Coronary Artery Disease

Prognostic Implications of Tc-99m Sestamibi Viability Imaging and Subsequent Therapeutic Strategy in Patients With Chronic Coronary Artery Disease and Left Ventricular Dysfunction

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OBJECTIVES	The aim of the study was to verify the prognostic implications of viability detection using baseline-nitrate sestamibi imaging in patients with left ventricular (LV) dysfunction due to chronic coronary artery disease (CAD) submitted to different therapeutic strategies.
BACKGROUND	The prognostic meaning of preserved viability in these patients is still debated. Sestamibi is increasingly used for myocardial perfusion scintigraphy and is being accepted also as viability tracer, but no data are available about the relationship between viability in sestamibi imaging, subsequent treatment, and patient's outcome.
METHODS	Follow-up data were collected in 105 CAD patients with LV dysfunction who had undergone baseline-nitrate sestamibi perfusion imaging for viability assessment and had been later treated medically (group 1), or submitted to revascularization, which was either complete (group 2A) or incomplete (group 2B).
RESULTS	Eighteen hard events (cardiac death or nonfatal myocardial infarction) were registered during the follow-up. A significantly worse event-free survival curve was observed in the patients of group 1 (p < 0.0002) and group 2B (p < 0.03) compared to those of group 2A. Using a Cox proportional hazard model, the most powerful prognostic predictors of events were the number of nonrevascularized asynergic segments with viability in sestamibi imaging (p < 0.003, risk ratio [RR] = 1.4), and the severity of CAD (p < 0.02, RR = 1.28).
CONCLUSIONS	Viability detection in sestamibi imaging has important prognostic implications in CAD patients with LV dysfunction. Patients with preserved viability kept on medical therapy or submitted to incomplete revascularization represent high-risk groups. (J Am Coll Cardiol 2000;36:739–45) © 2000 by the American College of Cardiology

In patients with chronic coronary artery disease (CAD) and left ventricular (LV) dysfunction, viable myocardium in asynergic regions subtended by a stenotic vessel may recover its function when adequate coronary flow is restored (1,2). If sufficient viable tissue is present, increase in global LV ejection fraction (EF) and improvement of clinical symptoms are usually registered after coronary revascularization (3–6). Other studies indicate that patients with preserved viability have a worse prognosis if kept on medical therapy than if submitted to coronary revascularization (5–16). Thus, the assessment of myocardial viability is very important to identify those who will benefit from a revascularization procedure. Various imaging methods are used, such as positron emission tomography (3), myocardial perfusion scintigraphy with thallium-201 (4), and low-dose dobutamine echocardiography (6). After initial concerns, also myocardial perfusion imaging with Tc-99m sestamibi (sestamibi), particularly in combination with nitrate adminis-

tration, has been demonstrated to give reliable results in the detection of viable hibernating myocardium and in the prediction of postrevascularization recovery (17–21). However, scanty data are available about the potential prognostic implications of viability detection using sestamibi. The aim of this study was to evaluate the outcome of patients with LV dysfunction due to chronic CAD, taking into account 1) the presence of viable myocardium in asynergic LV segments demonstrated using baseline-nitrate sestamibi single-photon emission computed tomography (SPECT), and 2) the subsequent therapeutic strategy.

METHODS

Patient selection. Between 1991 and 1997, a total of 115 patients with chronic CAD, reduced global LV function (LVEF <50% as assessed by echocardiography or radionuclide ventriculography), and severely abnormal regional wall motion in at least one coronary artery territory, were subjected in our laboratory to sestamibi imaging for viability detection. All patients were considered to be possible candidates for coronary revascularization. None of them had unstable angina or recent (<2 months) myocardial infarc-

Abbreviations and Acronyms

ANOVA	=	analysis of variance
CABG	=	coronary artery bypass grafting
CAD	=	coronary artery disease
CCS	=	Canadian Cardiovascular Society
CI	=	confidence interval
EF	=	ejection fraction
LV	=	left ventricular
NYHA	=	New York Heart Association
PTCA	=	percutaneous transluminal coronary angioplasty
RR	=	risk ratio
SPECT	=	single-photon emission computed tomography

tion. History of previous myocardial infarction was present in 90 subjects. Of the 115 patients, 2 were excluded because they refused coronary angiography, and 8 were lost at follow-up. Therefore, the study group included 105 patients (95 men and 10 women, mean age 60.6 ± 10.6, range 35 to 83 years). Patients were not randomized for medical treatment or coronary revascularization or, in the latter case, for percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) and complete or incomplete revascularization. The referring physicians made the decisions on clinical grounds, taking into account symptoms severity, response to therapy, coronary anatomy, patient preferences, and imaging data, including those of the present study.

Coronary angiography. All 105 patients underwent coronary angiography using the percutaneous transfemoral technique. Two experienced observers, who were unaware of patient data, using multiple projections evaluated percent diameter stenosis. Vessels showing $>50\%$ lumen reduction were considered diseased. The severity of CAD was estimated using an angiographic scoring system (coronary artery jeopardy score) ranging from 0 (no obstructions $>75\%$) to 12 (proximal obstructions of all three main coronary arteries) (22).

Sestamibi single-photon emission computed tomography (SPECT). The protocol included two separate studies, one after tracer injection at rest and the other after tracer administration during nitrate infusion, as previously described (18,19). Sestamibi dose was 20 to 25 mCi (740 to 925 MBq) in both instances. Images were collected approximately 1 h later using a single-head, large-field-of-view tomographic gamma camera equipped with an ultra-high resolution collimator, and with a 20% window centered on the 140-keV photopeak of technetium-99m. Sixty projections of 20 s each were acquired. Image reconstruction was performed using filtered backprojection, without attenuation or scatter correction, and the slices were realigned along the heart axis.

Image analysis. Sestamibi SPECT data were analyzed quantitatively. The short-axis slices from the first with apical activity, to the last with activity at the base, were used and their count profiles were generated by computer soft-
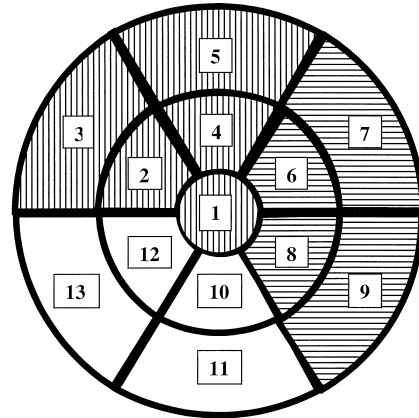

Figure 1. Diagram of the 13-segment model used for SPECT and echocardiography data analysis, showing the relation between each segment and the related coronary artery territory. Areas with vertical lines = left anterior descending artery; areas with horizontal lines = left circumflex artery; open areas = right coronary artery.

ware and plotted onto a two-dimensional volume-weighted polar map. The polar maps were divided into 13 segments, which were assigned to the related coronary artery distribution using an established scheme (19,23), as shown in Figure 1. Using an automated procedure, segment tracer activity was calculated as the total of the normalized counts of the pixels included within the segment divided by the pixel number. The segment with maximal activity was then normalized to 100 and the activity of the other segments was expressed as a percentage of the peak activity segment (19).

Definition of myocardial viability. The assessment of viability was restricted to the segments with resting wall motion abnormality as determined by two-dimensional echocardiography using a 13-segment model, matching with the SPECT one (18,19,23). The wall motion of each segment was scored from 1 (normokinesia) to 4 (dyskinesia) and segments with score ≥ 2 were considered asynergic (24). The perfusion images were evaluated using our established interpretation approach, which takes into account the baseline activity level, the nitrate activity level, and the nitrate-induced activity changes (19). Asynergic segments were defined viable if an activity increase greater than 10% was registered in nitrate SPECT compared to baseline imaging (19). Conversely, viability was excluded in the case of nitrate-induced decrease greater than 10%. Finally, in the segments with a nitrate-induced activity change between $\pm10\%$ of baseline activity, viability was considered to be present if activity in nitrate SPECT was $\geq 65\%$ (19).

Follow-up data. Patients were followed up by review of hospital records and by telephone contact with the patient, relatives, or referring physician. An investigator who was unaware of sestamibi results collected follow-up data. The mean follow-up period was 27 ± 22 months. The evaluated events were cardiac death and nonfatal myocardial infarction.

Statistical analysis. Values are presented as mean value ± standard deviation (SD). In the case of nominal variables, the median is indicated as well. Continuous variables were compared with the one-way analysis of variance (ANOVA) and nominal variables with the Kruskal-Wallis ANOVA. The comparisons of proportions were made using either the Fisher exact test or the chi-square test with Yates' correction as appropriate. Survival curves were constructed using the Kaplan-Meier method and were compared with the log-rank test. The Cox proportional hazards survival model was used to identify the independent predictors of patient's outcome. The STATISTICA 4.5 software package was used for all statistical calculations. A probability value of $p < 0.05$ was considered statistically significant.

RESULTS

General findings. The leading indication for viability imaging was effort or resting dyspnea in 36 patients, stable angina in the presence of LV dysfunction in eight cases, and prior myocardial infarction with evidence of LV dysfunction in 61 patients. Within this last group, 21 patients were asymptomatic, whereas 40 reported effort chest pain. The overall mean Canadian Cardiovascular Society (CCS) classification of angina severity was 1.3 ± 0.5 (median 1). The overall average New York Heart Association (NYHA) functional class was 1.5 ± 0.6 (median 1). The LVEF at the time of perfusion imaging was 33.9 ± 9.2%. A clearly depressed LV function (LVEF <40%) was registered in 70 patients. According to coronary angiography, 24 patients had one-vessel, 37 two-vessel, and 44 three-vessel CAD. The average coronary artery jeopardy score of the patient population was 6.3 ± 2.6, median 6, and range 2 to 12. The mean number of asynergic segments per patient was 7.8 ± 2.9, median 7, and range 2 to 13.

Sestamibi SPECT. According to sestamibi SPECT, only six patients did not show any viable asynergic segment. The remaining 99 patients showed a mean of 4.6 ± 2.6 viable asynergic segments, median 4, range 1 to 13. Taking into account the distribution of the viable asynergic segments in the three different coronary territories, all territories with significant CAD included viable myocardium in 44 patients, one-third in 4, one-half in 13, and two-thirds in 17 patients. Figure 2 shows an example of preserved viability in a patient with three-vessel CAD and severe LV dysfunction.

Patient treatment. Twenty-six patients were kept on medical therapy (group 1), and 79 were submitted to coronary revascularization (PTCA in 37 cases, CABG in 42 cases) (group 2). Independently of the adopted technique, the revascularization procedure involved all vessels with significant CAD in 55 patients (group 2A), and was incomplete in the remaining 24 patients (group 2B), involving one-third stenotic vessels in 5 cases, one-half in 10 cases and two-thirds in 9 cases. Group 1 showed a significantly higher NYHA class (1.8 ± 0.7, median 2) than did group 2 (1.43 ± 0.5, median 1, $p < 0.05$): no other significant
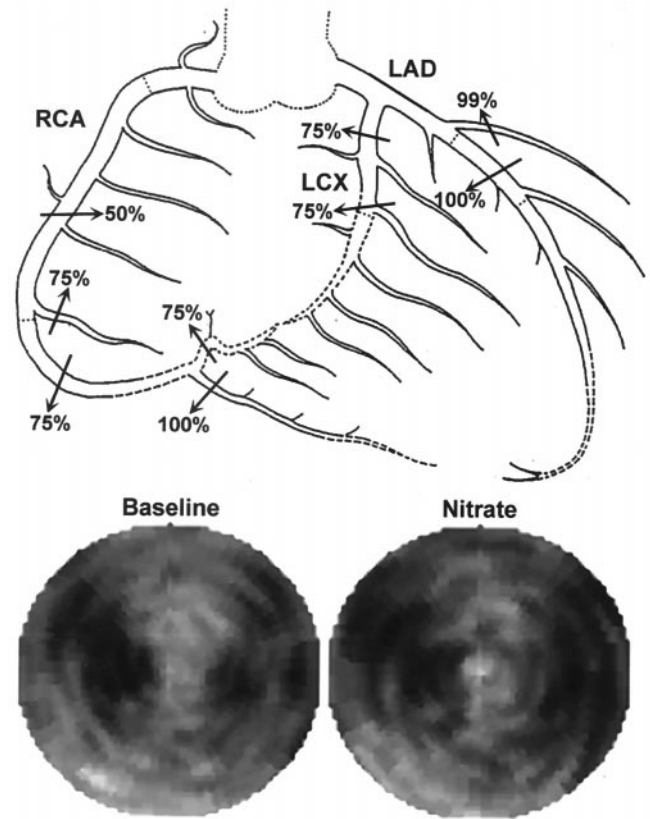

Figure 2. Diagram of the coronary artery tree **(upper panel)** and myocardial perfusion polar map displays **(lower panel)** of a patient with three-vessel CAD (coronary artery jeopardy score = 10) and severe LV dysfunction (NYHA functional class 2, LVEF 20%). On the baseline study, large moderate uptake defects are observed in the anterior and inferior wall, with clear increase in sestamibi activity on the nitrate study. The patient was refused by the surgeon for technical difficulties in performing CABG and for the high risk associated with the procedure. Therefore, the patient underwent successful PTCA on LCX (left circumflex artery), and on RCA (right coronary artery), whereas the LAD (left anterior descending) could not be treated. The patient had regional and global functional recovery (LVEF 40%), with disappearance of effort dyspnea, but died because of sudden death seven months after PTCA.

difference between the two groups was observed in the variables listed in Table 1, which compares the features of the patients included in the three different treatment groups. Group 2B showed a significantly more severe CAD than did group 1 and also a higher number of diseased vessels than group 2A. The other statistically significant difference between groups 2A and 2B was the higher rate of PTCA versus CABG in the latter group.

Follow-up evaluation. During follow-up, 18 events were registered. They included 11 sudden deaths, 1 death because of untreatable congestive heart failure, 3 fatal myocardial infarctions, and 3 nonfatal myocardial infarctions. The main demographic, clinical, angiographic and scintigraphic findings of the patients with events versus those without events are shown in Table 2. The most significant difference between the two groups was in the number of nonrevascularized asynergic segments with viability in sestamibi SPECT. The Kaplan-Meier survival curves showed a sig-

Table 1. Demographic, Clinical, Angiographic and Treatment Data of the Three Patient Groups (see text)

	Group 1 (n = 26)	Group 2A (n = 55)	Group 2B (n = 24)	p Value
Age (yrs)	63.7 ± 10.1	59.6 ± 10.3	59.5 ± 11.4	NS
Male gender	96%	87%	88%	NS
Myocardial infarction	85%	87%	83%	NS
Angina	38%	51%	42%	NS
CCS classification	1.3 ± 0.4 [1]	1.2 ± 0.5 [1]	1.3 ± 0.4 [1]	NS
NYHA functional class	1.8 ± 0.7 [2]	1.4 ± 0.5 [1]	1.5 ± 0.6 [1]	Gr. 1 vs. 2 < 0.05 Gr. 1 vs. 2a < 0.05
LVEF (%)	31.5 ± 10.2	35 ± 9	34 ± 8.4	NS
Diseased vessels	2 ± 0.7 [2]	2.1 ± 0.9 [2]	2.5 ± 0.5 [3]	Gr. 1 vs. 2b < 0.05 Gr. 2a vs. 2b < 0.05
Coronary artery jeopardy score	5.5 ± 2.5 [6]	6.5 ± 2.9 [6]	7 ± 2.1 [7]	Gr. 1 vs. 2b < 0.05
Asynergic segments	8 ± 3 [8]	7.8 ± 3 [7]	8 ± 3 [8]	NS
Viable asynergic segments	4.8 ± 2.4 [5.5]	4.5 ± 2.6 [4]	4.7 ± 2.9 [4]	NS
CABG/PTCA	NA	35/20	7/17	< 0.05

Gr. = group; n = number; NA = not applicable; [ ] = median; (other abbreviations: see text).

nificant difference between group 2A and both group 1 (p < 0.0002) and group 2B (p < 0.03). Conversely, no significant difference was observed between the survival curves of these last two groups (Fig. 3).

Determinants of cardiac events. Table 3 lists the variables found to be independent predictors of cardiac events during the follow-up according to Cox univariate analysis. In multivariate analysis using a backward stepwise procedure, a final model was selected (chi-square 18.8, p < 0.0001) including as predictive variables 1) the number of viable asynergic segments not submitted to revascularization (p < 0.0002, risk ratio [RR] = 1.4, 95% confidence interval [CI] = 1.19–1.65) and 2) the coronary artery jeopardy score (p < 0.02, RR = 1.28, 95% CI = 1.05–1.55). As shown in Figure 4, a significantly worse survival curve was observed in the patients with more than three viable asynergic segments not submitted to revascularization compared to those with one to three nonrevascularized viable segments and to those with complete revascularization of all viable asynergic segments.

DISCUSSION

Sestamibi and viability. It has been convincingly shown that sestamibi can be a valuable viability tracer, if SPECT imaging with uptake quantification is performed (17,20). Furthermore, both we and others demonstrated that sestamibi injection during nitrate administration could improve its accuracy in viability recognition (18,19,21). So far, however, no data were available about the possible prognosis implications of viability detection using sestamibi. In our study, we examined the relationship between viability in asynergic regions demonstrated using baseline-nitrate sestamibi SPECT and the outcome of CAD patients with LV dysfunction and treated with different therapeutic strategies. According to our results, the extent of viable asynergic myocardium not submitted to revascularization was a powerful predictor of subsequent events.

Comparison with previous studies. This study confirms previous reports that correlated myocardial viability and treatment strategy with the prognosis of CAD patients with LV dysfunction. Using positron emission tomography,

Table 2. Demographic, Clinical, Angiographic and Treatment Data of the Patients With Events Versus Those Without Events During the Follow-up

|	Events (n = 18)	No Events (n = 87)	p Value
Age (yrs)	64.3 ± 10.2	59.8 ± 10.6	NS
Male gender	78%	93%	NS
Myocardial infarction	72%	88%	NS
Angina	44%	46%	NS
CCS angina classification	1.4 ± 0.5 [1]	1.2 ± 0.4 [1]	NS
NYHA functional class	1.8 ± 0.5 [2]	1.4 ± 0.6 [1]	< 0.01
LVEF (%)	29.2 ± 7.9	34.9 ± 9.2	< 0.03
Diseased vessels (n)	2.3 ± 0.7 [2]	2.1 ± 0.8 [2]	NS
Coronary artery jeopardy score	7.5 ± 2.3 [7]	6.1 ± 2.7 [6]	< 0.05
Asynergic segments	8.7 ± 3.6 [9]	7.7 ± 2.8 [7]	NS
Viable asynergic segments	5.8 ± 3.1 [6]	4.4 ± 2.5 [4]	< 0.05
CABG/PTCA	5/5	37/32	NS
Nonrevascularized viable asynergic segments	3.3 ± 3 [2]	1.1 ± 2 [0]	< 0.001

n = number; [ ] = median; (other abbreviations: see text).
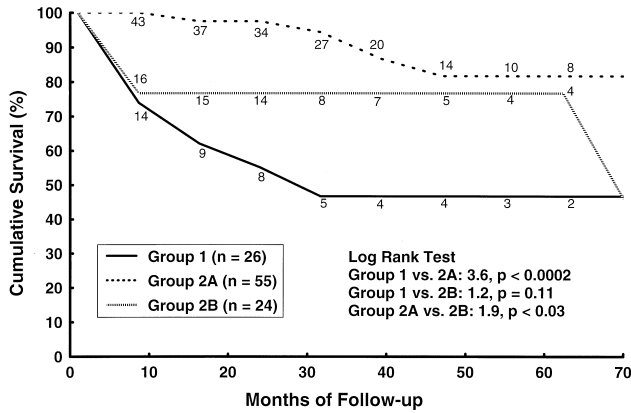
Figure 3. Kaplan-Meier survival curves of the three patient groups identified according to treatment (see text).

Figure 4. Kaplan-Meier survival curves of the three patient groups identified according to the number of viable asynergic segments not submitted to revascularization.

Eitzman et al. (7) and DiCarli et al. (10) registered a 50% and a 41% event rate, respectively, in medically treated patients with signs of preserved viability. Conversely, both the patients without viability and those that had been submitted to coronary revascularization had a clearly better event-free survival. Other investigators (8,9,11) reported similar findings. Using rest-redistribution thallium-201 SPECT, Gioia et al. (12) observed among the patients with viability a significantly worse survival rate (66% vs. 84%) in the medically than in the surgically treated group, and Cuocolo et al. (15) demonstrated that the amount of viable myocardium was the best predictor of cardiac death.

Examining only medically treated patients, Gioia et al. (13) registered a 74% survival rate in patients without redistribution versus 42% in those with redistribution, and Petretta et al. (14) demonstrated that the sum of viable segments in rest-redistribution thallium-201 SPECT was significantly higher in the patients with hard events than in those with soft events or without events. Using low-dose dobutamine echocardiography and comparing patients kept on medical therapy with others who underwent coronary revascularization, Afridi et al. (16) registered a significantly lower mortality in patients with evidence of viability and subsequent revascularization than in all other groups.

The role of revascularization completeness. Another observation of this study was that patients with viable myocardium submitted to an incomplete revascularization procedure still represent a high-risk group, with an event-free survival not significantly different from that of medically
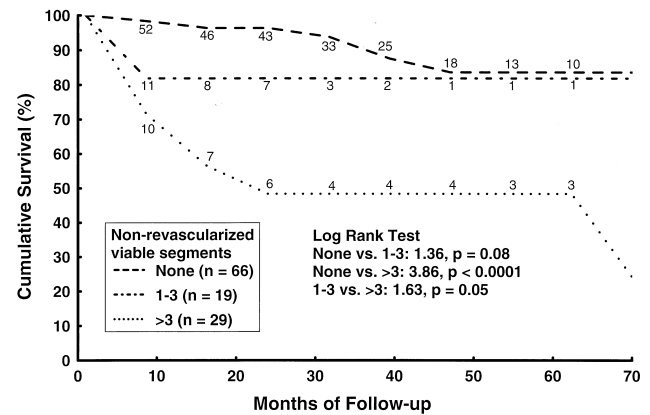
treated patients and clearly worse compared to those who underwent complete revascularization.

Various reports had already demonstrated a better prognosis after complete revascularization in patients submitted to CABG because of anginal symptoms, particularly if they had three-vessel CAD and LV dysfunction (25–27). So far, however, the issue has not been examined in patients in whom LV dysfunction is the main indication to CABG, and in such patients the superiority of surgery over medical therapy is still debated (28). More intricate is the problem of revascularization completeness using PTCA. Comparative studies suggest that PTCA may be an attractive alternative to CABG also in patients with multivessel CAD (29). The BARI study demonstrated a significant superiority of CABG over PTCA only in diabetic patients (30). Most recently, Bourassa et al. (31) reported that nine-year survival in multivessel CAD patients treated using PTCA was not compromised by an incomplete revascularization, which only determined a higher incidence of later CABG. None of these studies, however, focused on viability, and few data area viable in anginal patients with depressed LV function. Holmes et al. (32) suggested that PTCA achieves fairly good results in these patients. Faxon et al. (33) reported that incomplete revascularization was related to a worse prognosis only if segments with some degree of preserved wall motion were left untreated. Thus, considering the higher surgical risk in patients with depressed LV function, incomplete revascularization could be considered a reasonable achievement in many multivessel CAD patients. In this

Table 3. Predictors of Future Cardiac Events According to Univariate Cox Analysis

Variable	Chi-square	Risk Ratio	95% Confidence Interval	p Value
Nonrevascularized viable asynergic segments	12.3	1.34	1.15–1.55	< 0.0005
Completeness of revascularization (%)	8.9	0.98	0.97–0.99	< 0.003
NYHA functional class	6.6	2.78	1.28–6.04	< 0.02
Presence of complete revascularization	6	0.29	0.10–0.83	< 0.02
LVEF	5.9	0.93	0.89–0.98	< 0.02
Age	4.3	1.05	1–1.1	< 0.05
Coronary artery jeopardy score	3.9	1.18	1–1.4	< 0.05

scenario, the results of our study might be of interest because they suggest that, similarly to diabetic patients, the subjects with depressed LV and preserved viability also constitute a subset of patients who badly tolerate an incomplete revascularization procedure.

Study limitations. As for most reports on the same topic, the principal limitation of the present one is the study design, which was based on the retrospective evaluation of a patient cohort submitted to viability assessment, without randomization of the subsequent treatment. Although many clinical and instrumental parameters were not significantly different between the various treatment groups in our series, other variables could have biased the choice of the therapeutic option and, in the case of revascularization, the decision about the extent of the procedure. In particular, it cannot be excluded that concern for the high operative risk had led the referring physician to avoid revascularization or to limit its extent in patients with more severe CAD and LV dysfunction, therefore partly explaining the higher event rate of group 1 and group 2B patients. However, it must be considered that the already recognized value of viability detection should have encouraged us to perform a complete revascularization in patients with a positive imaging study, and this circumstance would increase the significance of our data. Another point is the possible concomitant presence of inducible ischemia as major determinant of adverse outcome. This problem was not explicitly accounted for in the study design, and its influence cannot be confidently assessed in our population. It must be considered, however, that in our hospital the current policy is to send to a viability study only those patients in whom there is no clear-cut evidence of inducible ischemia or in whom myocardial ischemia is difficult to identify—for instance, because of uninterpretable electrocardiogram or contraindications to stress testing.

Conclusions and clinical implications. The results of the present study confirm that detection of viable myocardium has an adverse prognostic meaning if the related coronary obstruction is not corrected by revascularization. Of course, the high hazard of revascularization in patients with LV dysfunction must be considered, although recent data suggest a relatively lower operative risk in patients with greater proportion of viable myocardium (34). Once the decision or revascularization has been taken, however, the completeness of the procedure should be a straightforward goal. Nevertheless, many different circumstances might justify the choice of an incomplete approach as an acceptable solution. With regard to this point, the results of the present study strongly support the option of always pursuing a complete procedure, even when confronting higher costs and greater patient discomfort, and possibly even despite higher risks. This conclusion, if confirmed by other, possibly prospective, studies, could have important consequences on the management of CAD patients with LV dysfunction.

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