Spontaneous Delayed Recovery of Perfusion and Contraction After the First 5 Weeks After Anterior Infarction
Evidence for the Presence of Hibernating Myocardium in the Infarcted Area

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Background In patients with ventricular dysfunction caused by stunning or hibernation, it is not clear when complete recovery of the salvaged myocardium occurs after acute myocardial infarction. The purpose of this study was to determine whether a delayed recovery of perfusion and contraction continues even after the subacute phase.

Methods and Results We prospectively studied 71 consecutive male patients with first uncomplicated Q-wave anterior infarction. Resting regional blood flow distribution and contraction were assessed quantitatively 5 weeks and 7 months after the acute phase by serial sestamibi tomography and two-dimensional echocardiography. Coronary angiography also was performed in 52 patients. Overall, at 7 months there was an improvement in the perfusion defect severity (1019±811 versus 1365±821 at 5 weeks, P<.001) as well as in the extent of abnormal wall motion (28±19% versus 32±15%, P<.001) and left ventricular ejection fraction (53±14% versus 50±13%, P<.01). Among the 68 of 71 patients showing resting perfusion defects at 5 weeks, two groups were identified: 47 (group 1) who showed a significant (beyond the reproducibility limits) 7-month reduction of the resting perfusion defect, and 21 patients (group 2) in whom the perfusion defect remained unchanged. Ejection fraction and the extent of abnormal wall motion significantly (P<.01) improved in group 1 but not in group 2. Despite the presence of a comparable perfusion defect size between the two groups at 5 weeks after infarction, group 1 already showed a better regional and global ventricular function (P<.05). No significant differences were found between the two groups regarding age, medical therapy, the extent of underlying coronary disease, thrombolysis in the acute phase, Thrombolysis in Myocardial Infarction grade of the infarct-related vessel, and presence of collaterals on angiography.

Conclusions After anterior Q-wave infarction, the recovery of perfusion and wall motion may continue well after the subacute phase. Several patients exhibit relative hypoperfusion in viable tissue as late as 5 weeks after infarction, and a significant improvement of perfusion in the affected area commonly is observed between 5 weeks and 7 months. This delayed improvement of perfusion is associated with a delayed improvement of contractile function in the infarcted area after the first 5 weeks, which may continue for up to 7 months, suggesting the presence of hibernating myocardium in the infarcted area. Despite similar perfusion defect sizes, the level of regional function can be different at 5 weeks, and measurements taken around this time may not accurately estimate the eventual recovery of function. (Circulation. 1994;90:1386-1397.)

Key Words • myocardium • myocardial infarction • reperfusion • isotopes

The time course of the recovery of myocardial perfusion and function after myocardial infarction (MI) remains unclear. Although most improvement takes place within the first 7 to 14 days,1,2 myocardial dysfunction may persist well beyond this period despite adequate antegrade reperfusion, and some recovery occasionally is found up to 6 months thereafter.3,4 A possible explanation for the delayed recovery may be the presence of recurrent episodes of subclinical ischemia, recurring myocardial stunning or, more likely, the presence of a flow-limiting residual stenosis that could cause myocardial dysfunction because of persistent hypoperfusion (hibernating myocardium).3,4 As a consequence, close evaluation of both regional perfusion and wall motion has been suggested to correlate these variables.3

99mTc methoxy-isobutyl-isonitrile (sestamibi) is a myocardial perfusion agent whose uptake and retention are related to regional myocardial blood flow and tissue viability.5-10 It is considered a promising tool for assessing the risk area in acute MI and the efficacy of various reperfusion strategies. Changes in the extent and severity of the perfusion defect on serial sestamibi imaging after thrombolytic therapy have been used to estimate the amount of myocardial salvage and also have been related to the patency of the infarct-related artery.11-17 Several studies have documented a strong correlation between the postintervention sestamibi defect size and
the enzymatic estimates of infarct size as well as the regional and global left ventricular (LV) function.

The aim of this study was to assess the evolution of the sestamibi estimate of myocardial risk area in a selected population of patients with first Q-wave anterior MI; furthermore, we examined the relation between changes in the perfusion defect size and changes in global and regional ventricular function.

Methods

Study Population and Protocol

The study population consisted of 71 consecutive male patients (49 ± 8 years old) with recent anterior MI who met the following inclusion criteria: (1) history of recent (4 to 6 weeks) first Q-wave anterior MI, (2) sinus rhythm and no conduction disturbances, (3) no angina at rest, (4) New York Heart Association functional class I or II, and (5) two-dimensional echocardiographic images of quality adequate for quantitative analysis. The diagnosis of acute MI was supported by (1) typical history of chest pain (>30 minutes), (2) abnormal Q waves (>30 milliseconds) in at least two adjacent precordial leads and in leads I and/or aVL, and (3) a typical pattern of serum myocardial enzymes. Exclusion criteria were (1) systemic diseases, (2) severe LV dysfunction (resting ejection fraction <25%), (3) low-threshold ischemia or residual angina uncontrolled by medical therapy, and (4) inability to participate in a prospective study for any logistic reason.

In all patients, resting regional myocardial perfusion and LV function were assessed by sestamibi single-photon emission tomography and two-dimensional echocardiography, respectively, performed on the same day. The scintigraphic and echocardiographic studies were performed 4 to 6 weeks after the necrotic episode (T1) and then repeated 6 months later (T7). All patients had to be stable between the two studies. An additional intermediate echocardiographic evaluation was performed at 4 months after the infarction. Cardioactive drugs were discontinued at least 48 hours before each evaluation.

The study protocol was approved by the local ethical committee on human research. Informed consent was obtained from all patients.

Sestamibi Imaging

Sestamibi was prepared by adding a maximum of 80 mCi sterile nonpyrogenic sodium pertechnetate solution (1 to 3 mL) to a lyophilized kit; the vial was placed in a shielded boiling water bath for 10 minutes and then allowed to cool. After the tracer injection (25 mCi/70 kg), a light meal was provided to the patients to accelerate the hepatobiliary clearance of the tracer and improve the heart-to-background ratio.

Scintigraphic images were obtained 90 to 120 minutes after the injection with a rotating camera (Apex 409, Elscint) equipped with a high-resolution, parallel-hole collimator. A ±10% energy window centered on the 140-keV photons was used. The camera head was rotated in an 180° arc in a circular orbit from the 30° right anterior oblique to the 30° left posterior projection, with 3° increments of 25 seconds, in a step-and-shoot mode. Total acquisition time was 25 minutes. Data were collected in a 64×64 array with a pixel size of 4.5 mm. Particular care was taken to avoid major artifacts during the acquisition, such as patient motion.

Transaxial slices were reconstructed using a filtered back-projection algorithm with a modified Wiener filter with a 0.8 dumping factor, without attenuation or scatter correction; flood correction was applied during reconstruction. The spatial resolution in the transaxial plane was 8 mm. Short-axis and long-axis (horizontal and vertical) tomograms were reconstructed from the transaxial slices. All studies were processed by a single experienced operator (Dr Marcassa), who was unaware of the patients’ clinical and functional data.

Short-axis slices were reconstructed from the transaxial sections, and polar maps of the regional sestamibi distribution were displayed. Each polar map was normalized for peak myocardial activity and compared with the normal limits obtained in 50 sex-matched and age-matched subjects with no evidence of coronary artery disease; pixels with tracer uptake falling more than 2.5 SD below mean normal values were considered abnormal.

The abnormal area on each short-axis slice first was multiplied by a correction factor that takes into consideration differences in myocardial slice mass from apex to base and corrects for spatial distortion inherent in displaying a three-dimensional volume two dimensionally. Corrected abnormal areas then were summed to obtain the total extent of the LV defect. The severity of a tracer uptake defect also was calculated: each pixel was assigned to categories expressing the degree below the reference value (from ~2.5 SD, with 0.5-SD step). Pixels within the same SD category were summed and multiplied by a correction factor that takes into account the SD category and the spatial distortion; values from all SD categories then were summed to obtain the total defect severity (expressed as arbitrary units).

In 20 patients (randomly selected from a group of 135 consecutive patients with Q-wave anterior MI who underwent sestamibi tomography in our laboratory), the sestamibi defect severity was obtained in duplicate fashion by repeating image processing and quantitative analysis after 2 weeks. The intraobserver variability of the method was assessed by linear regression analysis (regression line: y = 0.97x + 309; r = 0.98; P < .001). To assess changes in the perfusion defect from T1 to T7, the defect severity was considered, thus taking into account both the depth and extent of the perfusion defects. Reductions in the perfusion defect between the T1 and T7 studies were considered significant when changes in defect severity beyond the 95% confidence limits of the method variability were observed.

Echocardiographic Data Acquisition and Analysis

All patients underwent a complete echocardiographic study in multiple views (Hewlett-Packard 77020A); the positions of the patient and transducer were noted for use in serial studies. The method of data acquisition, image digitalization, and the computerized system for the automatic detection and quantification of regional wall motion and LV function have been described elsewhere. Briefly, the three apical views (four and two chambers and apical long-axis) were analyzed to assess ventricular function from three different planes and to explore six different ventricular walls from the base to the apex of the heart. The endocardial contour of each view was divided automatically into 23 segments of equal length, so that the entire ventricular wall was represented by a total of 69 segments. By comparison with our normal database, the presence of abnormal wall motion was detected automatically when the fractional shortening area from end diastole to end systole of each segment was less than 2 SD of the mean values in healthy subjects. The extent of wall motion abnormalities was expressed as a percentage of the total endocardial length (WMA%).

The LV ejection fraction (EF) was calculated with the biplane area-length method. All measurements were derived in blinded fashion by a single experienced operator (Dr Giannuzzi) from three consecutive cardiac cycles, and the mean values were considered. Intraobserver variability values in endocardial contouring and in the evaluation of end-systolic and end-diastolic endocardial surface area by our quantitative analysis in healthy subjects and in patients with MI have been reported.

Coronary Angiography

According to the protocol design, cardiac catheterization was performed in the 6-month interval between the two scintigraphic...
Studies. After intracoronary nitroglycerin administration, selective angiograms were obtained in at least two projections for the right coronary artery and at least four for the left coronary artery. The presence of a significant (>50% coronary diameter reduction) stenosis was assessed by use of caliper measurements in two orthogonal projections by one experienced observer (Dr Silva Orrego) who was unaware of other information. The Thrombolysis in Myocardial Infarction (TIMI) grade of the infarct-related vessel flow and the presence of collateral circulation also were assessed. A TIMI grade of 0 or 1 defined an occluded artery; an infarct vessel without significant stenosis or with a TIMI grade flow of 2 or 3 defined a patent artery. The vascular attribution of scintigraphic and echocardiographic regions to the conventional anatomic distribution of the major coronary arteries was performed according to the division proposed by the Cedars-Sinai Laboratory and by the American Society of Echocardiography, respectively.

**Statistical Analysis**

Data are reported as mean±SD. Normality of the data distribution was verified. The extent and severity of the sestamibi perfusion defects, LV volumes, LVEF, and WMA% at T1 and T7 were compared by Student’s t test for paired data. Baseline characteristics between groups were compared by unpaired Student's t test for continuous variables and the χ² test to determine the significance of differences in rates of occurrence. Serial changes in the echocardiographic variables were estimated by one-way ANOVA for repeated measures. When two different groups were compared for scintigraphic and echocardiographic variables at T1 and T7, a one-way ANOVA combined with Scheffé's test was used. The correlations between sestamibi defect severity and LVEF, wall motion score, and peak creatine kinase were assessed by linear regression analysis. A probability value of P<.05 (two-tailed) was considered significant.

**Results**

The initial study population consisted of 79 patients. Six patients originally enrolled in the study were later excluded because of worsening angina or extensive coronary artery disease requiring late coronary revascularization (bypass or angioplasty); 2 other patients died (1 sudden death and 1 cancer) during the T1 to T7 period. The remaining 71 patients were considered for the purposes of this study. Their mean age was 49±8 years. In the acute phase, 49 patients (69%) who were admitted within 6 hours of the onset of symptoms (average, 1.7±1.1 hours) received thrombolytic treatment (streptokinase in 39, urokinase in 5, TPA in 4, anistreplosate in 1). Mean peak serum creatine kinase value was 2805±1979 IU/mL.

**Coronary Anatomy**

Coronary angiography, available in 52 patients (73%), was performed in the 6-month interval between the two scintigraphic studies (on average, 95±12 days from T1 study), while the patients were stable. Significant stenoses involving one and two vessels were found in 36 (69%) and 12 (23%) patients, respectively. The infarct-related vessel stenosis involved the proximal left anterior descending artery in 23 patients (48%) and its mid-distal portion in 25 (52%). In 4 patients (8%), no significant stenosis was documented. A patent infarct-related vessel was found in 29 patients (56%), including 27 patients with a TIMI grade of 3 and 2 patients with a TIMI grade of 2 of their infarct vessel. Angiographically visible collaterals toward the infarct-related vessel were observed in 16 patients (31%).

In 19 other asymptomatic patients, coronary angiography was either not performed because of patients' refusal or not included in the present study because the scheduled procedure was postponed until after the T7 study because of logistic problems. On average, these patients had a better resting ventricular function (LVEF, 56±12% versus 48±13%, P<.05; WMA%, 26±14% versus 34±15%, P=.05) and less-severe perfusion defects (extent, 25±17% versus 33±13%, P=.06; severity, 983±823 versus 1425±835, P=.05) compared with patients who underwent coronary angiography between T1 and T7.

**Perfusion and Contraction Data at the First (T1) and 7-Month (T7) Studies**

Sestamibi defect size (extent and severity) as well as LVEF and WMA% at the T1 and T7 studies are reported in Table 1. At the T1 study, sestamibi uptake defects and wall motion abnormalities were observed in 68 (96%) and 70 (98%) patients, respectively. Perfusion and wall motion abnormalities always were observed in the region supplied by the left anterior descending artery. The amount of hypoperfused left ventricle varied widely, from 2% to 55%; the WMA% ranged from 4% to 61%. For the group as a whole, a significant reduction in both the extent and severity of the perfusion defects was observed at T7 imaging as well as a significant improvement in the LVEF values and the WMA%.

According to the changes in the defect severity observed in the T1 and T7 studies, the sestamibi perfusion defect size became smaller in 47 patients (69%, group 1) (Figs 1 and 2) and remained unchanged in 21 (31%, group 2) (Fig 3). The clinical and angio-
graphic characteristics of the two groups are reported in Table 2. No significant differences were found between the two groups regarding age, thrombolysis in the acute phase and time-to-thrombolysis from onset of symptoms, medical therapy in the 6-month interval, the extent of underlying coronary disease, infarct vessel patency, and presence of collaterals on angiography.

Fig 4 shows plots of the distribution of sestamibi defect severity that incorporate all the patients included in the serial evaluation. No significant differences between the two groups were observed regarding the extent and severity of perfusion defects in the T1 study. Despite their comparable perfusion defect sizes, in group 2 the LVEF was significantly lower and the WMA% higher (Table 3). In group 1 but not group 2, the WMA% and the LVEF significantly improved in the T7 study. In all group 1 patients, the improvement in resting sestamibi uptake occurred in the tomographic area conventionally assigned to the left anterior descending artery vascular territory. Serial changes in the WMA%, LVEF, and LV volumes in the two groups also are reported in Fig 5.

Effect of Thrombolytic Treatment on Resting 7-Month Perfusion and Function Evolution

The sestamibi defect size, LVEF, and WMA% at the T1 and T7 studies as well as the infarct vessel TIMI grade found in the 49 patients who underwent systemic thrombolysis and the 22 who received conventional therapy in the acute phase are reported in Table 4. In the T1 study, neither the extent nor the severity of the perfusion defects were significantly different between the two treatment groups. In the T7 study, a significant improvement in the defect size, LVEF, and WMA% was observed in both groups.

Sestamibi Defect Size Evolution and Infarct-Related Artery Status

No significant differences were observed between group 1 and group 2 regarding the incidence of patent infarct vessel (TIMI grades 2 and 3) as well as the average TIMI grade and mean percent stenosis (Table 2). Changes in the extent and severity of defects in the T1 and T7 study were comparable between the 23 patients with an occluded vessel and the 29 patients with an open infarct-related vessel (Table 5).

Correlation Between Sestamibi Defect Size and Conventional Indexes of Infarct Size

Although in the T1 study the perfusion defect severity correlated inversely with the LVEF ($r = -0.70$) and the WMA% ($r = -0.66$), the correlation at T7 was stronger ($r = -0.81$ and $r = -0.78$, respectively). A similar pattern was observed for the correlation between the T1 and T7 defect severity and the peak creatine kinase values ($r = 0.57$ for the T1 study and $r = 0.72$ for the T7 study). However, no correlation was found between the changes in T1 to T7 resting hypoperfused myocardium and the following variables: the T1 LVEF ($r = 0.13$), the T1 WMA% ($r = 0.02$), the T1 to T7 changes in LVEF ($r = 0.11$), or the T1 to T7 changes in WMA% ($r = 0.09$).
The correlations between the sestamibi defect severity and LVEF, WMA\%, and peak creatine kinase values in group 1 and group 2 are reported in Table 6. Although in group 1 patients the correlations were stronger in the T7 than in the T1 study, no differences were observed between the two studies in group 2 patients.

Discussion

The measurement of infarct size has important implications for the risk stratification of patients with recent MI. However, the predischARGE assessment of LVEF and wall motion may be misleading because of the presence of both perinecrotic stunning and hyperdynamic function in remote areas. Accordingly, delayed assessment of ventricular function or, alternatively, estimation of infarct size with quantitative myocardial perfusion imaging at the time of discharge has been suggested.\(^5\,\text{a}\,\text{b}\)

The chemical and physical properties of \(^{99m}\text{Tc}\)-sestamibi would make it an ideal agent for the accurate assessment of myocardium at risk and the final infarct size. In animal models of coronary occlusion-reperfusion, the tracer injection during occlusion has provided accurate estimates of the myocardium at risk,\(^1\,\text{a}\,\text{b}\,\text{c}\,\text{d}\,\text{e}\) as well as reliable measurements of the final infarct size when injected late after reperfusion.\(^6\) In patients with acute MI, serial changes in myocardial perfusion assessed by sestamibi imaging have been used as a measure of myocardial salvage in evaluating the efficacy of thrombolytic therapy,\(^1\,\text{a}\,\text{b}\,\text{c}\,\text{d}\) for assessing the patency of the infarct-related artery,\(^1\,\text{a}\,\text{b}\,\text{c}\) and for the comparison of various reperfusion strategies.\(^1\,\text{a}\,\text{b}\,\text{c}\,\text{d}\)

Assessment of salvaged myocardium following reperfusion therapy by serial sestamibi imaging also has been found to predict late (2 to 6 weeks) functional recovery.\(^6\,\text{a}\,\text{b}\,\text{c}\,\text{d}\,\text{e}\)

Our study is one of the few in which regional myocardial function and perfusion have been assessed at the same time and at serial times after infarction. Surprisingly, our data indicate that in many patients the recovery of both perfusion and wall motion in the infarcted area may continue well after the subacute phase. Furthermore, in contrast to the patients who show no delayed improvement, the patients who exhibit improved contraction and perfusion in the infarcted area at 7 months already show a better regional and global ventricular function at 5 weeks after infarction, despite the presence of a comparable perfusion defect size between the two groups of patients.

Late Improvement of Perfusion Within the Infarcted Area

To our knowledge, this is the first study to demonstrate a delayed spontaneous improvement in perfusion to the infarcted area after the first 5 weeks after infarction. A significant spontaneous reduction in the sestamibi defect size up to 7 months after acute MI was observed in two thirds of the patients (69\%). The reduction in the perfusion defect size was associated with an improvement in regional WMA\% and LVEF at both 4 and 7 months.

In experimental studies, myocardial sestamibi uptake and retention have been found to relate to coronary blood flow and myocardial viability\(^1\,\text{a}\,\text{b}\,\text{c}\) if the tracer is not injected early after reperfusion and imaging is not
performed soon afterward. Thus, in theory, changes in the tracer myocardial uptake may be ascribed to changes in either regional blood flow (delivery), cellular extraction and retention (reflecting cell membrane integrity), or both. Since the T1 study was carried out 5 weeks after the acute phase, the presence of some myocardial stunning in the infarcted area cannot be excluded. However, in experimentally induced stunned myocardium, sestamibi uptake was shown to be not significantly affected. Thus, changes in sestamibi uptake between T1 and T7 imaging are unlikely to be related to the presence of reperfused but still dysfunctional myocardium.

Our findings of improved tracer distribution in the infarct area 7 months after infarction suggest some delayed improvement of the regional delivery (myocardial blood flow) to the jeopardized area from T1 to T7. Such an improvement was unrelated to the thrombolytic treatment, the patency of the infarct-related vessel, the presence of collateral circulation, or the degree of LV dysfunction 5 weeks after the event. Several potential mechanisms could lead to such a late increase in perfusion. One possible explanation is that collateral vessels to the jeopardized area developed or were recruited during this interval. Most collateral vessel development and patency variation of the infarct-related vessel occur within the first 2 weeks after acute MI. We performed the T1 study 5 weeks after the infarction; thus, it seems unlikely that major changes in collaterals or infarct vessel patency occurred after this time. Furthermore, we did not find significant differences in angiographically visible collaterals between patients who showed an improved sestamibi defect at 7 months and those who did not. However, the limitations of coronary angiography in the assessment of collaterals are well known; this technique can identify only vessels greater than 100 μm in diameter and, although it can demonstrate the presence of epicardial collateral vessels, it does not provide information regarding the distribution of collateral flow within the myocardium.

Another possibility is that the blood flow to the infarct area was reduced 5 weeks after infarction because of a persistently impaired coronary reserve. After a brief period of ischemia, reduced coronary vasodilator capacity and the presence of microvascular stunning, causing prolonged impairment of coronary vasodilation, have been documented in animals. Although it seems unlikely that vascular stunning would last for 5 weeks after a single ischemic episode, we cannot rule out the possibility that these patients continued to exhibit recurrent episodes of brief, silent ischemia in the salvaged, viable myocardium as a result of coronary spasm, thrombosis, or both. If this were the case, vascular stunning could well persist for several weeks after the infarction. Furthermore, an abnormal resistive vessel function in the vascular bed distal to a coronary artery stenosis has been shown to persist for days, even months, after successful coronary angioplasty and to cause impaired coronary vasodilator response. Fifty percent of our patients who showed improved sestamibi distribution in the infarcted area in the 7-month imaging had severe (>90%) infarct-related vessel stenosis. In the presence of such a severe coronary obstruction, preservation of resting blood flow in the jeopardized area has been related to a preserved coronary reserve.
resulting in decreased stenosis severity, late improvement in anterograde blood flow and, possibly, a decrease in the frequency and/or severity of subclinical episodes of ischemia; and a consequent decrease in the microvascular stunning induced by brief ischemic episodes) may coexist in our patient population and contribute to the late increase in perfusion.

In segments exhibiting substantial improvement in wall motion at T7, the reduction in perfusion defect size could be partially accounted for by a partial volume effect wherein the perfusion defect may have been overstated at T1 because of abnormal segmental contraction. However, such an explanation appears less likely, because a comparable perfusion defect size was seen in group 1 and 2 patients at T1, despite the presence of a significantly different regional contraction.

### Perfusion-Function Matching

To our knowledge, this is the first study demonstrating that regional myocardial function in the infarcted area can improve after the first 5 weeks following an acute infarction in a sizable number of patients. Several previous studies that examined the time course of recovery of myocardial function after reperfusion in acute MI found that regional function may improve significantly within days\(^{1,3,6}\) but have not generally observed a further improvement after the first 2 weeks. Other studies evaluating serial changes in global LV function after coronary reperfusion were unable to document further improvement of LVEF at 3\(^{41}\) or 12 months\(^{42}\) compared with the predischarge values. Overall, after coronary reperfusion the magnitude of the improvement in LV function is modest,\(^{41}\) and the changes in the extent of abnormal wall motion seem related more to the adequacy than to the timing of reperfusion.\(^{41,42}\) Our finding of a further improvement in function after the first 5 weeks is novel and intriguing.

Perhaps the most perplexing finding of this study was that at 5 weeks the myocardial contractile dysfunction was less severe in group 1 than in group 2 patients, despite the fact that their perfusion defects were similar. There are several possible explanations. First, there could be a difference in the time course of recovery between posts ischemic contractile impairment (myocardial stunning)\(^{3,43}\) and blood flow impairment (vascular stunning).\(^{33}\) In open-chest dogs subjected to a brief (15-minute) coronary occlusion followed by reflow, an impairment in resting flow was still present 4 hours after reperfusion, and this impairment did not correlate with the degree of impairment of mechanical performance in the posts ischemic myocardium.\(^{33}\) Second, it seems probable that group 2 patients had infarctions with a larger transmural extent than group 1 patients, as reflected by the higher peak creatine kinase levels. This could explain our observation that the extent of the sestamibi defect was similar in the two groups at 5 weeks, yet the WMAs were more pronounced in group 2 than in group 1. Although the size of the risk area was the same, the amount of viable tissue within the risk area could have been less in group 2 than in group 1. This would also explain why group 2 did not show any improvement in function (because most of the risk area was infarcted). Finally, the discrepancy between the perfusion defect and the regional function in groups 1 and 2 at 5 weeks might also reflect a difference in the degree of stunning...
caused by recurrent, brief episodes of ischemia or a relative insensitivity of sestamibi imaging to transmural differences in perfusion. Most patients have a complex admixture of fibrotic and viable tissue in the infarcted area. Since the regional sestamibi uptake represents the average perfusion of the entire area, relatively small differences in flow to the viable portion of this area may be difficult to discern.

In our study there were no significant differences in sestamibi defect size and ventricular function between the patients who received thrombolytic therapy and those who did not (Table 4) or between patients with patent or occluded infarct-related arteries (Table 5). While we cannot rule out the possibility that such differences could become apparent with larger sample sizes, our results are not incongruent with those of other investigators. Many large placebo-controlled trials of thrombolytic therapy have documented improved long-term survival in treated patients without a significant effect on LV function.44 Indeed, the discrepancies between the effects of coronary reperfusion on LV function and survival have been the focus of increasing interest over the last years44-46 and have provided a rationale for postulating that the presence of an open infarct-related vessel may be beneficial by mechanisms other than limitation of infarct size.45-47

Clinical Implications

In our study, a significant improvement in sestamibi uptake in the infarcted area occurred spontaneously and concomitantly with an improvement in regional and global ventricular function. The condition of initial hypoperfusion with subsequent concordant improvement in perfusion and function meets the definition of hibernating myocardium.4 Interestingly, in our study these changes were unrelated to the status of the infarct-related artery (patent versus occluded) or to the therapeutical approach in the acute phase (thrombolysis versus conventional treatment). Furthermore, the conventional definition of hibernating myocardium implies a flow restoration to the dysfunctional area secondary to an active revascularization procedure (ie, bypass or coronary angioplasty). In the population investigated, such a flow restoration occurred spontaneously. Thus, our study suggests that myocardial hibernation may be a common condition in the initial weeks or months after infarction.

Previous studies have demonstrated a strong correlation between predischarge sestamibi defect size at rest and LVEF and regional wall motion at the time of discharge,12,17 at 6 weeks,13,14 as well as at 1 year.49 In our study, a significant inverse correlation was found between the defect severity and the LVEF and wall motion score 5 weeks after the event; this correlation was even stronger at the 7-month evaluation, particularly in those patients who showed a significant improvement in their sestamibi uptake. A similar pattern was observed for the correlation between T1 and T7 defect size and the peak creatine kinase level. The closer correlation between sestamibi defect size and conventional estimates of infarct size at 7 months suggests some overestimation of the true infarct size by sestamibi imaging at our first evaluation. The finding of some underestimation of the salvaged myocardium on sestamibi imaging performed 5 weeks after the infarction raises questions about whether an even earlier evaluation (ie, in the subacute phase or at predischarge) can accurately quantify the real extent of the scarred area.

**Table 3.** Scintigraphic and Echocardiographic Data at 5-Week (T1) and 7-Month (T7) Imaging in Patients With (Group 1) or Without (Group 2) Improvement of Their Resting Perfusion Defect

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=47)</th>
<th>Group 2 (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T7</td>
</tr>
<tr>
<td>Sestamibi defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent, %</td>
<td>33±13</td>
<td>22±15†</td>
</tr>
<tr>
<td>Severity</td>
<td>1386±845</td>
<td>820±754†</td>
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<tr>
<td>Left ventricular ejection fraction, %</td>
<td>52±13</td>
<td>55±14§</td>
</tr>
<tr>
<td>Wall motion abnormalities, %</td>
<td>31±15</td>
<td>26±19§</td>
</tr>
<tr>
<td>End-diastolic volume index, mL/BSA</td>
<td>59±14</td>
<td>60±17</td>
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<tr>
<td>End-systolic volume index, mL/BSA</td>
<td>30±15</td>
<td>29±18</td>
</tr>
</tbody>
</table>

BSA indicates body surface area.

*P<.05 and †P=.01 vs group 1. §P<.05; ¶P<.01, and ‡P<.001 vs T1.
Underestimation of myocardial viability in the setting of hibernating myocardium by sestamibi imaging recently has been acknowledged.50-56 Most of the experimental studies assessing sestamibi uptake and retention have been conducted in isolated cultured myocardial cells or in animal models of coronary occlusion-reperfusion in which blood flow and delivery of the tracer are different from the clinical setting. In the presence of a flow-limiting residual stenosis inducing persistent myocardial dysfunction (hibernation), sestamibi may not differentiate fibrotic tissue from viable myocardium with chronically reduced perfusion; because this agent tracks blood flow but does not redistribute appreciably, it could be responsible for false scar defects on resting images. Preliminary reports comparing sestamibi uptake and metabolic [18F]fluorodeoxyglucose imaging in patients with chronic coronary artery disease showed

**TABLE 4.** **Scintigraphic and Echocardiographic Results at 5 Weeks (T1) and 7 Months (T7) According to the Therapeutic Strategy in the Acute Phase**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Thrombolysis</th>
<th>No Thrombolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±7</td>
<td>49±10</td>
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<tr>
<td>Peak creatine kinase, IU/mL</td>
<td>3223±3031</td>
<td>1930±1484*</td>
</tr>
<tr>
<td>Sestamibi defect extent, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>34±13</td>
<td>29±14</td>
</tr>
<tr>
<td>T7</td>
<td>27±16</td>
<td>22±16</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.01</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Sestamibi defect severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1498±662</td>
<td>1067±642</td>
</tr>
<tr>
<td>T7</td>
<td>1122±862</td>
<td>787±672*</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>48±13</td>
<td>52±12</td>
</tr>
<tr>
<td>T7</td>
<td>51±15</td>
<td>55±13</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.05</td>
<td>NS</td>
</tr>
<tr>
<td>Wall motion abnormalities, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>33±15</td>
<td>31±16</td>
</tr>
<tr>
<td>T7</td>
<td>30±19</td>
<td>26±18</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Infarct vessel: TIMI grade</td>
<td>2.1±1.2</td>
<td>1.1±1.2*</td>
</tr>
<tr>
<td>Infarct vessel: patency</td>
<td>24/36 (67%)</td>
<td>5/16 (31%)*</td>
</tr>
</tbody>
</table>

Timi indicates Thrombolysis in Myocardial Infarction. 
*P<.05 vs thrombolysis group.

**TABLE 5.** **Scintigraphic and Echocardiographic Results at 5 Weeks (T1) and 7 Months (T7) According to the Infarct Vessel Patency**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>No Patency</th>
<th>Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51±8</td>
<td>49±7</td>
</tr>
<tr>
<td>Thrombolysis, N (%)</td>
<td>12 (52)</td>
<td>24 (83)*</td>
</tr>
<tr>
<td>Time to thrombolysis, h</td>
<td>1.8±0.9</td>
<td>2.0±1.2</td>
</tr>
<tr>
<td>Sestamibi defect extent, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>34±14</td>
<td>32±13</td>
</tr>
<tr>
<td>T7</td>
<td>26±17</td>
<td>27±15</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sestamibi defect severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1482±921</td>
<td>1385±793</td>
</tr>
<tr>
<td>T7</td>
<td>993±850</td>
<td>1127±834</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>50±12</td>
<td>47±14</td>
</tr>
<tr>
<td>T7</td>
<td>53±14</td>
<td>49±15</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.05</td>
<td>NS</td>
</tr>
<tr>
<td>Wall motion abnormalities, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>32±13</td>
<td>36±17</td>
</tr>
<tr>
<td>T7</td>
<td>29±18</td>
<td>31±21</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

*P<.05 vs no-patency group.
that resting sestamibi imaging underestimated residual viability in dysfunctioning regions.\textsuperscript{51,52,56}

**Limitations of the Study**

The therapeutic approach in the acute phase (thrombolytic treatment or conventional therapy) was not randomized, and the effect of thrombolysis was evaluated retrospectively. Women as well as patients with resting LVEF values of <25% or exertional angina uncontrolled by medical therapy were not included in this study. Furthermore, patients who had extensive coronary artery disease and/or required coronary revascularization (bypass or angioplasty) between the two studies were excluded. Thus, the observed improvement in sestamibi uptake may not necessarily apply to other groups of patients with recent MI.

We did not measure myocardial blood flow directly. Changes of regional perfusion were assessed by an indirect flow measurement, namely, the uptake of a radionuclide whose distribution is largely flow-dependent.\textsuperscript{78}

The primary goal of our study was not to correlate coronary angiography with ventricular function or sestamibi defect size but rather to serially examine the relation between changes in myocardial perfusion and function. Angiographic data were not available in all patients. Since coronary angiography was carried out at an average of 3 months from the first echocardiographic and scintigraphic evaluation, it is possible that the status of the infarct vessel (and collaterals) at the time of the angiogram may have been different from that at the time of the noninvasive studies. This could have contributed to the lack of relation observed between wall motion improvement, sestamibi defect reduction, and vessel patency or collaterals. However, this study was performed after a long interval from the acute phase and in clinically stable patients. Catheterization was planned at 4 months after acute infarction, a time when a relatively stable state of vessel patency should have been achieved. Although delayed changes in the infarct vessel patency or angiographically visible collaterals can be ruled out only by serial coronary angiography, the very few data available from serial angiographic evaluations performed in the subacute phase of MI documented only small changes in diameter stenosis, patency, and distal collateralizations of the infarct-related vessel.\textsuperscript{57} As mentioned earlier, several reports found that most collateral development and patency variation in the infarct-related vessel develop within the first 2 weeks after MI.\textsuperscript{28,31}

**Conclusions**

Although reperfusion therapy may be followed by an improvement in perfusion at serial imaging at 2 to 7 days, it has been well documented that the improvement in contraction of the salvaged myocardium does not occur immediately after spontaneous or therapeutic reperfusion. The timing of complete recovery of perfusion or function has not been clearly defined. Our results indicate that after anterior Q-wave infarction, the recovery of perfusion and wall motion in the infarcted area may continue well after the subacute phase. In several patients, a reduced perfusion in viable tissue seems to be present as late as 5 weeks after infarction, and a spontaneous improvement in the myocardial tracer uptake in the infarct area may occur in a sizable number of patients between 5 weeks and 7 months after the event. This delayed improvement of perfusion is associated with a delayed improvement of contractile function in the infarcted area, which may continue up to 7 months after the acute event.

Our results suggest the occurrence of myocardial hibernation in the area of infarction in a significant proportion of patients. Thus, the eventual extent of recovery may not be assessed accurately by measurements of LV function taken at the time of discharge or even at 5 weeks. Furthermore, the use of predischarge perfusion imaging to document the benefit of reperfusion strategies and to assess the final scarred area may be misleading. With similar sestamibi defect sizes, the level of regional function can be different at 5 weeks, which demonstrates that measurements of defect size taken around this time may not be a good predictor of the eventual recovery of function. Other imaging techniques, aimed at an accurate detection of residual viability in dysfunctioning area, should be taken into account.

**Acknowledgments**

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