The Role of Sestamibi Scintigraphy in the Radioisotopic Assessment of Myocardial Viability

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The relationship between sestamibi uptake as a marker of myocardial viability and postrevascularization function recovery is still to be defined. We studied 14 patients (13 males, 1 female, mean age 55 ± 7 yr, range 35 to 64 yr) with sestamibi scintigraphy, quantitative coronary angiography and two-dimensional echocardiography. Sestamibi uptake was quantified from planar images and expressed as percent of maximal activity in each projection using a 13-segment model. All defects were subgrouped on the basis of the severity of reduction in sestamibi uptake; the limit of viability was set at 2.5 s.d. below the normal uptake (55%). Echocardiography was analyzed using a score index ranging from 1 (normokinesis) to 4 (dyskinesis) and a corresponding regional model. Before revascularization, 42 segments were grouped as normal (coronary stenosis <50% and normal function, Group 1); of the remaining 140 segments related to >50% coronary stenosis, 67 had normal wall motion (Group 2) and 73 showed regional dyssynergies (Group 3). Sestamibi percent activity was high in Group 1 and significantly reduced in both Group 2 and 3 segments. Pre- and postrevascularization echocardiography was compared in all patients. Sestamibi sensitivity and specificity in the detection of postrevascularization recovery of function was 83% and 71%, respectively; positive predictive accuracy was 79%. The presence of a severe defect identified most of those segments with wall motion abnormalities that did not recover following coronary revascularization; however, sestamibi overestimated rest perfusion defects in 25% of territories supplied by stenotic coronary arteries that had normal wall motion at rest. Sestamibi appears to be primarily a perfusion agent that can provide limited information regarding viability.

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In the last few years, new ^{201}Tl protocols have shown that apparent 4-hr "persistent" defects frequently overestimate myocardial scarring and that these defects may be reversed by tracer reinjection or by delaying the control scan up to 72 hr (*1–3*). This reinjection or late reversibility has been shown to be a reliable marker of myocardial viability when compared to perfusion/metabolic imaging using positron emission tomography or function recovery following coronary revascularization (*3,4*).

Recently, the physical properties of sestamibi have expanded the diagnostic yield of this ^{99m}Tc-based compound from the assessment of transient ischemia to the estimation of salvaged myocardium following thrombolytic therapy (*5–8*). However, whether rest sestamibi uptake reflects viability beyond blood flow distribution is yet to be defined. Published data suggest that sestamibi activity may be depressed in segments with normal wall motion (*9*) and that regions with severe reduction of tracer uptake at rest may contain viable myocardium as well (*10*).

The purpose of the present study was to compare sestamibi uptake in different categories of segments before coronary revascularization in order to assess its role in predicting postrevascularization functional recovery, the most accurate index of potential viability.

MATERIALS AND METHODS

Study Population

The study population consisted of 14 patients with regional wall motion abnormalities at rest due to previous myocardial infarction, who were referred to the nuclear cardiology laboratory for the assessment of myocardial viability. Patients with recent myocardial infarction or unstable angina were not studied. The patients ranged in age from 35 to 64 yr (mean 55); there were 13 men and 1 woman. Previous myocardial infarction occurred in all patients at least 9 wk before the scintigraphic study. The site of myocardial infarction was anterior in five, anterior and inferior in one, inferior in four, posterior in one and posterior and inferior in three patients, respectively. Medical therapy was discontinued at least 24 hr before all scans; no patient was receiving beta-blockers at the time of the radioisotopic, echocardiographic or ventriculographic study. All patients were studied with rest sestamibi and gave informed consent as part of a protocol approved by the Ethical Committee on Human Studies of the Hospital of Pisa in February 1991.

In order to compare different categories of segments independently from the follow-up study, segments were grouped according to coronary anatomy and regional function into three subsets: Group 1—normal function and absence of significant coronary stenosis; Group 2—segments with normal function but significant coronary stenosis and Group 3—dyssynergic segments in vascular stenotic territories. As an additional inclusion criterion, all patients underwent a successful revascularization procedure, consisting of coronary bypass graft in nine patients and coronary angioplasty in the remaining five patients.

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Sestamibi Imaging Protocol and Analysis

Each patient was injected at rest with 15 mCi (555 MBq) of sestamibi (Du Pont de Nemours, Germany; dose range 10–22 mCi) followed by a 10-cc flush with 0.9% NaCl. The patients were encouraged to have a light meal to accelerate liver washout in order to improve the image quality. Imaging commenced at 60–90 min following tracer injection in the anterior projection, followed sequentially by 45- and 70-degree left anterior oblique views. All sestamibi images were recorded in preset counts, typically with collection of at least 1 million counts on a small field of view mobile camera (Apex 415M, Elscint, Israel) using a high-resolution, parallel-hole collimator and a 20% window centered on the 140-keV gamma ray peak of ^{99m}Tc.

Rest left ventricular sestamibi uptake was assessed quantitatively in each of the standard 13 segments generally used for planar perfusion studies. Each segment was then assigned to one of the three coronary vascular territories as previously described (*11,12*). The assignment of the apex to a specific coronary territory was variable and based on the coronary angiogram and on the presence of adjacent defects. A total of 182 territories were identified and analyzed in the 14 patients with ventricular dysfunction.

Quantitative analysis of sestamibi images was performed using previously described computer-assisted methods for circumferential profile analysis. Sestamibi images were quantitated by performing modified interpolative background correction adjusted to handle studies of planar ^{99m}Tc agents. Briefly, a background area was generated automatically from the smoothed frame and background subtracted from the unsmoothed raw image. The program allows the background region of interest (ROI) to cross areas of intense extracardiac uptake without propagating error into the background-subtracted myocardial image. This method has been previously described and validated in patients studied with planar sestamibi scintigraphy (*13,14*). Segments corresponding to valve planes were excluded in all studies because of their higher interobserver variability. The count activities within the myocardial sectors were expressed as percent of the peak activity in each view. Perfusion defects were subgrouped on the basis of the severity of reduction in tracer activity; the lower limit for normal was set at 55% of the peak that represents 2.5 s.d. below normal uptake. An example of a standard sestamibi quantitative analysis is shown in Figure 1.

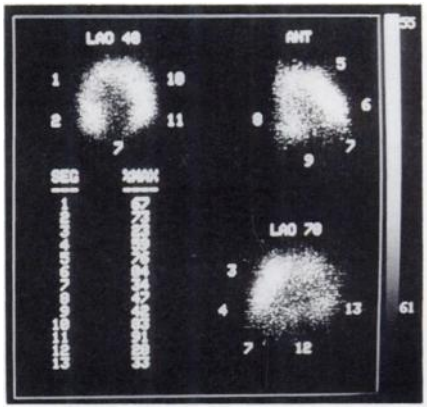

FIGURE 1. Analysis of the regional tracer activities was performed for sestamibi by dividing three images (LAO 40, ANT, LAO 70) into 13 ROIs representing proximal and distal septal, anterior, anterolateral, posterolateral, inferior, posterior and the apex. The value resulting from the quantitative analysis (%MAX) is displayed in each segment (SEG).

Two-Dimensional Echocardiography

Commercially available wide-angle phased-array imaging systems (Hewlett-Packard 77020 or Toshiba Sonolayer FFA270A-2.5 and 3.5 MHz transducers) were used. Areas of abnormal wall motion were identified in multiple views by moving the ultrasound transducer through various positions. The recordings on videotape were analyzed off-line using a quad format by two experienced independent observers blind to the clinical, angiographic and scintigraphic data. A wall motion score was attributed to each single segment at rest by dividing the left ventricle into 13 segments: apex; proximal and distal septal, anterior, anterolateral, posterolateral, posterior and inferior wall (*15*). This segmentation is adapted following the 20-segment model proposed by the American Society of Echocardiography (*16*), with the apex considered as a single segment and only two septal segments taken into account in order to match the nuclear segmentation. According to the recommendations of the American Society of Echocardiography, segmental wall motion was graded using a score index ranging from 1 (normokinesis) to 4 (dyskinesis). All segments were visualized and scored. Discrepancies between the observers were rare and were resolved by consensus. Improvement of regional wall motion >1 grade at the follow-up study was considered as an index of recovery of function in the dyssynergic segments.

Coronary Angiography and Contrast Ventriculography

All patients underwent coronary angiography in multiple projections and left ventriculograms were obtained in biplane views within 2 wk from radioisotope and echocardiographic studies. Ejection fraction was calculated from biplane angiography according to previously described protocols (*17*). All angiograms were reviewed by an independent expert who had no knowledge of the scintigraphic and echocardiographic results. Digital computer-assisted calipers (Kontron, Germany) were used to measure stenotic arterial segments that were quantified as minimal cross-sectional areas. Stenoses of more than 50% reduction of the normal cross-sectional area were considered significant. Collateral circulation was graded visually on a four-point scale, depending on the degree of opacification of the occluded vessel as previously described (*18*). Arteries with partial or complete filling of the epicardial segment via collaterals (grades 2–3) were defined as having an efficient collateral circulation.

Follow-up Study

In patients undergoing coronary bypass graft, an attempt was made to revascularize all major branch vessels with 50% or greater stenosis independently from the demonstration of regional myocardial viability. Baseline echocardiography was obtained in all patients at an average of 12 ± 2 wk following coronary angioplasty or surgery and analyzed blindly. No patient had clinical evidence of preoperative or postangioplasty myocardial infarction nor received beta-blockers or inotropic drugs at the time of this echocardiographic evaluation. In angioplasty patients, the occurrence of restenosis was ruled out by exercise stress test and stress echocardiography. To allow for an accurate comparison, wall motion abnormalities were defined at baseline and during the follow-up only by echocardiography.

Statistical Analysis

Data are presented as mean ± standard deviation (s.d.). Differences in sestamibi quantitative mean percent peak activity in different groups were analyzed by analysis of variance (multiple comparison) using the Scheffe's test. Within each group, differences between different categories were assessed using the unpaired t-test. A probability (p) value of < 0.05 was considered significant.

RESULTS

Baseline Study

General Findings in the Study Population. All patients showed coronary artery disease. Coronary angiography showed single-, double- and triple-vessel disease in 1, 9 and 4 patients, respectively. Average ejection fraction was 43% ± 9%; echocardiography and contrast ventriculography showed regional wall motion abnormalities at rest in all patients. Patient data are shown in Table 1. A good correlation was found between the anatomical site of dyssynergies and the site of sestamibi perfusion defects in all patients.

Results in Different Segment Groups. Forty-two segments had normal wall motion and coronary stenosis <50% (Group 1); the remaining 140 segments were perfused by stenotic coronary arteries and were further subdivided into Group 2, 67 segments with normal wall motion, and Group 3, 73 segments with definite regional wall motion abnormalities.

Group 1. Average minimal cross-sectional area in the corresponding coronary artery was 26% ± 16%. Sestamibi activity in these segments was 80% ± 10% of the peak. This value was not different from that obtained in a population of 10 normal subjects previously studied in our laboratory (79% ± 10% of the peak, p = ns) (*19*) and was close to that reported for sestamibi studies in segments without significant coronary arterial narrowing (*20*). Only one segmental value in this group fell below the cut-off value of 55% of the peak (Fig. 2). A value of 54% was detected in the apex of Patient 5.

Group 2. The average minimal cross-sectional area of the stenosis was 87% ± 13%. This value was significantly higher than that observed in Group 1 patients. In this group of 67 segments, sestamibi activity averaged 61% ± 9% of the peak ($p < 0.05$ versus Group 1 sestamibi activity). Seventeen segments in this group, or 25%, showed a regional activity ≤55% of the peak. The average coronary stenosis in these segments was 93% ± 9% and was significantly higher than that observed in the remaining segments with a normal uptake that showed an average stenosis of 85% ± 14% ($p < 0.05$) (Fig. 2).

Group 3. This group consisted of 73 segments with hypokinesis (29 segments) or akinesis (44 segments) and an average cross-sectional area of 94% ± 8%. This value was significantly higher than that observed in Group 2 segments ($p < 0.05$). Sestamibi activity averaged 58% ± 14% of the peak; this value was statistically lower than the Group 1 value ($p < 0.05$) but was not different from the average sestamibi activity detected in segments of Group 2 with significant coronary stenosis but without wall motion abnormalities (p = ns). Twenty-eight segments of this group showed an activity ≤55% of the peak. The corresponding average coronary stenosis was 96% ± 4% and did not differ from that observed in segments with an activity >55% of the peak (94% ± 9%, p = ns) (Fig. 2). Sestamibi uptake in the 29 hypokinetic segments of Group 3 averaged 60% ± 14% of the peak and was not statistically different from the average uptake detected in akinetic segments (57% ± 15% of the peak, p = ns) (Fig. 2).

TABLE 1
Patient Data

Patient no.	Age (yr)	Gender	Site WMA	Site PD	Time from MI (wk)	N. vessels (>50%)	LVEF (%)	Type revasc
1	53	M	Ant-Api	Ant-Api	36	2	56	CABG
2	59	M	Inf	Inf-Post	49	3	30	CABG
3	53	M	Inf-Api	Inf-Api	14	3	50	CABG
4	57	M	Ant-Api	Ant-Api	98	2	51	CABG
5	64	M	Inf	Inf	32	2	47	CABG
6	57	M	Post-Inf-Api	Post-Inf	18	2	42	CABG
7	56	M	Ant-Inf	Ant-Inf	32	2	38	CABG
8	54	M	Post	Post	22	3	36	CABG
9	62	M	Post-Inf	Inf	60	2	41	CABG
10	55	M	Ant-Api	Ant-Api	116	3	32	PTCA
11	59	M	Inf-Api	Inf-Api	25	2	48	PTCA
12	63	F	Ant	Ant	9	2	41	PTCA
13	51	M	Ant-Api	Ant-Api	24	2	28	PTCA
14	35	M	Post-Inf	Inf	52	1	58	PTCA

Ant = anterior, Api = apical, CABG = coronary artery bypass surgery, Inf = inferior, LVEF % = left ventricular ejection fraction, N. vessel (>50%) = number of vessels with >50% reduction of the normal cross sectional area, PD = sestamibi perfusion defects at rest, Post = posterior; PTCA = percutaneous transluminal coronary angioplasty, Type revasc = type of coronary revascularization and WMA = echocardiographic site of wall motion abnormalities.

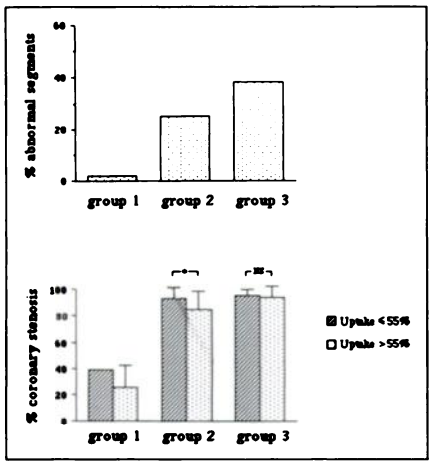

FIGURE 2. Individual patient's data. (Top) The percentage of abnormal segments in each group increased from Group 1 (normal wall motion and not significant coronary stenosis) to Group 3 (abnormal wall motion and severe coronary stenosis). (Bottom) Comparative distribution of percent coronary stenosis in the three groups. The abnormal segment of Group 1 showed a coronary stenosis of 39%. In segments of Group 2, abnormal sestamibi uptake was correlated to a more severe coronary stenosis, while Group 3 segments with normal and abnormal uptakes showed the same degree of coronary narrowing. The asterisk indicates $p < 0.05$.

Follow-up Study

Nine patients of our series underwent coronary bypass surgery and five had selective percutaneous transluminal coronary angioplasty (Table 1). In the surgical group, 21 stenotic vessels received a graft. In patients undergoing coronary angioplasty, 7/10 vessels were successfully dilated. The remaining three vessels were not related to dyssynergic segments of Group 3. Of the 73 dyssynergic segments in Group 3, 42, or 57%, showed an improved wall motion at the follow-up study. The average minimum lesion cross-sectional area was 92% ± 9% and 95% ± 6% in improved and unchanged segments, respectively (p = ns). Of these 42 segments, 14 were hypokinetic and 28 akinetic at the baseline study. At follow-up echocardiography, 18 segments showed normalized wall motion and 24 were scored as hypokinetic. Twenty-two of the 42 segments which showed improved wall motion showed a complete coronary occlusion with an efficient collateral circulation in 20. Of the 31 segments which did not benefit from coronary revascularization, 12 were related to a complete coronary occlusion without collateral circulation in all. The average percent activity of sestamibi in viable and necrotic segments, defined according to postoperative changes in wall motion, was 66% ± 12% versus 48% ± 10% of the peak ($p < 0.05$). Ten of 31 segments that did not improve following coronary revascularization showed a sestamibi activity >55% of the peak (false-viable). Sestamibi sensitivity and specificity in detecting postoperative improvement of regional wall motion following coronary revascularization were 83% and 71%; positive and negative predictive accuracies were 79% and 76%, respectively. The number of segments correlating to the presence of electrocardiographic Q-waves was not different in necrotic (60%) and in viable segments (54%), respectively (p = ns).

DISCUSSION

In this study, we investigated the significance of rest sestamibi abnormalities in patients with abnormal regional wall motion undergoing coronary revascularization. Our data suggest that although sestamibi is able to separate viable from necrotic segments according to postoperative criteria, some problems arise from the preoperative characterization of dyssynergic segments.

Sestamibi as a Marker of Viability

Although the clinical efficacy of sestamibi as a perfusion tracer is similar to that of ^{201}Tl (*21,22*), its role in the clinical evaluation of myocardial viability is still uncertain (*7,22–24*). Results from clinical studies are generally difficult to interpret because of the inability to dissociate the contribution of flow from that of regional viability. Similarly, experimental studies are not able to separate stunned from infarcted myocardium and the effect of variable flow during reperfusion (*11,25–28*). Although published reports to date have demonstrated excellent agreement between the type of perfusion defects observed by sestamibi and by standard stress/redistribution ^{201} Tl scans, it remains to be seen whether recent ^{201}Tl protocols are superior to sestamibi images for the assessment of viability (*29*). The present data demonstrate that resting myocardial perfusion can be reduced to a moderate degree while contractile function is maintained. This is demonstrated in our series by the reduced sestamibi uptake in Group 2 segments with normal wall motion and more severe coronary artery stenosis (Fig. 3). These findings indicate that a significant

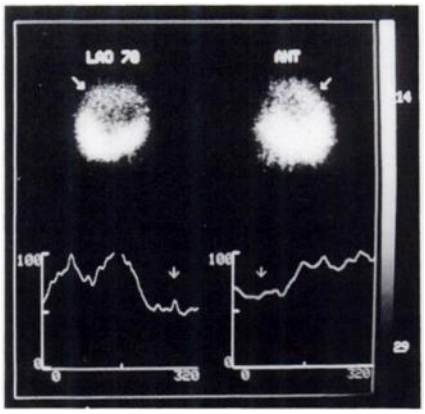

FIGURE 3. Background-subtracted sestamibi left anterior oblique 70° (LAO 70) and anterior (ANT) projections obtained following rest sestamibi injection. These images show defects of uptake in the proximal and anterolateral segments; these defects are confirmed by the relative angular profiles (arrows). This patient showed a 96% stenosis of the left anterior descending coronary artery with normal wall motion in this territory.

reduction of sestamibi uptake in a baseline scan is related to a more severe coronary stenosis leading to the occurrence of resting hypoperfusion. Whether this phenomenon reflects higher sensitivity of sestamibi to low to moderate reduction of coronary blood flow at rest is still to be defined in experimental models of graded, progressive coronary occlusion.

Our results also indicate that a reduction of sestamibi uptake at rest below 2.5 s.d. of normal values identifies most segments that will not benefit from coronary revascularization. This is partly limited by the fact that a sizable percentage (25%) of Group 2 segments with normal wall motion showed the same degree of perfusion defect at rest.

The seven segments in Group 3 with preoperative sestamibi uptake below the normal limits and functional recovery (false-necrotic) had an average uptake of 46 ± 5% of the peak. Again, sestamibi tended to overestimate myocardial scarring in segments that showed a definite improvement of contractile function following coronary revascularization. These observations could partly explain previous investigations reporting a general underestimation by sestamibi of viable myocardium with respect to ^{201}Tl and the occurrence of fixed perfusion defects in a significant percentage of territories with normal wall motion at rest (*9,10*). These data suggest that sestamibi may only cautiously be used as a viability agent.

Imaging Strategy for the Detection of Viable Myocardium

Our results raise an important clinical question: is it or is it not favorable to have a marker of viability that is independent of wall motion abnormalities? Assessment of residual viability using ^{201}Tl is less dependent from the assessment of regional function since this tracer has been reported to be more accurate in the detection of normal, viable and necrotic areas with more exact threshold values (*3*). In this context, the "on-off" signal provided by ^{201}Tl is clinically more useful and may even be used to decide whether to catheterize a patient with ventricular dysfunction. For sestamibi studies, this decision is more difficult to obtain since its uptake may be related to moderate blood flow reduction at rest without any abnormality of regional contractility. For this reason, quantitative uptake of sestamibi should always be obtained and the incidence of "false necrotic" segments considered.

Quantitative coronary angiography was not useful in the search of reversible dyssynergies since viable and necrotic segments showed the same average coronary stenosis. However, in agreement with previous reports (*30*), the development of an efficient collateral circulation was present in 92% of viable and in none of the necrotic segments, respectively.

Limitations of the Study

In this study, we applied a rigid classification of segments based on presence and absence of coronary stenosis and wall motion abnormalities. This division into three subsets was matched against regional percent activities of sestamibi. It can be sometimes difficult to assign this or that segment to a definite category and the limitations of quantitative coronary angiography should be considered. Furthermore, even if accepted segmentation schemes for isotopic and echocardiographic data have been applied, the actual anatomic correlation is less than perfect.

Although available in our institution, we did not use SPECT protocols, since planar imaging allowed better standardization of sestamibi background subtraction and quantitative analysis (*14*).

In order to minimize the possible interaction between perfusion and function, we studied only patients with chronic coronary artery disease and excluded all patients with acute myocardial infarction. In these patients, sestamibi could offer the additional advantage to detect, even with a single post-treatment rest injection, high risk patients in whom a large defect area (ischemia + necrosis) might indicate a more watchful approach (*8,28*). Further clinical studies are needed to delineate the "dynamic" application of sestamibi in this study population. Another limitation of this study derives from the fact that no sestamibi studies were obtained during follow-up so that no correlation could be obtained between improved perfusion and wall motion. Finally, our series consisted of a relatively small number of patients, although all of them underwent coronary revascularization procedures and follow-up echocardiography.

CONCLUSIONS

The results of the present study suggest that the role of rest sestamibi imaging in the assessment of myocardial viability is limited by a significant overestimation of myocardial scarring. This limitation should be carefully considered in the assessment of perfusion defects at rest in patients with severe coronary artery stenoses with or without previous myocardial infarction. Whether this relatively inexpensive technique provides comparable information with ^{201}Tl scintigraphy and with more sophisticated and expensive positron emission tomography remains to be investigated. Our data confirm that sestamibi is primarily a perfusion agent; results about its role in defining myocardial viability require further clinical experience.

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