, no significant increase in ejection fraction could be expected. On the contrary, if >75% of these segments were viable, the expected improvement in ejection fraction value could amount to about 45% of the baseline value.

Functional Outcome According to the Applied Treatment. The evolution of the functional parameters is shown in Figure 2.

In the medically treated group, 4 patients reported a stabilization of their complaints at the 6-mo follow-up, 2 worsened and 1 improved under maximum medical therapy. Mean ± SD difference compared with the baseline value was 1.6% ± 6.8% in ejection fraction ($P = 0.56$) and 5 ± 17 volume units in end-systolic volume ($P = 0.46$). A slight increase in mean end-diastolic volume was noted (10 ± 22 volume units, $P = 0.25$). The global wall motion score was 42.7 ± 6.4 at baseline and 38.6 ± 10.4 at follow-up ($P = 0.55$).
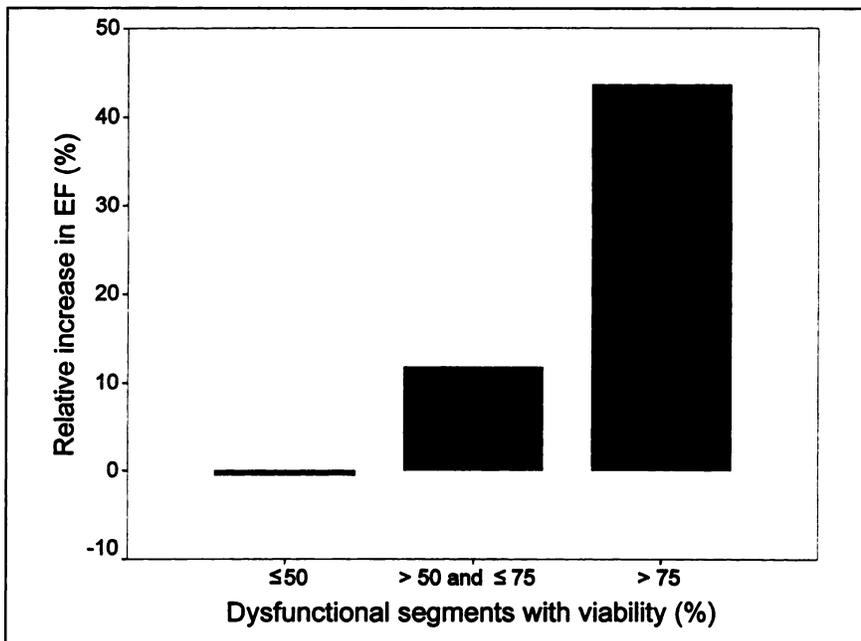
FIGURE 1. Mean improvement in ejection fraction (EF) at follow-up compared with baseline values ($EF_{post} - EF_{pre}/EF_{pre} \times 100$) according to ratio of viable/totally dysfunctional segments. Viability is defined as either ≥60% of peak sestamibi activity or mismatched uptake with BMIPP at least 10% less than sestamibi in severely hypokinetic or akinetic segments.
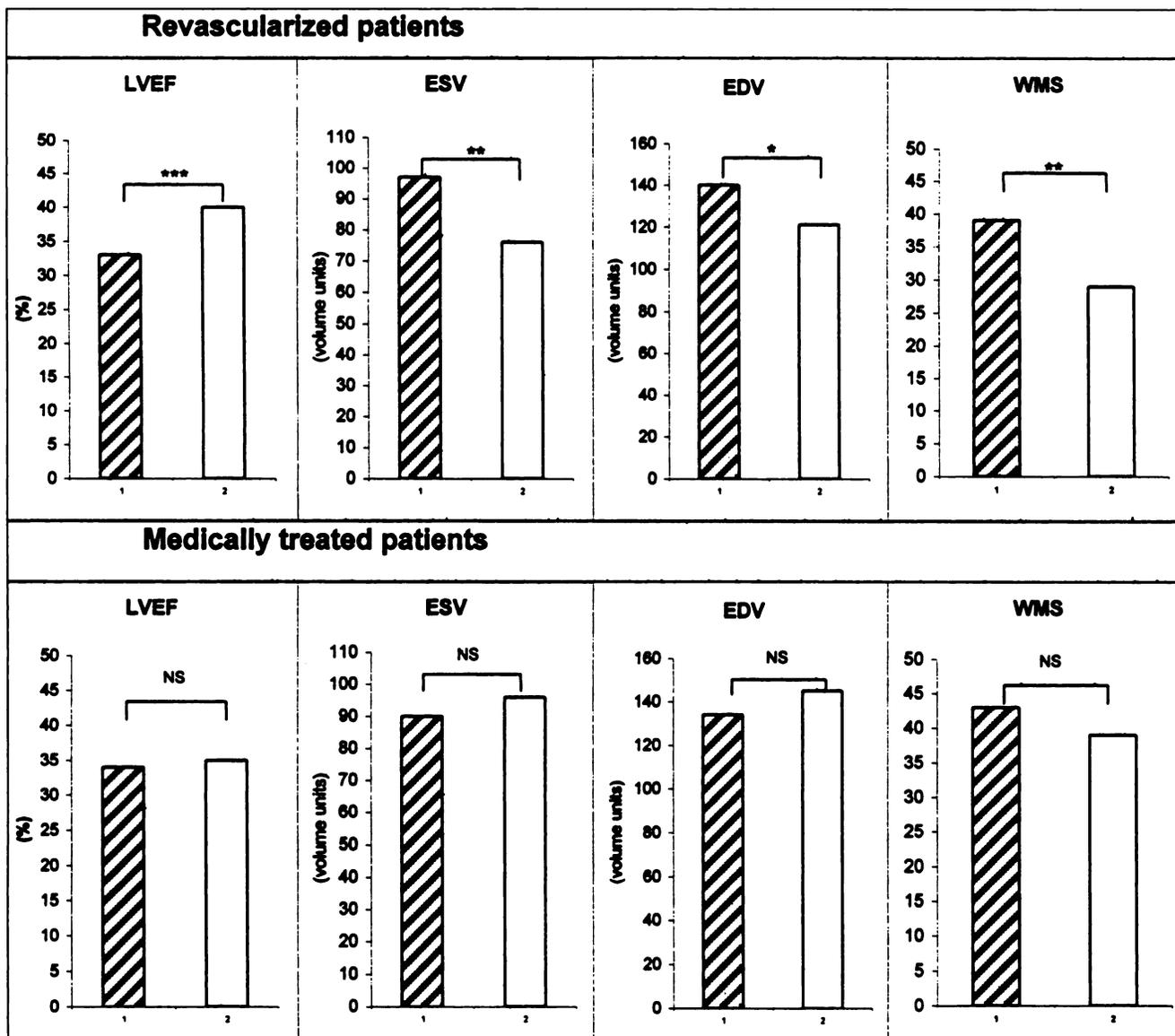
FIGURE 2. Bar graph showing evolution of left ventricular ejection fraction (LVEF), ventricular volumes (end-systolic volume [ESV], end-diastolic volume [EDV]) and global wall motion score (WMS) between baseline (hatched bars) and follow-up (open bars) in revascularized and medically treated patients. *$0.01 < P \leq 0.05$; **$0.001 < P \leq 0.01$; ***$P \leq 0.001$, NS = not significant.

On a patient basis, significant viability was noted in 3 patients at baseline. At follow-up, 1 deteriorated, another showed regional improvement without change in ejection fraction value and the last significantly improved in both regional and global function. In this patient, coronary angiography repeated 1 y after the first tests because of resurgence of severe angina and dyspnea showed disease progression and the development of large collaterals with almost complete retrograde filling of the infarct-related artery.

In the revascularized group, 12 of 13 patients had significant viability at baseline. At follow-up, all patients had clinical improvement. The mean ± SD increase in ejection fraction was 7.4% ± 4.5% ($P < 0.001$), and the decrease in end-diastolic and end-systolic volumes was

-19 ± 27 and -21 ± 27 volume units, respectively ($P = 0.04$ and 0.02, respectively). The global wall motion score amounted to 38.8 ± 7.4 at baseline and 28.8 ± 8.1 at follow-up ($P < 0.001$). In 2 patients whose myocardium was considered viable, no significant changes in ejection fraction and end-systolic volume were observed, despite clinical improvement. According to the criteria for global improvement, these patients were considered therapeutic failures. However, a significant increase in ejection fraction compared with the 6-mo value was noted in 1 of the patients at 1-y follow-up.

One year to 17 mo after the first tests, another radionuclide angiogram was obtained for 7 patients (6 revascularized, 1 medically treated) in whom >50% of the severely dysfunctional segments were still mismatched at the 6-mo

follow-up. A further increase in ejection fraction compared with the 6-mo value was noted in 5 of 6 revascularized patients, and significant deterioration was noted in the medically treated patient. Sestamibi and BMIPP images of one of these patients are shown in Figure 3.

Evolution of Sestamibi and BMIPP Uptake, and Regional Contractility According to the Applied Treatment. For this part of the analysis, only the segments with a wall motion score > 2 were considered.

At baseline and at follow-up, mean sestamibi uptake was 38% ± 23% and 41% ± 25%, respectively (P = 0.08), and mean BMIPP was 39% ± 23% and 39% ± 24%, respectively, in the medically treated group, whereas mean sestamibi uptake increased from 44% ± 20% to 52% ± 21% (P < 0.001) and mean BMIPP uptake increased from 32% ± 23% to 46% ± 24% (P < 0.001) in the revascularized group.

Interestingly, a majority of mismatched segments was still noted in 8 patients (of whom 7 were in the revascularized group). In 7 of the patients, radionuclide angiography was repeated at 1 y, showing a further increase in ejection fraction compared with the 6-mo value in 83% of the revascularized patients and a worsening in the medically treated patients.

By echocardiography, regional improvement was noted in 85 of 107 segments (79%) in the revascularized group and 20 of 62 segments (32%) in the medically treated group. Because of a low segmental uptake, sestamibi was only 54% accurate in predicting segmental reversibility (sensitivity 32%, specificity 89%) when using a ≥60% uptake as a threshold for viability. To optimize the value of sestamibi analysis with regard to the prediction of regional recovery, ROC curves were generated to determine the best cutoff of uptake in dysfunctional segments predicting the evolution of regional contractility. A value of 40% sestamibi uptake was found optimal. However, even when this optimized threshold value was used, sestamibi remained mildly predictive of segmental outcome, with a sensitivity and specificity of 70% and 52%, respectively, and no significant difference in accuracy (63%). On the other hand, the addition of the BMIPP data
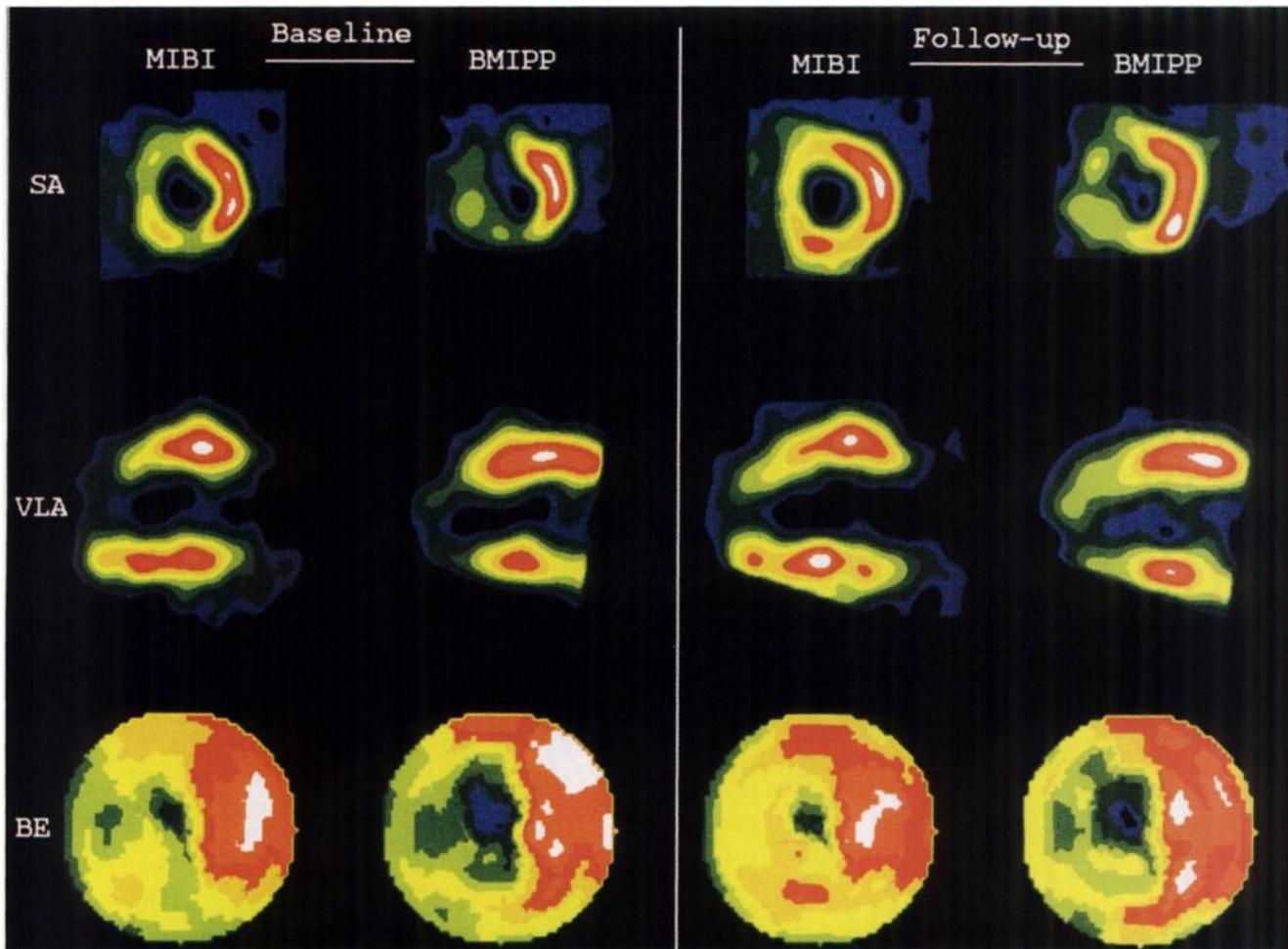
FIGURE 3. Midventricular short-axis (SA), vertical long-axis (VLA) and bull's eye (BE) images of 45-y-old man with 37-wk-old anteroseptal infarction associated with extended akinesis (9 segments). Baseline EF amounted to 37%, and 8 of 9 segments were mismatched. Six months after CABG, EF did not significantly change (39%) although patient was clinically symptom free. On scintigraphy, 6 of 9 segments with baseline dysfunction were still mismatched, despite increased sestamibi and BMIPP uptake. At 1 y, EF amounted to 44%.

significantly improved the test accuracy up to 80%, with a sensitivity of 87%, a specificity of 69% and positive and negative predictive values of 82% and 76%, respectively. The diagnostic performances of the different scintigraphic approaches for predicting regional improvement are summarized in Figure 4.

DISCUSSION

In patients with chronic severe left ventricular dysfunction due to a myocardial infarction, the combination of sestamibi and BMIPP is helpful to differentiate the patients whose function will improve function at follow-up from those whose function will not. The different distribution patterns reported in the early phase of the infarction are also observed in the chronic phase and have the same significance: a mismatching with BMIPP more decreased than the perfusion is highly associated with functional improvement, whereas a matched decreased uptake reliably identifies myocardial scarring.

In this study, mismatching was a 73% predictor of global recovery and an 87% predictor of segmental recovery, and matching was an 80% predictor of the absence of improvement in ejection fraction and ventricular volumes and a 76% predictor of unchanged regional wall motion.

BMIPP Metabolism and Its Relationship with Ischemia

BMIPP follows the initial biochemical pathways of native free fatty acid uptake, transport and β-oxidation (4), and its uptake is closely related to the intracellular concentration of adenosine triphosphate required to initiate fatty acid oxidative catabolism (17). In pathologic conditions with impaired myocardial oxygen supply, alteration of the use of fatty acids as an energy substrate for the production of high-energy phosphate can result in an increased backdiffusion and a decreased tissue concentration of BMIPP and, hence, mismatching with flow tracers.

In ischemic myocardium, it has been postulated that regions with a discordant BMIPP uptake less than perfusion

FIGURE 4. Bar graph shows sensitivity (SENS), specificity (SPEC) and accuracy (ACC) of sestamibi with ≥60% uptake (solid bars), ROC curve analysis–defined threshold of sestamibi uptake (=40% uptake; open bars) and combination of BMIPP and sestamibi (hatched bars) to predict regional outcome. *0.01 < $P \le 0.05$; **0.001 < $P \le 0.01$; ***$P \le 0.001$, NS = not significant.
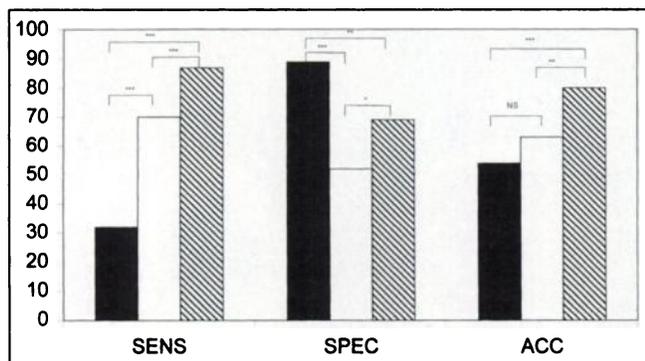
represent jeopardized tissue, in which a metabolic shift from fatty acid oxidation to the less oxygen-consuming use of glucose for the production of high-energy phosphate has occurred (18). However, this feature has been more clearly shown in acute or subacute coronary syndromes than in chronic ischemia, in which data reporting the behavior of BMIPP related to perfusion are scarce and quite contradictory. On the one hand, Sloof et al. (7) recently reported a reverse mismatched uptake with BMIPP higher than ^{201}Tl in chronically ischemic myocardial tissue showing metabolic activity by FDG SPECT. Because free fatty acid oxidation is partially maintained in cases of chronic hypoxia, it could be postulated that less BMIPP undergoes oxidation and that a higher proportion is incorporated into the endogenous lipid pool, thereby resulting in an uptake of BMIPP more than perfusion in chronic viable myocardium. On the other hand, also using ^{201}Tl, Tamaki et al. (19) observed an equally or more severely decreased BMIPP than ^{201}Tl uptake in both recent and old infarctions, although with a lower frequency in the latter. In particular, these investigators noted no reverse mismatching in their patients with chronic infarction (8).

Methodologic factors such as differences in scatter might be at least partially responsible for these discrepancies. In our study, in which scatter correction was applied, most segments that did not show an equally decreased BMIPP, and sestamibi uptake showed the classic mismatching with BMIPP less than sestamibi, a reverse mismatching being noted in only 1 patient.

Predictive Value of Sestamibi with Regard to Functional Outcome

Because intracellular retention of sestamibi is dependent on the negative transmembrane potential of the mitochondria, this tracer is theoretically well suited for assessment of myocardial viability. However, in chronic ischemic heart disease, sestamibi underestimates myocardial viability compared with FDG PET (20), despite an increased extraction efficiency at low flow rates (21). Indeed, studying patients with chronic coronary artery disease, Altehoefer et al. (20) observed that 13%–48% of the segments with a sestamibi uptake of ≤60% of the peak activity showed >70% FDG uptake and reported a negative predictive value for sestamibi of about 84% when using a threshold of uptake of ≤30% of peak activity. Quantitation of the uptake, administration of nitrates before imaging or acquisition of a redistribution image after resting sestamibi injection have been proposed as approaches to partially surmount the limited ability of sestamibi to identify viable tissue (22).

In this study, mean segmental sestamibi uptake in the dysfunctional segments amounted to 42%, indicating severely compromised perfusion. Therefore, sestamibi was only mildly accurate for predicting regional functional outcome when a threshold of 60% of the peak activity was used to discriminate between viable and nonviable myocardium. However, even after optimization of the cutoff of uptake by means of ROC curve analysis, performance

remained moderate. Our results confirm the assumption made by Altehoefer et al. (20) that sestamibi might be less useful for predicting viability in chronic ischemic heart disease than in acute myocardial infarction, because reduced blood flow may become the major determinant of uptake in the chronic phase. Because it is known that the presence of jeopardized viable myocardial tissue is associated with poor outcome in the absence of revascularization, additional information is mandatory in cases of decreased sestamibi uptake to better discriminate between ischemic but viable and nonviable myocardium.

Additional Value of BMIPP for Predicting Functional Improvement

In keeping with the results reported for the acute phase of a myocardial infarction (6), we noted a significant relationship between a mismatched sestamibi/BMIPP uptake and functional improvement and between matching and the absence of recovery.

On an individual-patient basis, sestamibi/BMIPP imaging was 75% accurate in predicting functional outcome at the 6-mo follow-up, with 11 of 15 patients with a majority of mismatched segments showing significant improvement when a rather strict criterion was applied to consider functional recovery, combining a >5% increase in ejection fraction and a >10-volume-unit decrease in end-systolic volume. With the use of less severe criteria ("or" instead of "and"), the accuracy increased to 85%.

On a regional basis, adding BMIPP to the sestamibi data significantly improved the value of scintigraphy for predicting functional outcome. Combining perfusion and metabolism reliably differentiated the segments that improved from those that did not, with a global accuracy of 80% and a sensitivity and specificity of 87% and 69%, respectively. These results are similar to the 85% accuracy of the combined BMIPP/sestamibi method noted by Franken et al. (6) in the early phase of infarction and to the 80% accuracy, 88% sensitivity and 73% specificity of FDG PET reported by Bax et al. (23) in reviewing pooled data of patients with chronic coronary artery disease and left ventricular dysfunction. Our findings indicate that, whereas sestamibi alone is suboptimal for identification of chronically ischemic but viable myocardium, its combination with BMIPP is a reliable tool for this purpose.

Influence of Revascularization on the Uptake of Sestamibi and BMIPP

Before treatment, the mean segmental sestamibi uptake in the dysfunctional segments was not significantly different in the patients who underwent revascularization and in those who were conservatively treated.

At the 6-mo follow-up, a significant increase was noted in both sestamibi and BMIPP uptake only in the revascularized group, clearly showing that both flow and metabolism had effectively been improved by the procedure. Interestingly, uptake increase with BMIPP was higher than with sestamibi. This observation suggests that free fatty acid use might improve after adequate restoration of flow in old myocardial infarctions, as also noted by Yoshida et al. (24), who found a decreased BMIPP washout rate after revascularization in chronic ischemic heart disease only in the patients without restenosis.

Despite increased segmental sestamibi uptake, the mean value remained lower than the 60% uptake usually considered as the normal lower limit. This might be due either to the presence of an admixture of normal and necrotic cardiomyocytes, whereby the mean uptake is still depressed despite functional amelioration of the cells that were jeopardized but viable before treatment, or to an incomplete cellular redifferentiation 6 mo after revascularization, because it is postulated that this process is likely to be prolonged in cases of chronic severe hypoperfusion (25). The observation that a majority of segments had a mismatched pattern in 7 of 13 patients 6 mo after revascularization and that the mismatch was associated with a further increase in ejection fraction at 1-y follow-up in most of them might support the hypothesis of a delayed cellular redifferentiation in patients with severe hibernation.

Study Limitations

In this study, the decision to revascularize was based principally on technical feasibility, but scintigraphy was also integrated in the decision-making process. Although this attitude might have biased the results, we found it justified by the bulk of literature reporting the accuracy of noninvasive methods to predict reversibility of myocardial dysfunction after revascularization, especially taking into account the potential risks of such a procedure in patients with severe left ventricular dysfunction. Another limitation concerns the choice of sestamibi instead of ^{201}Tl as the perfusion tracer, because some investigators have reported a higher accuracy for the latter in viability assessment. However, because this statement is controversial and differences in energy spectra between iodine and thallium might influence the interpretation of the results as a result of differences in soft-tissue attenuation, we preferred to use sestamibi. Lastly, we studied a small group of highly selected patients, and our results require confirmation in a larger population of patients with chronic ischemic heart disease.

CONCLUSION

In patients with chronic myocardial infarction and severe left ventricular dysfunction, sestamibi alone is a suboptimal predictor of functional outcome at follow-up. Adding the metabolic information provided by BMIPP to the perfusion study produces an accuracy for predicting recovery similar to that reported for the acute phase of infarction and to the results provided by FDG PET in chronic ischemic heart disease. A mismatched uptake with BMIPP less than perfusion in dysfunctional segments, indicating the presence of jeopardized but viable myocardium, correlates significantly with improvement in global and regional function after restoration of flow, hence emphasizing the usefulness of

performing revascularization even in the chronic phase of infarction.

Six months after revascularization, BMIPP uptake significantly increases, suggesting improved free fatty acid use. However, a predominant mismatched pattern is still noted in the segments with baseline dysfunction in many patients and is often associated with a further increase in ejection fraction at 1 y, potentially indicating that the cellular dedifferentiation due to severe chronic hypoperfusion requires a prolonged time from which to recover.

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