Technetium-99m sestamibi imaging to predict left ventricular ejection fraction outcome after revascularisation in patients with chronic coronary artery disease and left ventricular dysfunction: comparison between baseline and nitrate-enhanced imaging

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Abstract. Acceptance of technetium-99m sestamibi as a tracer of myocardial viability is growing, particularly when nitrate-enhanced imaging is used. However, few data are available on the ability of ^{99m}Tc-sestamibi to predict the evolution of global left ventricular ejection fraction (EF). The aim of this study was to examine the ability of resting and nitrate ^{99m}Tc-sestamibi single-photon emission tomography (SPET) to predict EF changes after revascularisation in patients who have chronic coronary artery disease with left ventricular dysfunction. Using baseline resting and nitrate ^{99m}Tc-sestamibi SPET, we studied 61 patients scheduled for revascularisation because of left ventricular dysfunction. EF was estimated using two-dimensional echocardiography before and after the intervention. A post-revascularisation improvement of ≥5 EF units was defined as significant. Using a 13-segment model, ^{99m}Tc-sestamibi activity was quantified and the nitrate-induced activity changes calculated. Three different criteria for detecting viability (defined as post-revascularisation reversible dysfunction) in asynergic segments were compared: (1) resting ^{99m}Tc-sestamibi activity ≥60%; (2) nitrate ^{99m}Tc-sestamibi activity ≥65%; and (3) nitrate-induced increase >+10% or nitrate-induced increase ≤+10% and nitrate activity ≥65%. EF increased significantly in 32 patients. The number of viable asynergic segments was significantly higher in these patients than in the remaining 29 subjects, and the difference was greater (P<0.0002) using definition (3) than using either baseline (P<0.002) or nitrate activity (P<0.0005). There was a significant relationship between EF changes and number of viable asynergic segments: Spearman R=0.38, P<0.005 using baseline; Spearman R=0.39, P<0.002 using nitrate activity; and Spearman R=0.55, P<0.000005 using definition (3). According to receiver operating characteristic (ROC) curve analysis, this last criterion achieved the best results (81% sensitivity, 69% specificity and 75% accuracy), with an area under the ROC curve of 0.838; this area was significantly larger than when using either baseline (0.744, P<0.02) or nitrate activity (0.747, P<0.005). ^{99m}Tc-sestamibi SPET appears able to predict the evolution of global left ventricular EF after revascularisation, thereby confirming the value of ^{99m}Tc-sestamibi as a tracer of myocardial viability. The combination of baseline resting and nitrate imaging seems to significantly improve the diagnostic accuracy of ^{99m}Tc-sestamibi SPET for this particular purpose.

Keywords: Ejection fraction – Nitrates – Revascularisation – Technetium-99m sestamibi – Viability

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Introduction

Technetium-99m sestamibi is an established myocardial perfusion tracer for the diagnosis of coronary artery disease and risk stratification, but its value for the detection of myocardial viability has been disputed. In spite of favourable experimental results [1, 2, 3], early clinical studies suggested that ^{99m}Tc-sestamibi imaging underes-

timates viable myocardium compared with other methods such as thallium-201 perfusion scintigraphy or positron emission tomography [4, 5]. Later reports, however, demonstrated a good relationship between myocardial viability and ^{99m}Tc-sestamibi uptake [6, 7, 8]. Most importantly, it was found that ^{99m}Tc-sestamibi single-photon emission tomography (SPET) had good ability to predict functional recovery of asynergic segments after coronary revascularisation [9, 10]. A further increase in ^{99m}Tc-sestamibi diagnostic reliability was achieved by performing nitrate-enhanced imaging [11, 12, 13, 14, 15]. Although the evolution of regional function is the most frequently used reference standard for evaluating viability detection methods, improvement in global left ventricular function is probably the most important clinical goal of coronary revascularisation [16]. Good diagnostic accuracy for the prediction of improvement in global left ventricular function has been demonstrated for positron emission tomography [17, 18, 19], ^{201}Tl imaging [20, 21] and dobutamine echocardiography [19, 20, 22, 23], but virtually no data are available for ^{99m}Tc-sestamibi SPET. The aim of this study was to evaluate the ability of ^{99m}Tc-sestamibi SPET to predict changes in global left ventricular function after coronary revascularisation, and in addition to examine the possible contribution of nitrate-enhanced imaging in this respect.

Materials and methods

Patient population. The study population was selected from among all those patients who underwent ^{99m}Tc-sestamibi SPET for the detection of myocardial viability in our laboratory. Inclusion criteria were: (a) diagnosis of chronic coronary artery disease confirmed by coronary angiography, (b) known left ventricular dysfunction with ejection fraction (EF) <50%, (c) presence of clear regional wall motion abnormality in at least one coronary artery territory, (d) an already scheduled revascularisation procedure and (e) willingness to participate in the study. Exclusion criteria were: (a) recent (<3 months) myocardial infarction or unstable angina, (b) heart disease other than coronary artery disease and (c) a history of prior revascularisation procedures. Of the potentially eligible patients, 22 were excluded after initial enrolment because the revascularisation procedure was incomplete. The final study cohort comprised 61 patients (54 men and 7 women, mean age 60.7±11 years, range 30–77).

Study protocol. All patients underwent baseline resting and nitrate-enhanced ^{99m}Tc-sestamibi SPET. A few days before or after the scintigraphic studies and under stable clinical conditions, global left ventricular EF was assessed by two-dimensional echocardiography. The subsequent revascularisation procedure involved all stenotic vessels. At least 3 months later, a follow-up control using two-dimensional echocardiography was performed to assess the changes in global left ventricular EF. The Ethics Committees of our institutions approved the study protocol and informed consent was obtained from each patient.

Functional evaluation. Both echocardiographic studies were collected at rest with the patient in the left lateral decubitus position using commercially available echocardiographic equipment (SSD-870, Aloka, Tokyo, Japan or Sonos 2000, Hewlett Packard, Palo Alto, Calif.) with 2.5- to 3.5-MHz transducers. Multiple imaging sections were obtained for each study and recorded on videotape. All studies were analysed off-line by two experienced observers who were blinded to the clinical, angiographic and scintigraphic data and to the acquisition sequence. For wall motion analysis, the left ventricle was divided into 13 segments [11], and wall motion and thickening of each segment were scored as follows: 1=normal, 2=hypokinesia, 3=akinesia, 4=dyskinesia [11]. Discrepancies were resolved by consensus. For calculation of the left ventricular EF, the biplane Simpson's method as recommended by the American Society of Echocardiography was applied on three consecutive cardiac cycles examined with the apical four-chamber view, and the mean of the three measured values was used [24]. Improvement in global left ventricular EF after revascularisation was arbitrarily defined as an increase ≥5 EF units in the follow-up control compared with the baseline value [23].

^{99m}Tc-sestamibi SPET. The protocol included two separate studies, one after tracer injection at rest and the other after tracer administration during nitrate infusion, as previously described [10]. The ^{99m}Tc-sestamibi dose was 740–925 MBq (20–25 mCi) in both instances. For the nitrate study, patients received 10 mg of isosorbide dinitrate in 100 ml of isotonic saline solution administered over 20 min. ^{99m}Tc-sestamibi was injected after 15 min of infusion or earlier if either a decrease of >20 mmHg in systolic blood pressure or a systolic blood pressure <90 mmHg was registered [10]. Tomographic projections were collected approximately 1 h later using either a single-head (Apex SP4, Elscint, Haifa, Israel) or a dual-head (Vertex, ADAC, Milpitas, Calif.) large-field-of-view tomographic gamma camera equipped with ultra-high-resolution collimators, and with a 20% window centered on the 140-keV photopeak of ^{99m}Tc. Image reconstruction was performed using filtered back-projection, without attenuation or scatter correction, and the slices were re-aligned along the heart axis. For the quantitative evaluation of SPET images, the short-axis slices from the first with apical activity to the last with activity at the base were used. Their count profiles were generated by computer software and plotted onto a two-dimensional volume-weighted polar map, which was then divided into 13 segments, matching the echocardiographic ones [15]. Using an automated procedure, segment tracer activity was calculated as the total of the counts of the pixels included within the segment divided by the pixel number. The segment with maximal activity was then normalised to 100 and the activity of the other segments was expressed as a percentage thereof [15].

Criteria for myocardial viability. The assessment of viability was restricted to the segments with resting wall motion abnormality (scores 2–4) as determined by two-dimensional echocardiography. Three different criteria were used to define the likelihood that a segment would be viable, i.e. display functional recovery following revascularisation. The first criterion was based on the baseline activity level, and reversible dysfunction was defined as likely in asynergic segments with a ^{99m}Tc-sestamibi activity value ≥60% [9]. According to the second criterion, reversible dysfunction was regarded as likely in asynergic segments with nitrate activity ≥65% [15]. The third criterion was based on the nitrate-induced activity changes [15, 25]. Functional recovery was considered likely in asynergic segments with a nitrate-induced increase in ac-

tivity (expressed as a percentage of baseline activity) of greater than 10%, and was excluded when there was a nitrate-induced decrease of greater than 10%. If a segment had a nitrate-induced change of between +10% and –10%, reversible dysfunction was defined on the basis of nitrate activity ≥65%, as in the second criterion [12, 15, 25].

Statistical analysis. Variables are expressed as mean ± standard deviation. Continuous variables were compared with one-way analysis of variance using the Tukey post-hoc test and nominal variables with the Kruskal-Wallis analysis of variance. Comparison of proportion was made with the Fisher exact test. The relationship between amount of EF change and viability was analysed using the Spearman non-parametric correlation coefficient. Receiver operating characteristic (ROC) curves were constructed to identify the best cut-off of viable dysfunctional segments to differentiate between patients with and patients without an EF increase of ≥5 EF units after revascularisation. The relative accuracy of the three different viability criteria applied to ^{99m}Tc-sestamibi SPET was evaluated by comparing the related ROC curves using Wilcoxon statistics [26]. A P value <0.05 was considered statistically significant.

Results

Patient characteristics

A history of prior myocardial infarction was registered in all patients; the anterior wall was involved in 33 cases, the inferior wall in 20 and both sites in 8. According to coronary angiography performed immediately before the revascularisation procedure, 23 patients had one-vessel, 19 two-vessel and 19 three-vessel coronary artery disease. Of a total of 793 analysed segments, 477 showed abnormal wall motion. The mean left ventricular EF before revascularisation was 34.2%±9% (range 15%–49%); a clearly depressed EF (≤40%) was registered in 46 patients.

Follow-up control

The revascularisation procedure was coronary artery bypass grafting in 34 patients and percutaneous transluminal coronary angioplasty in 27. In the post-revascularisation echocardiographic control, the mean EF was 39.3%±10% with a range of 17%–60% (P<0.0002 vs pre-revascularisation EF). A ≥5 EF units increase was registered in 32 patients (from 33.2%±9% to 43.8%±9%, P<0.0002). In the remaining 29 cases, no significant change was observed (from 35.3%±9% to 34.3%±9%) in the post-revascularisation value. Among these patients, the EF was decreased in 16, unchanged in 3 and increased by <5 EF units in 10. Table 1 describes the main clinical, angiographic and echocardiographic variables of the patients with a significant post-revascularisation increase in EF versus those of the patients with unchanged global left ventricular function. Statistically significant differences between the two groups were found with respect to the number of stenosed vessels and the relative rate of bypass grafting versus angioplasty, both of which were higher in the patients with improved EF, and the pre-revascularisation EF, which was lower in these same patients.

^{99m}Tc-sestamibi SPET versus EF outcome

In baseline ^{99m}Tc-sestamibi SPET, the criterion for viability was fulfilled in 231 asynergic segments, with a mean of 3.8±3 segments/patient. In nitrate ^{99m}Tc-sestamibi images, a total of 219 segments were found to be probably viable according to criterion 2, with an average of 3.6±2.9 segments/patient (NS vs baseline SPET). Finally, using the combined criteria (3) of nitrate-induced changes and nitrate activity, 259 segments were classified as probably viable, with a mean of 4.2±3 segments/patient (P<0.05 vs baseline and P<0.0005 vs nitrate SPET). Figure 1 shows an example of nitrate-induced changes in sestamibi uptake. Table 2 shows the mean number of viable segments/patient according to the

Table 1. Comparison of demographic, clinical and instrumental findings between patients with and patients without significant left ventricular ejection fraction improvement after coronary revascularisation

	EF increase ≥5 EF units	EF increase <5 EF units	*P*
Male/female	27/5	27/2	NS
Age (yr)	62±10	60±12	NS
Prior anterior infarction	41%	55%	NS
No. of stenotic vessels	2.2±0.8	1.6±0.7	<0.005
CCS	1.5±0.5	1.2±0.4	NS
NYHA	1.7±0.7	1.6±0.7	NS
Pre-rev. EF	33.2±9	35.3±9	<0.05
Asynergic segments	8.3±3	7.3±3	NS
PTCA/CABG	10/22	17/12	<0.02

CCS, Canadian Cardiovascular Society classification of angina severity; EF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; Pre-rev., pre-revascularisation

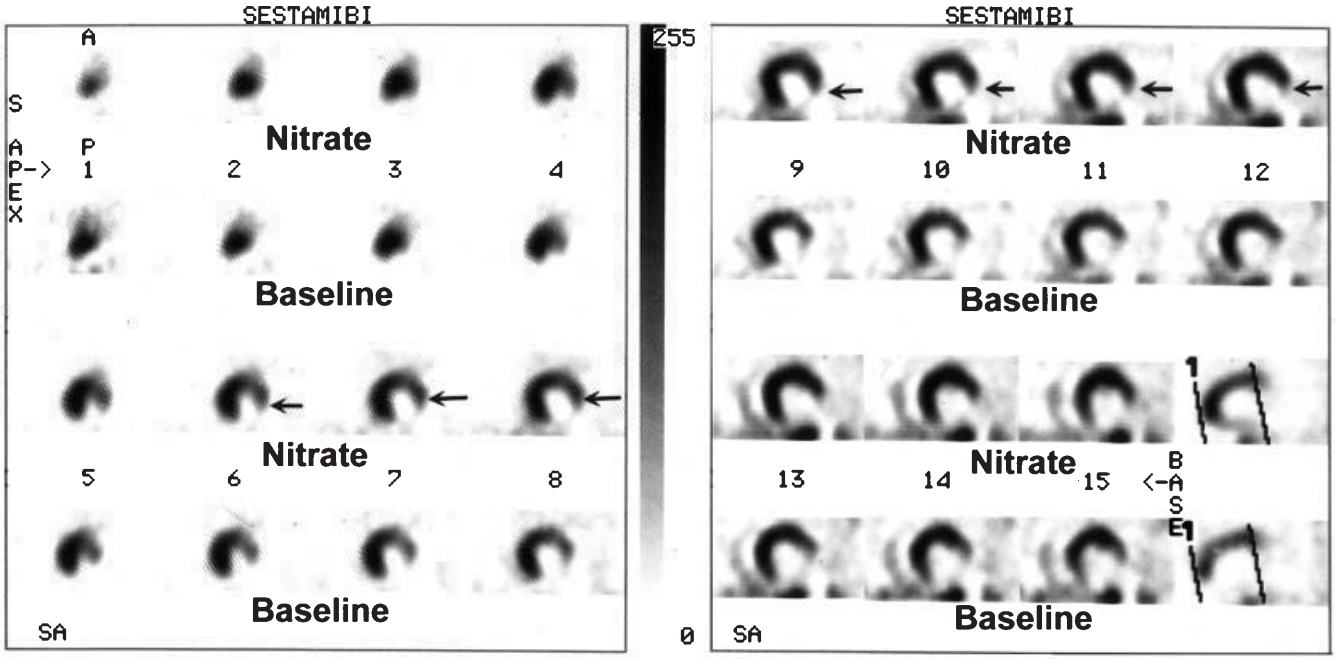

Fig. 1. Short-axis slices of a patient with two-vessel coronary artery disease and previous inferior myocardial infarction: a severe inferior uptake defect appears unchanged on baseline and nitrate images, while tracer uptake in the lateral wall shows a clear increase in the nitrate study (*arrows*). After revascularisation, wall motion improved in the lateral wall and left ventricular EF increased from 39% to 47%

Table 2. Comparison of asynergic segments classified as viable according to ^{99m}Tc-sestamibi SPET between patients with and patients without significant improvement in left ventricular ejection fraction after revascularisation

Definition of viability	EF increase ≥5 EF units	EF increase <5 EF units	*P*
Baseline activity ≥60%	4.9±3.1*	2.5±2.1	<0.002
Nitrate activity ≥65%	4.8±3.1**	2.2±2	<0.0005
Nitrate-induced activity change >+10% or ≤+10% with nitrate activity ≥65%	5.9±2.7*,**	2.4±2.1	<0.0002

EF, Left ventricular ejection fraction
*P<0.01; **P<0.0002

three different viability criteria in patients with versus patients without a significant improvement in EF post revascularisation. A significant difference between the two patient groups was observed and was higher when the nitrate-induced changes (criterion 3) were considered. Similarly, the correlation between EF changes after revascularisation (expressed as post- minus pre-revascularisation EF) and number of viable dysfunctional segments was higher using the definition based on nitrate-induced changes (Spearman R=0.55, P<0.000005) than using either nitrate activity (Spearman R=0.39, P<0.002) or baseline activity (Spearman R=0.38, P<0.005).

According to ROC curve analysis, the best threshold for the prediction of global left ventricular EF increase in baseline SPET using criterion 1 was the presence of >3 viable dysfunctional segments, with 67% sensitivity, 79% specificity and 72% overall accuracy. Using nitrate SPET and criterion 2, the best cut-off value was identified at >4 viable dysfunctional segments, with 56% sensitivity, 86% specificity and 70% overall accuracy. The areas under the two ROC curves were not significantly different (0.744 for baseline SPET and 0.747 for nitrate SPET). Using the nitrate-induced changes (criterion 3), the best cut-off was set at >3 viable dysfunctional segments, with 81% sensitivity, 69% specificity and 75% overall accuracy. The area under the ROC curve was 0.838, which was significantly larger than when using baseline SPET (P<0.02) or nitrate SPET (P<0.005) (Fig. 2).

Discussion

Improvement in regional function after revascularisation is usually considered a reliable indicator of the presence of viable hibernating myocardium within asynergic areas. Therefore, this criterion has been extensively adopted to verify the reliability of diagnostic techniques for

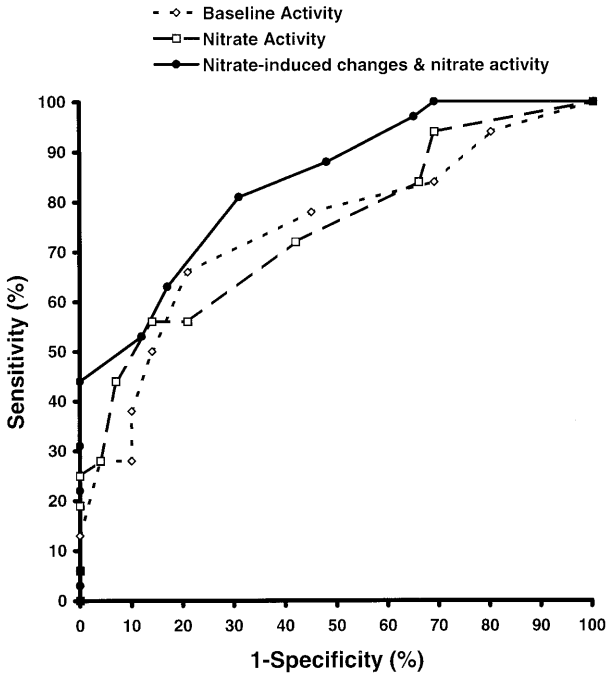

Fig. 2. ROC curves to identify the best cut-off value in the number of asynergic segments defined as viable by ^{99m}Tc-sestamibi SPET (according to the three different viability definitions, see text) for the prediction of significant improvement in left ventricular EF after revascularisation

the non-invasive detection of myocardial viability. Although regional post-revascularisation recovery as a reference standard for viability is superior to the comparison between different imaging methods, its clinical value is limited. Increase in global left ventricular function, improvement in heart failure symptoms and improvement in prognostic outcome are the most relevant parameters for evaluation of the clinical success of coronary revascularisation [16]. Among these, evolution of the global left ventricular function is the easiest to assess, this being done by comparison of the pre- and post-revascularisation EF values. Evidence exists that positron emission tomography, dobutamine echocardiography and ^{201}Tl imaging are able to predict the evolution of the global left ventricular EF [17, 18, 19, 20, 21, 22, 23]. Quantitative analysis of baseline resting and nitrate ^{99m}Tc-sestamibi SPET has recently been accepted as an alternative reliable approach to the detection of viability using myocardial perfusion tracers [9, 10, 11, 12, 13, 14, 15]. The relationship between EF evolution after revascularisation and ^{99m}Tc-sestamibi viability data, however, is still uncertain. A relationship has been described between the extent and severity of ^{99m}Tc-sestamibi defects and the post-revascularisation changes in left ventricular EF [14]. The relationship appeared slightly better using the nitrate images than the baseline ones. The SPET studies, however, were analysed by comparison with a normal database used for resting perfusion studies in stress-rest scintigraphy. This approach is not currently used in most viability studies, which are commonly based on estimation of the relative tracer activity and on identification of the most reliable activity threshold. Therefore, this study was undertaken in a larger patient population to establish the relationship between ^{99m}Tc-sestamibi uptake and left ventricular EF evolution and to assess the ability of ^{99m}Tc-sestamibi imaging to recognise those patients who will benefit from a revascularisation procedure in terms of an improvement in global left ventricular EF. Furthermore, the additional contribution of nitrate-enhanced imaging was evaluated.

According to our results, the group of patients with improved left ventricular EF had a significantly higher number of viable segments on ^{99m}Tc-sestamibi imaging than those with an unchanged global function. Furthermore, there was a significant relationship between the increase in EF after revascularisation and the number of dysfunctional segments with preserved viability on ^{99m}Tc-sestamibi SPET. Finally, it was possible to identify a cut-off value in the number of viable asynergic segments per patient detected by ^{99m}Tc-sestamibi, which allowed the recognition or exclusion of significant EF improvement after revascularisation with reasonable accuracy. Therefore, ^{99m}Tc-sestamibi SPET appears to be a valuable method for the imaging of myocardial viability even when the clinical end point is the evolution of global left ventricular function. It is interesting that the pre-revascularisation EF was significantly lower in the group with a favourable EF outcome. This finding was also reported by vom Dahl and colleagues [18] and emphasises the importance of viable hibernating myocardium in determining the clinical outcome in patients who have chronic coronary artery disease with left ventricular dysfunction.

When the nitrate-induced changes in ^{99m}Tc-sestamibi activity were considered, the difference in terms of viable dysfunctional segments between patients with EF improvement and those without EF improvement appeared more pronounced than when using either baseline resting or nitrate images alone. Similarly, the relationship between number of viable asynergic segments and left ventricular EF increase after revascularisation appeared closer using the combined criteria based on nitrate-induced activity changes. Most importantly, the results of the ROC curve analysis indicated that the approach based on both nitrate-induced changes and nitrate activity was the most effective method, with a significantly larger area under the curve than when using either baseline ^{99m}Tc-sestamibi activity or nitrate activity criteria alone. The advantage of considering the nitrate-induced changes and not just baseline or nitrate data alone is in agreement with the results of most previous reports about the use of nitrate-enhanced sestamibi imaging for the detection of myocardial viability [11, 12, 13, 15, 27]. As regards the mechanisms by which nitrates increase blood flow to hypoperfused myocardial segments, both

dilatation of stenotic epicardial vessels and improvement of collateral circulation have been described [28, 29]. Furthermore, the well-known decrease in left ventricular preload and afterload induced by nitrates could reduce the subendocardial compressive forces and improve subendocardial perfusion. This could support the usefulness of changes in nitrate-induced activity for differentiating between hibernating myocardium and subendocardial scar [30].

The results of ^{99m}Tc-sestamibi imaging appear well comparable with those achieved using other more established techniques. Ragosta and colleagues [21] reported that six of ten patients with >7 viable segments on planar ^{201}Tl rest-redistribution scintigraphy had a significant improvement in EF after bypass surgery, while in the 11 patients with ≤7 viable segments, EF remained unchanged. In a larger patient population, Vanoverschelde and colleagues [20] found that ^{201}Tl stress-redistribution-reinjection SPET had a sensitivity of 72% and a specificity of 73% for the prediction of improvement in global left ventricular function after revascularisation. In the same study, low-dose dobutamine echocardiography achieved a sensitivity of 88% and a specificity of 77%. Using a low dose–high dose dobutamine protocol, Bax and colleagues [23] and Pasquet and colleagues [19] respectively obtained a sensitivity of 86% and 93% and a specificity of 90% and 51% for the prediction of EF outcome. The latter group [19] also demonstrated an increase in dobutamine specificity (90%) without a decrease in sensitivity when the delta EF during low dose infusion and not the number of viable (or ischaemic) segments was considered. In the same patients, perfusion/metabolism positron emission tomography achieved a sensitivity of 78% and a specificity of 50% for predicting a significant increase in EF after revascularisation [19].

Various limitations must be considered when examining the results of this study. The inclusion of patients with moderately depressed left ventricular function could be criticised, because viability might not be the most important reason for revascularisation in these subjects. This limitation is present in many other reports addressing the issue of viability detection [4, 6, 9, 10, 12, 13, 15, 17, 18, 20]. In addition, it is interesting to note that of the 15 patients in our series with an EF between 40% and 49%, eight (53%, the same proportion as in the entire study cohort) showed a significant improvement at follow-up; this confirms the role of hibernating myocardium in their left ventricular dysfunction. The criteria used to define a segment as probably viable were based on previous data about baseline and nitrate sestamibi imaging for the detection of regional viability [9, 12, 15]. The choice does not exclude the possibility that other criteria might be more effective in detecting viability. However, comprehensive analysis of this problem was beyond the scope of the present study, which aimed exclusively to ascertain whether there is a relationship between regional viability detected using sestamibi and global left ventricular EF outcome after revascularisation, and to examine the additional value of nitrate-enhanced imaging in respect of this specific issue. The time interval between coronary revascularisation and collection of follow-up data is a contentious issue. The interval adopted in this study was comparable to that chosen in many other reports [9, 18, 19, 21, 22, 23]. However, the possibility of later improvement cannot be excluded and unfortunately its influence on the results cannot be determined. Similarly, although ruled out on the basis of clinical evaluation and, when necessary, exercise stress testing, the occurrence of bypass occlusion or of restenosis of dilated vessels before the follow-up control is theoretically possible, since the study protocol did not include post-revascularisation coronary angiography or perfusion imaging. Finally, as previously stated, other parameters related to the evolution of global left ventricular function, including clinical symptoms and prognostic outcome, need to be considered before reaching definite conclusions as to the importance of using a particular imaging technique to guide the choice of therapy [16, 31].

Conclusion

The results of this study confirm the value of ^{99m}Tc-sestamibi as a tracer of myocardial viability and show that it can be used for the prediction of global left ventricular EF outcome. Our findings also demonstrate that nitrate administration appears to improve the ability of ^{99m}Tc-sestamibi imaging to correctly recognise viable hibernating myocardium. The predictive values achieved by the combination of baseline and nitrate imaging are in agreement with those reported using other more established techniques and support the use of nitrate-enhanced ^{99m}Tc-sestamibi SPET when detection of myocardial viability is a major diagnostic issue.

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