Predicting revascularization outcome in patients with coronary artery disease and left ventricular dysfunction (data from the SEMINATOR

Predicting Revascularization Outcome in Patients With Coronary Artery Disease and Left Ventricular Dysfunction (Data from the SEMINATOR Study)

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A main goal of revascularization in patients with chronic ischemic cardiomyopathy is to improve global left ventricular (LV) function. This study aimed to verify whether it is possible to predict an increase in LV ejection fraction (EF) after revascularization on the basis of the extent of LV asynergy, myocardial viability, and revascularization completeness. We studied 77 patients with chronic LV ischemic dysfunction using baseline resting and nitrate-enhanced technetium-99m sestamibi single-photon emission computed tomography. Regional wall motion and global LVEF were assessed with echocardiography before and after revascularization, which was complete in 51 patients and incomplete in 26. The number of viable asynergic segments included in revascularized coronary artery territories was the strongest predictor of significant (≥5 EF U) functional improvement in univariate discriminant analysis. According to multivariate stepwise discriminant analysis, this parameter, together with the number of baseline asynergic segments, allowed the detection of patients with significant LVEF improvement with 75% accuracy. With use of a multivariate regression model, including the 2 mentioned variables, the measure of postrevascularization LVEF increase could be accurately quantified (R^2 0.43, p <0.000001). In conclusion, this study suggests that the severity of baseline asynergy, the extent of myocardial viability, and the completeness of revascularization are the main determinants of postrevascularization functional recovery in patients with LV ischemic dysfunction, and that on the basis of these variables it is possible to predict the measure of LVEF increase.

(Am J Cardiol 2002;89:1369–1373)

Viable dysfunctional myocardium is expected to recover after coronary revascularization.[1,2] Therefore, imaging methods that detect myocardial viability are currently used in patients with chronic coronary artery disease and left ventricular (LV) dysfunction to orient the therapeutic choices.[3–9] In these patients, the goal of treatment is to improve global LV function, and possibly heart failure symptoms and prognosis.[2,10–13] Thus, it would be important to predict the functional gain in the individual patient. A relation exists between extent of viable myocardium and improvement in global LV ejection fraction (EF).[4,8,9,12,14–17] However, other variables should be considered, such as baseline extent of asynergy, amount of viable myocardium within the dysfunctional area, coronary artery status, and feasibility of a complete revascularization. Few data exist on the ability of viability imaging to quantify the degree of global functional improvement that should be expected. The aim of the SEstaMIbi with Nitrate Administration To predict the Outcome of Revascularization (SEMINATOR) study was to evaluate patients with chronic coronary artery disease and moderate-to-severe LV dysfunction submitted to the best possible revascularization procedure on the basis of their coronary artery status in order to identify which parameter best predicts the achievement and extent of global LV functional improvement.

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METHODS

Patient population: Patients were selected according to the following criteria: diagnosis of chronic coronary artery disease confirmed by coronary angiography, known LV dysfunction with EF ≤40%, presence of clear regional wall motion abnormality, scheduled revascularization procedure, and willingness to participate in the study. Exclusion criteria were recent myocardial infarction or unstable angina, heart disease other than coronary artery disease, and history of prior revascularization. The study cohort included 77 patients (70 men and 7 women, mean age 61 ± 11 years).

Study protocol: All patients underwent baseline resting and nitrate technetium-99m sestamibi (sestamibi) single-photon emission computed tomography (SPECT) to define myocardial viability and 2-dimensional echocardiography to assess LVEF. The referring physician decided the modality and the complete-

0002-9149/02/$–see front matter
PII S0002-9149(02)02349-4

TABLE 1 Comparison of Demographic, Clinical, and Instrumental Findings Between Patients With and Without Significant EF Improvement After Coronary Revascularization

	EF increase ≥5 EF Units (n = 40)	EF increase <5 EF Units (n = 37)
Men/women	35/5	35/2
Age (yrs)	60 ± 10	61 ± 12
Prior anterior wall infarct	16 (40%)	17 (46%)
No. of stenotic arteries	2.4 ± 0.7	2 ± 0.8*
New York Heart Association functional class	1.8 ± 0.7	1.7 ± 0.7
EF before revascularization (%)	30.3 ± 7.2	31.2 ± 7.1
Asynergic segments	9.1 ± 2.8	8.6 ± 3.1
Viable asynergic segments	6.1 ± 2.9	4.1 ± 3†
Coronary angioplasty/bypass surgery	16/24	21/16
Complete revascularization	27 (68%)	24 (65%)
No. of revascularized vessels	2.1 ± 0.8	1.5 ± 0.8†
Viable asynergic segments in revascularized territories	5.7 ± 2.7	2.6 ± 2‡

*p <0.05;†p <0.005; ‡p <0.000005.

ness of the revascularization procedure. At least 3 months later, a follow-up control using 2-dimensional echocardiography was performed to assess changes in LVEF. Nitrates and β-adrenergic blocking agents were withdrawn 48 hours before all tests. The ethics committees of our institutions approved the study protocol and informed consent was obtained from each patient.

Functional evaluation: Echocardiograms were registered with the patients lying in the left lateral decubitus position using commercially available echocardiographic equipment. Multiple views were obtained for each study and recorded on videotape for off-line analysis. Images were evaluated by 2 experienced observers, unaware of the clinical, angiographic, and scintigraphic data, and of the acquisition sequence. The left ventricle was divided into 13 segments,[7] and wall motion and thickening of each segment were scored as follows: 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia.[7] Discrepancies were resolved by consensus. For LVEF calculation, the biplane Simpson's method was applied on 3 consecutive cardiac cycles examined with the apical 4-chamber view and the mean of the measured values was used.[18] Improvement in LVEF after revascularization was arbitrarily defined as an increase ≥5 EF units in the follow-up compared with the baseline value.[12]

Sestamibi SPECT: The protocol included 2 separate studies, 1 after tracer injection at rest and the other after tracer administration during nitrate infusion. The nitrate administration protocol has been previously described.[7] Sestamibi dose was 740 to 925 MBq (20 to 25 mCi) in both instances. SPECT studies were acquired 1 hour later using large field-of-view tomographic gamma cameras equipped with high-resolution collimators, and with a 20% window centered on the 140 keV photopeak of technetium-99m. Image reconstruction was performed using filtered back projection. After transaxial reconstruction, the slices were realigned along the heart axis. For the quantitative evaluation of SPECT images, count profiles of the short-axis slices were generated by computer software and plotted onto a volume-weighted polar map, which was then divided into 13 segments, matching with the echocardiographic segments.[19] With use of an automated procedure, mean tracer activity of each segment was calculated. The segment with maximal activity was normalized to 100 and the activity of the other segments was expressed as a percentage of the peak activity segment.[19]

Criteria for myocardial viability: The assessment of viability was restricted to the segments with resting wall motion abnormality (scores 2 to 4) as determined by echocardiography. Myocardial viability was considered present in asynergic segments with a nitrate-induced activity increase (expressed in percentage of baseline activity) >10%, and was excluded in the case of nitrate-induced decrease >10%; if a segment had a nitrate-induced activity change between ±10% of baseline activity, myocardial viability was defined to be present on the basis of nitrate activity ≥65%.[13,17,19]

Statistical analysis: Variables are expressed as mean ± SD. Continuous variables were compared with the Student's *t* test for paired or independent data, as appropriate, using the Bonferroni correction in case of multiple comparisons. Ordinal variables were compared with the nonparametric Mann-Whitney U test. The comparison of proportion was made with the Fisher's exact test. The parameters that best differentiate between patients with and without LVEF increase of ≥5 EF units after revascularization were selected using stepwise discriminant analysis. To identify the optimal thresholds of the selected parameters, receiver-operating characteristics curves were constructed. The relation between amount of LVEF change (expressed in percentage of the prerevascularization value) and its possible predictors was investigated using stepwise multivariate regression. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics: A history of prior myocardial infarction was registered in 72 patients. The mean New York Heart Association functional class was 1.8 ± 0.7. According to coronary angiography, 18 patients had 1-vessel, 25 had 2-vessel, and 34 had 3-vessel coronary artery disease. Of a total number of 1,001 analyzed segments, 684 showed abnormal wall motion, with a mean of 8.9 ± 2.9 asynergic segments per patient. Mean LVEF before revascularization was 30.7 ± 7% (range 15% to 40%). According to baseline-nitrate sestamibi SPECT, dysfunctional segments fulfilling the criteria for myocardial viability were detected in 74 patients, with a mean of 5.2 ± 3.1 viable asynergic segments per patient.

Follow-up control: The revascularization procedure was coronary artery bypass grafting in 38 patients and

TABLE 2 Results of Discriminant Analysis for Predicting Significant EF Improvement After Coronary Revascularization

Variables in Univariate Analysis	Step	F Value	p Value	Canonical Correlation	p Value	Classification Matrix	
						True Positive	True Negative
No. of stenotic vessels		5.05	<0.03			22	25
Viable asynergic segments		8.6	<0.005			21	26
No. of revascularized vessels		11.9	<0.001			29	22
Viable asynergic segments in revascularized territories		31.7	<0.000001			22	30
Stepwise discriminant analysis							
Viable asynergic segments in revascularized territories	1	40.3	<0.000001				
No. of asynergic segments	2	6.8	<0.02				
Function				0.60	<0.000001	30	28

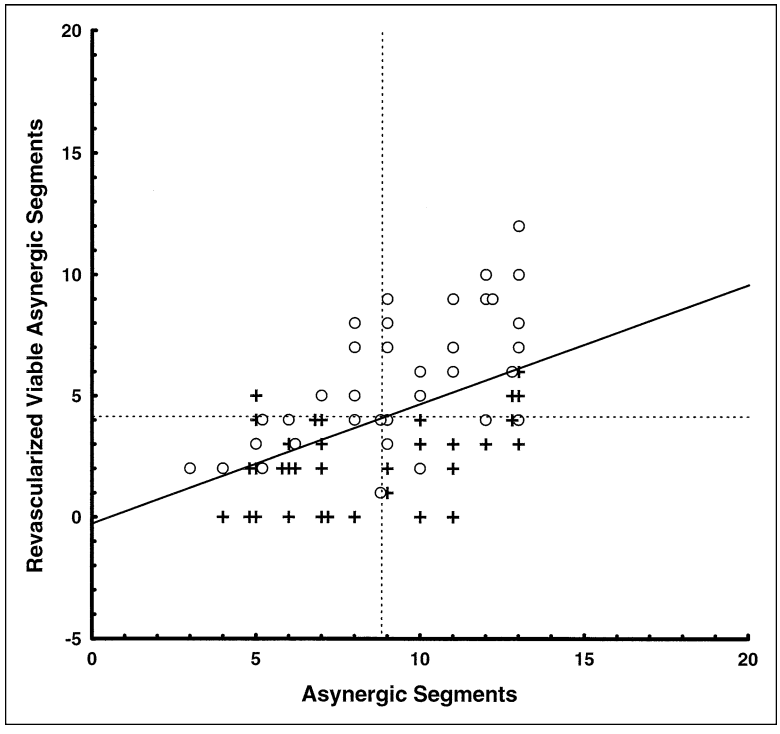

FIGURE 1. Scatterplot showing the relation between number of asynergic segments and number of revascularized viable asynergic segments in patients with *(circles)* versus without *(crosses)* significant LVEF increase after revascularization. The *continuous line* indicates the discriminant function; *dashed lines* indicate the cutoff values of the variables as determined by univariate analysis.

percutaneous transluminal coronary angioplasty in 39. The revascularization procedure was complete in 51 patients. In the remaining 26 patients, the revascularization procedure could not involve all stenotic vessels, but just 1 of 3 in 7 patients, 1 of 2 in 8 patients, and 2 of 3 in 11 patients. Perioperative infarction was excluded on the basis of clinical and enzymatic data in all patients. Recurrent ischemia was ruled out by clinical observation and negative exercise stress testing whenever necessary. In the postrevascularization echocardiographic control, mean LVEF was 36 ± 9% (range 17% to 55%; p <0.00001 vs before revascularization). A ≥5 EF unit increase was registered in 40 patients (from 30.3 ± 7.2% to 41.5 ± 7.4%, p <0.00001). In the remaining 37 cases, no significant change was observed in the postrevascularization value (from 31.2 ± 7.1% to 30.1 ± 7%).

Predictors of LVEF improvement: Patients with significant LVEF improvement differed from those without LVEF increase in the number of coronary arteries with significant stenosis, in the number of viable asynergic segments, in the number of revascularized vessels, and above all in the number of viable asynergic segments included in revascularized coronary territories (Table 1). To define the determinants of significant LVEF improvement, the following variables were submitted to univariate and to stepwise multivariate discriminant analysis: number of stenotic vessels, number of asynergic segments, baseline LVEF, number of viable asynergic segments, number of vessels submitted to revascularization, number of revascularized viable asynergic segments. Table 2 lists which variables were significant in univariate discriminant analysis and the related diagnostic reliability according to the classification matrix. Stepwise discriminant analysis selected the number of revascularized viable asynergic segments and the number of asynergic segments as predictors of significant LVEF improvement (Table 2, Figure 1). The derived function had a very significant canonical correlation, and its classification matrix achieved 75% sensitivity, 76% specificity, and 75% overall accuracy (Table 2, Figure 1). These 2 variables can be merged in 1 single parameter by calculating their ratio (number of revascularized viable asynergic segments over number of asynergic segments). According to the receiver-operating characteristics curve constructed using this ratio, the optimal threshold to differentiate between patients with and without LVEF increase of ≥5 EF units after revascularization was ≥0.45, with 75% sensitivity and 87% specificity (Figure 2).

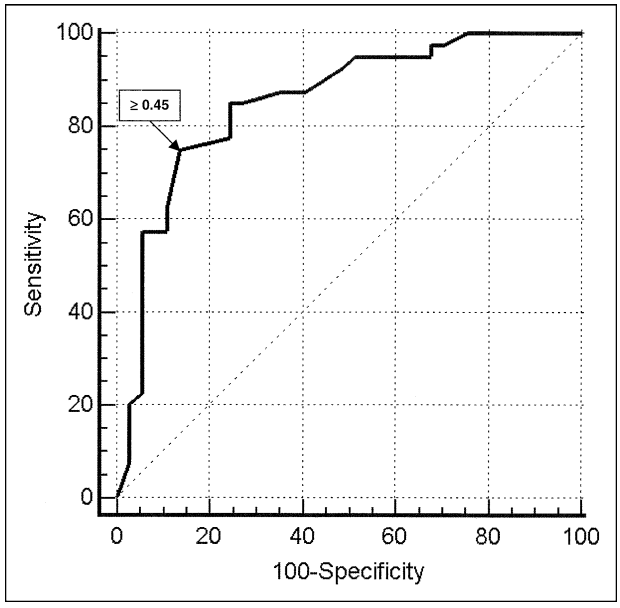

FIGURE 2. Receiver-operating characteristic curve to identify the best cutoff of the ratio of number of revascularized viable asynergic segments over the number of asynergic segments for predicting significant LVEF improvement after revascularization.

Estimate of LVEF changes: According to stepwise multiple linear regression, the number of revascularized viable asynergic segments (β = 0.64, p <0.000001), the prerevascularization LVEF (β = −0.38, p <0.001), and the number of asynergic segments (β = −0.35, p <0.005) were the significant predictors of LVEF changes expressed in percentages of the prerevascularization value. The coefficient of determination R^2 was 0.43 (p <0.000001). Using the derived equation, the percent change after revascularization could be predicted with good accuracy (Figure 3).

DISCUSSION

In patients with chronic coronary artery disease and LV dysfunction, the presence of viable myocardium within asynergic areas is necessary for functional recovery after revascularization. In these patients, coronary revascularization procedures usually present a relatively high risk.[20] Therefore, care must be given to identify patients in whom the potential benefit of revascularization overwhelms the procedure hazard. Several studies have addressed the relation between presence of viable myocardium and improvement in global LV function, mostly considering the increase in LVEF.[4,8,9,12,14–17] In general, the larger the extent of viable myocardium, the higher the likelihood of achieving a significant increase in LVEF.[4,8,9,12,14–17] However, the capability of viability assessment to predict LVEF changes quantitatively is not yet established. Furthermore, complete revascularization of all stenotic vessels is not always possible in the clinical practice and this could affect the degree of improvement.

According to our results, a significant LVEF increase after revascularization can be accurately predicted on the basis of the number of viable asynergic segments included in the territories submitted to revascularization corrected by the total number of asynergic segments. The univariate discriminant function model selected the number of viable asynergic segments included within revascularized territories as the most significant predictor of LVEF increase. This is reasonable because it is straightforward that viable myocardium cannot improve in regional wall motion or contribute to the increase in global LVEF if not effectively revascularized. However, different from what is performed in study protocols, achievement of complete revascularization is not always possible or considered desirable in daily clinical practice, particularly when angioplasty is the chosen approach.[21] The study results suggest a method to predict the likely change in global LV function taking into account the planned extent of revascularization. This could be helpful in deciding between increased complexity and risk of revascularization and possible achievement of greater functional gain.

A second important finding of this study is that the relation between extent of viable asynergic myocardium and postrevascularization functional improvement must be corrected to take into account the baseline extent of dysfunctional tissue. This means that although a minimal number of viable segments must be effectively revascularized, their influence on LVEF changes is related to the baseline extent of the asynergic area. The number of viable asynergic segments submitted to revascularization separates patients with from those without significant functional recovery, but discrimination between the 2 groups is clearly improved if the number of asynergic segments is also considered, as indicated by the line (in Figure 1) showing the discriminant function. Therefore, the minimal threshold value of viable asynergic segments necessary for predicting a significant functional recovery after revascularization must be increased in patients with larger baseline dysfunction. In practice, the ratio of the 2 above-mentioned parameters can be used, obtaining a very good diagnostic reliability.

A third interesting finding is that the expected LVEF change can be reasonably predicted on the basis of the number of viable asynergic segments submitted to revascularization. The stepwise multivariate regression model selects the number of asynergic segments and the baseline LVEF value as additional significant predictors. Although the error of this quantification is not negligible, this result is interesting for 2 reasons. First, it demonstrates a direct relation between extent of myocardial viability and extent of functional improvement, with a correlation that is well comparable to what has been registered using the dobutamine-induced changes in LVEF.[14] Second, in patients with particularly high operative risk or in whom the revascularization results are uncertain, it would be possible to quantify the predicted functional recovery, giving to both the clinician and the patient an additional piece of information to orient the therapeutic choice. It is conceivable that a great potential gain in global func-

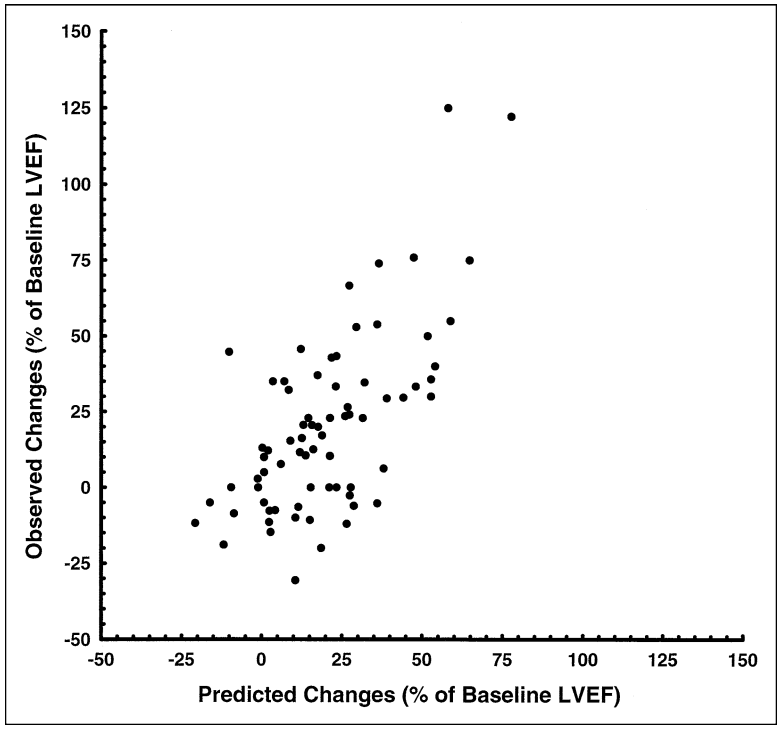

FIGURE 3. Scatterplot showing the relation between the observed change in LVEF after revascularization (expressed as percentage of prerevascularization value) and the corresponding value predicted according to multivariate regression analysis.

tion would encourage performing a more aggressive treatment than the expectation of a borderline significant increase of 5 EF units.

Some limitations of the study must be considered. A small number of patients had just moderate LV impairment. However, the degree of LV dysfunction of the study cohort is comparable to several other similar studies.[5,8–11,15,16] The criteria used to define the presence of myocardial viability have been demonstrated to be the most accurate, but a simplified approach based on the sole assessment of nitrate-enhanced uptake could probably be equally effective.[17] Finally, it cannot be excluded that a larger number of patients would have shown LV functional recovery if the follow-up control had been delayed,[22] although the interval of 3 months has been widely used in reports on viability.[5,6,8,12,14]

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