JACC Vol. 31, No. 5
April 1998:1002–10

Biphasic Response to Dobutamine Predicts Improvement of Global Left Ventricular Function After Surgical Revascularization in Patients With Stable Coronary Artery Disease

Implications of Time Course of Recovery on Diagnostic Accuracy

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Objectives. **This study sought to evaluate the time course of improvement of left ventricular (LV) dysfunction in stable patients and its implications on the accuracy of dobutamine echocardiography for predicting improvement after surgical revascularization.**

Background. **Little is known about the optimal timing for evaluation of postrevascularization recovery of the contractile function of viable myocardium.**

Methods. **Sixty-one patients with chronic ischemic LV dysfunction scheduled for elective surgical revascularization were prospectively selected. They underwent dobutamine echocardiography (5 to 40 μg/kg body weight per min) and radionuclide ventriculography both preoperatively and at 3-month follow-up. At 14 months, another evaluation of LV function was obtained. To analyze echocardiograms, a 16-segment model and a five-point scoring system were used. Dyssynergic segments were considered likely to recover in the presence of a biphasic contractile response to dobutamine. Improvement of global function was defined as a ≥5% increase in LV ejection fraction (LVEF).**

Results. **Of the 61 patients, LVEF improved in 12 at 3 months and in 19 at late follow-up (from 32 ± 8% to 42 ± 9%, $p < 0.0001$). The frequency and time course of improvement of LVEF were similar in patients with mild and severe LV dysfunction. A biphasic response, identified in 186 of the 537 dyssynergic segments, was predictive of recovery in 63% at 3 months and in 75% at late follow-up. The positive predictive value was best in the most severe dyssynergic segments (90% vs. 67%). Other responses were highly predictive for nonrecovery (92%). The sensitivity and specificity for improvement of global function on a patient basis (≥4 biphasic segments) were 89% and 81%, respectively, at late follow-up.**

Conclusions. **Serial postoperative follow-up studies demonstrate incomplete recovery of contractile function at 3 months. The diagnostic accuracy of dobutamine echocardiography for predicting recovery is dependent on three factors: the combining of low and high dobutamine dosages, the severity of regional dyssynergy and the timing of evaluation.**

(J Am Coll Cardiol 1998;31:1002–10)

Coronary artery bypass graft surgery (CABG) can improve symptoms, prognosis and left ventricular (LV) function in selected patients (1). The noninvasive identification of myocardial regions with a high and low probability of functional improvement after revascularization is crucial to the decision to perform revascularization procedures in individual patients with multiple, severe wall motion abnormalities (2). Because the presence of viable myocardium favorably influences prognosis after revascularization (3–6), these procedures may even serve as an attractive alternative to heart transplantation.

The contractile response of dyssynergic regions to "low dose" dobutamine in conjunction with echocardiography has been proposed as a simple method for the assessment of residual viable myocardium capable of recovering its contractile function, both spontaneously in patients early after myocardial infarction (7–11) and after revascularization in patients with stable, chronic ischemic heart disease (12–20). Recent data suggest that jeopardized myocardium—a combination of myocardial viability and inducible ischemia—is more likely to recover after revascularization than viable myocardium that is not in jeopardy (16). However, all previous studies using dobutamine echocardiography have been limited by the lack of an independent method to verify changes in ventricular function (12–20).

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Manuscript received June 5, 1997; revised manuscript received December 31, 1997, accepted January 13, 1998.

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Published by Elsevier Science Inc.

0735-1097/98/$19.00
PII S0735-1097(98)00067-9

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CI = confidence interval
ECG = electrocardiogram, electrocardiographic
LV = left ventricular
LVEF = left ventricular ejection fraction

The accuracy of predicting recovery of contractile function after revascularization may depend on several factors, such as the response to dobutamine both at low and high doses (16) and the severity of baseline segmental dysfunction (11,15). Furthermore, it is unclear what the optimal timing is, to evaluate recovery of contractile function after revascularization. Given the severity of structural changes observed in hibernating myocardium (21–23), it is likely that recovery of function after revascularization is delayed for several months.

Therefore, we designed a prospective study to evaluate 1) the accuracy of dobutamine echocardiography to predict recovery of regional and global LV dysfunction after successful CABG in patients with a wide range of chronic LV dysfunction; and 2) the time course of functional improvement after CABG using both serial echocardiographic and radionuclide ventriculographic studies, thus defining the optimal timing to determine the diagnostic value of dobutamine echocardiography in this clinical setting.

Methods

Patient enrollment. From January 1993 to April 1995, all patients with coronary artery disease and LV dysfunction at rest who were scheduled to undergo CABG at the Thoraxcenter were screened for enrollment in the study. The study protocol was approved by the Institutional Review Board. Inclusion criteria included symptoms of stable coronary artery disease, previous acceptance for elective surgical revascularization, LV ejection fraction (LVEF) <50% on contrast ventriculography and one or more abnormal contractile segments on the preoperative (<3 weeks before operation) rest echocardiogram (16-segment left ventricular [LV] model). Furthermore, a subsequent uneventful surgical revascularization procedure was required to proceed with the protocol. Exclusion criteria included unstable angina, recent myocardial infarction (<3 months), significant (>50%) left main stem stenosis, (hemodynamically) significant valvular disease, poor echocardiographic quality or the inability to obtain written, informed consent. Of the 89 preoperative, eligible patients, 28 were excluded. The reasons for exclusion were resection of infarcted areas in addition to myocardial revascularization in 13 patients, perioperative death in 6 (7%), perioperative nonfatal myocardial infarction in 2, poor echocardiographic quality in 3, inability to obtain written, informed consent in 2, death on the waiting list for the operation in 1 and death early in the follow-up period (at 10 weeks) in 1. Of the patients who died perioperatively, two deaths were due to pump failure and four were due to perioperative myocardial infarction. Of the 61 patients finally included in the present study, 5 (8%) underwent CABG as an alternative to heart transplantation.

Study protocol. Each patient underwent low and high dose dobutamine stress echocardiography and radionuclide ventriculography within 3 weeks before the operation. All patients underwent uneventful, isolated CABG (by definition). The decision to revascularize was based on clinical criteria. The results of the dobutamine stress echocardiographic and radionuclide studies were withheld from the physicians managing the patients. Adequate revascularization of a dyssynergic segment was considered achieved if, on review of the operative report and preoperative coronary arteriogram, bypass grafts were placed on the stenotic major branches supplying the dyssynergic segments. After the operation, patients were followed up to a maximum of 19 months. At the 3-month follow-up visit, both rest and low and high dose dobutamine stress echocardiography and rest radionuclide ventriculography were repeated. At 14-month follow-up, two-dimensional rest echocardiography and radionuclide ventriculography (for the third time) were performed.

Dobutamine stress echocardiography. Before the test, patients were asked to discontinue beta-blockers for 36 h. All other cardiac medications (e.g., calcium antagonists, nitrates and angiotensin-converting enzyme inhibitors) were continued. The dobutamine stress test was performed as follows: a two-dimensional transthoracic echocardiogram in standard views and a 12-lead electrocardiogram (ECG) were recorded with the patient at rest. Dobutamine was infused through an antecubital vein at dosages of 5 and 10 μg/kg body weight per min for 5 min at each dose (these two steps were considered as "low dose"). Subsequently, three other steps from 20 to 40 μg/kg per min (3 min each) were added. Finally, atropine (up to 1 mg) was injected when 85% of the predicted maximal (men [220 − age] × 85%, women [200 − age] × 85%) heart rate had not been reached (24). A three-lead ECG was monitored continuously, and a 12-lead ECG was recorded every minute. Cuff blood pressure was measured at each stage. The test was interrupted prematurely if 85% of the predicted maximal heart rate was reached or if severe chest pain, ST segment deviation >2 mm, significant ventricular or supraventricular arrhythmia, systolic blood pressure fall >40 mm Hg or any other intolerable side effect occurred during the test.

The echocardiogram was monitored throughout the test, and the last minute of each stage, including recovery, was recorded on videotape. The echocardiographic images were also digitized on optical disk (Vingmed CFM 800) or on floppy disk (Esaote Biomedica SIM 7000) and displayed side by side in quad screen format to facilitate the comparison of images at rest and at various stages of the test.

Analysis of echocardiograms. The interpretation of echocardiograms was done by two experienced observers who had no knowledge of the clinical, radionuclide, angiographic and previous echocardiographic results of the individual patients. In case of disagreement, a third observer reviewed the study and a majority decision was attained. The assessment was

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based on both the digitized images displayed in a quad screen format and a review of the images recorded on the videotape. For analysis of wall motion, the left ventricle was divided into 16 segments, as recommended by the American Society of Echocardiography (25). The wall motion, including wall thickening, of each segment was semiquantitated using a five-point scoring system: 1 = normal wall motion and thickening; 2 = mildly hypokinetic; 3 = severely hypokinetic; 4 = akinetic; and 5 = dyskinetic. We defined a segment as severely hypokinetic in the presence of minimal wall thickening with very limited inward motion (during the first half of systole); as akinetic in the absence of systolic wall motion and thickening, confirmed by M-mode echocardiographic tracing whenever possible; and as dyskinetic in the presence of systolic outward motion with thinning. Wall thickening was primarily utilized for the classification of wall motion, preventing the problem of postoperative paradoxic septal motion. Also, to reduce the confounding effect of tethering from adjacent segments, segmental wall thickening was analyzed only during the first half of systole.

During dobutamine infusion, abnormally contracting segments at rest were classified into four different patterns of contractile response: biphasic, defined as improvement at low dose and worsening at peak stress; sustained improvement, defined as improvement at low dose without further deterioration at peak stress; worsening, defined as direct worsening with no improvement at any stage; and no change, defined as unchanged wall motion abnormality throughout the test.

We previously reported a low level of interobserver and intraobserver variability for the classification of rest wall motion (agreement 84% and 87%, respectively) and the response to low dose dobutamine (agreement 92% and 94%, respectively) in a comparable patient group (15).

Myocardial ischemia was judged to be present when there was worsening of the segmental score by ≥1 (in normally contracting segments or dyssynergic segments showing worsening or a biphasic response). As previously reported, ischemia was not considered when akinetic segments at baseline became dyskinetic at stress without improvement during low dose dobutamine infusion (26).

Follow-up echocardiograms were compared with the correspondent preoperative rest images. The observers had no knowledge of the preoperative dobutamine results. For each segment, functional postoperative recovery was defined as a decrease of one or more grades. A change from dyskinetic to akinetic was not considered to be improved contractile function.

Radionuclide ventriculography. Equilibrium radionuclide ventriculography was performed at rest with the patient in the supine position after intravenous administration of 555 MBq of technetium-99m. Images were acquired with a small field of view gamma camera (Orbiter, Siemens Corp.) oriented in the 45° left anterior oblique position with a 5° to 10° caudal tilt. The LVEF was calculated by an automated technique. Improvement of global LV function after revascularization was defined as an increase in LVEF by at least five points (e.g., from 30% to 35%). This cutoff was chosen because it is higher than 2 SD of the interobserver and intraobserver variability of the measurements of the radionuclide LVEF in our laboratory.

Statistical analysis. Age, number of stenotic coronary arteries, LVEF, heart rate and systolic blood pressure are expressed as the mean value ± SD. Differences within continuous variables over time were evaluated by analysis of variance for repeated measures or by the paired Student *t* test when appropriate. Stepwise logistic regression models were fitted to identify independent predictors of improvement of LVEF 14 months after revascularization; the variables tested were age, gender, previous CABG, previous infarction, diabetes mellitus, hypertension, vessel disease, presence of collateral circulation, LVEF before revascularization, preoperative medication and response during dobutamine infusion. Significance for all tests was set at $p = 0.05$. Sensitivity, specificity and positive and negative predictive values rely on the standard definition and are reported with the 95% confidence intervals (CI).

Results

Patients. A total of 61 patients were included in the study (mean age 61 years [range 43 to 77], 49 men and 12 women). All patients were symptomatic, 57 had angina pectoris (29 in New York Heart Association functional class II, 28 in class III) and 29 had dyspnea on effort (26 in functional class II, 3 in class III). Fifty-nine patients had a history of myocardial infarction (median 24 months before study [range 4 to 210]). The mean number of significantly stenosed coronary arteries was 2.7 ± 0.5, and the mean LVEF was 33% (range 17% to 49%). The baseline characteristics of the study group, stratified into two groups according to LVEF (>35% vs. ≤35%), are summarized in Table 1. Medication taken by patients before versus after revascularization included angiotensin-converting enzyme inhibitors in 40 versus 40 patients, respectively, beta-adrenergic blocking agents in 44 versus 41, nitrates in 50 versus 10, calcium antagonists in 41 versus 20 and diuretic agents in 18 versus 20.

Baseline characteristics. Of a total of 976 myocardial segments, 19 were not adequately visualized by echocardiography and 28 were not revascularized. Therefore, 929 segments were available for serial analysis. Abnormal rest wall motion was seen in 537 segments (58%). Mild hypokinesia was observed in 240 segments; 82 segments were severely hypokinetic; 205 were akinetic; and 10 were dyskinetic.

Clinical and functional postoperative outcome. Three months after revascularization, only 3 patients had angina pectoris and 13 had dyspnea on effort (all in functional class II). At late follow-up (median 14 months [range 11 to 19]), two patients suffered from angina pectoris and 14 had dyspnea on effort (all in functional class II).

At 3 months, 136 (25%) of the 537 dyssynergic and revascularized segments showed recovery of wall motion at rest, as assessed with rest echocardiography. Recovery was observed in 67 of 240 mildly hypokinetic, 35 of 82 severely hypokinetic, 32 of 205 akinetic and 2 of 10 dyskinetic segments. At late follow-up, an additional 33 segments (25 mildly hypokinetic, 4

Table 1. Characteristics of Entire Study Group According to Left Ventricular Ejection Fraction

	LVEF >35% (n = 22)	LVEF ≤35% (n = 39)
Men/women	16/6	33/6
Age (yr)	61 ± 8	60 ± 9
Hypertension	10 (45%)	9 (23%)
Diabetes mellitus	4 (18%)	7 (18%)
Previous CABG	3 (14%)	3 (8%)
Old MI	21	38
Q wave/non–Q wave MI	14/7	33/5
Angina pectoris	20 (91%)	37 (95%)
Effort dyspnea	5 (23%)	24 (62%)
Coronary arteriography	22	39
3-vessel disease	14 (64%)	29 (74%)
2-vessel disease	7 (32%)	9 (23%)
1-vessel disease	1 (5%)	1 (3%)
LVEF (%)	41 ± 4	28 ± 5
Dyssynergic segments	151 (45%)	386 (65%)
Mild hypokinesia	78	162
Severe hypokinesia	9	73
Akinesia/dyskinesia	64	151
Biphasic response	55	131

Data presented are number (%) of patients or segments or mean value ± SD. CABG = coronary artery bypass graft surgery; F = female; LVEF = left ventricular ejection fraction; M = male; MI = myocardial infarction.

severely hypokinetic and 4 akinetic segments) showed recovery of contractile function, resulting in a total of 169 segments (31%) that showed recovery of contractile function late after revascularization. Furthermore, eight severely hypokinetic or akinetic segments, already recovered at 3 months, showed further improvement at late follow-up. Thus, functional recovery was found more frequently in mildly or severely hypokinetic than in akinetic/dyskinetic segments (41% vs. 19%, $p < 0.001$). The timing of recovery was not delayed in segments showing the most severe wall motion abnormalities. At 3 months, recovery was already complete in 81% of the severely hypokinetic or akinetic/dyskinetic segments, compared with 73% of the mildly hypokinetic segments. Deterioration of rest wall motion was noted in 8 (29%) of the 28 nonrevascularized dyssynergic segments, in 35 (7%) of the 537 revascularized dyssynergic segments at 3 months and in 47 (9%) of the 537 at late follow-up. Of these 47 segments, 29 were ischemic during dobutamine infusion before revascularization.

At 3 months, 12 patients showed a ≥5% improvement in LVEF. At late follow-up, an additional seven patients improved, resulting in a total of 19 with improvement (Fig. 1). Thirteen of these patients had a preoperative LVEF ≤35%. Figure 1 depicts the functional outcome in patients stratified according to LVEF. It appears that frequency and time course of improvement of LVEF are similar in patients with mild and severe LV dysfunction. Figure 2 shows the magnitude and time course of improvement of global LV function in the individual 19 patients with improvement at late follow-up. The LVEF increased from 32 ± 8% to 37 ± 12% at 3 months and to 42 ± 9% at late follow-up ($p < 0.0001$). For the entire study group, LVEF did not change significantly (from 33 ± 8% to 35 ± 10%).

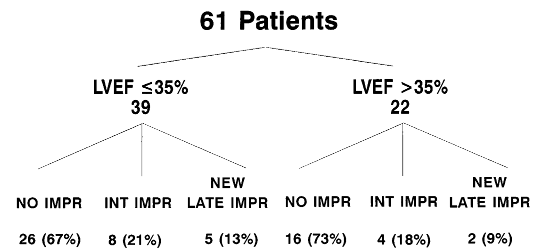
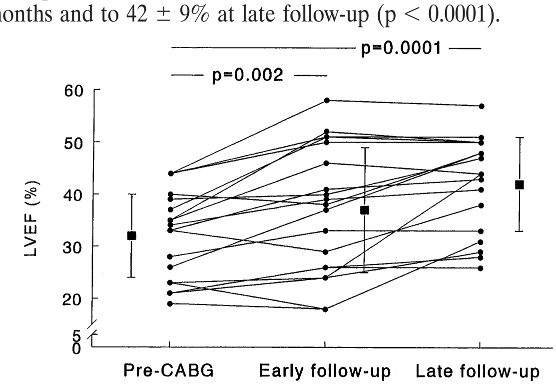


Figure 1. Diagram demonstrating the frequency and timing of postoperative improvement of LVEF of ≥5% in patients with a preoperative LVEF ≤35% versus >35%. NO IMPR = no improvement; INT IMPR = improvement at 3 months; NEW LATE IMPR = late improvement between 3 months and 1 year.

Results of dobutamine stress echocardiography. No serious complications occurred during the test. Heart rate increased from 71 ± 13 beats/min at rest to 136 ± 14 beats/min at peak stress ($p < 0.0001$). Systolic blood pressure did not change significantly (127 ± 18 mm Hg at rest to 125 ± 22 mm Hg at peak stress). Heart rate but not systolic blood pressure increased significantly with low dose dobutamine, compared with baseline values (83 ± 19 beats/min and 126 ± 20 mm Hg, respectively). Five patients were taking beta-blockers during the preoperative dobutamine stress test. Forty-five patients received the maximal 40-μg/kg per min dose of dobutamine. Atropine was administered to 28 patients. Angina occurred in 40 patients (66%), and ST segment deviation in 40 patients (66%). The reasons for termination of the test were angina (n = 39), attainment of >85% maximal heart rate (n = 20) with or without signs of myocardial ischemia, wall motion abnormalities (n = 1) and hypotension (n = 1).

Myocardial ischemia was demonstrated in 343 (37%) of 929 segments: in 100 normally contracting, 159 mildly hypokinetic, 53 severely hypokinetic and 31 akinetic segments. Myocardial ischemia was detected in 60 patients, with a mean of 5.9 segments per patient. Inducible myocardial ischemia de-

Figure 2. Graph showing the time course of improvement of LVEF after CABG in the 19 patients who significantly improved at late follow-up. The mean LVEF increased from 32 ± 8% to 37 ± 12% at 3 months and to 42 ± 9% at late follow-up ($p < 0.0001$).



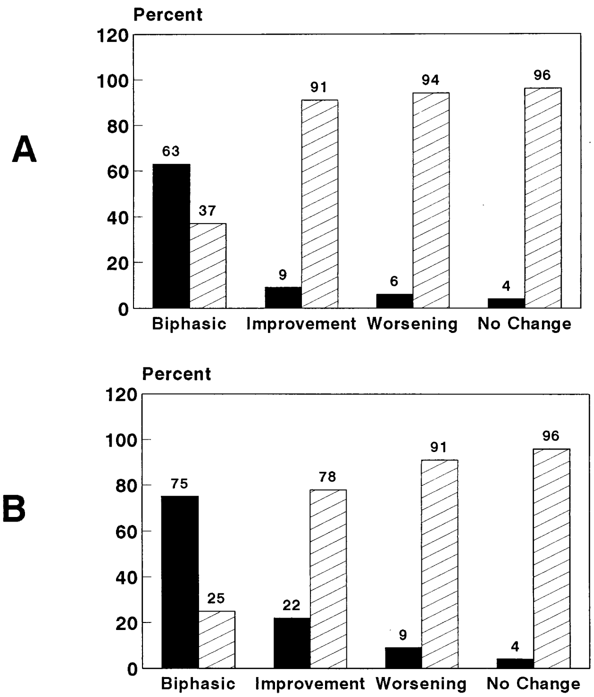


Figure 3. Bar graph demonstrating prediction of recovery of regional ventricular function 3 months (**A**) and 14 months (**B**) after surgical revascularization related to the different types of responsiveness to dobutamine infusion preoperatively. **Solid bars** = recovery (%); **hatched bars** = no recovery (%).

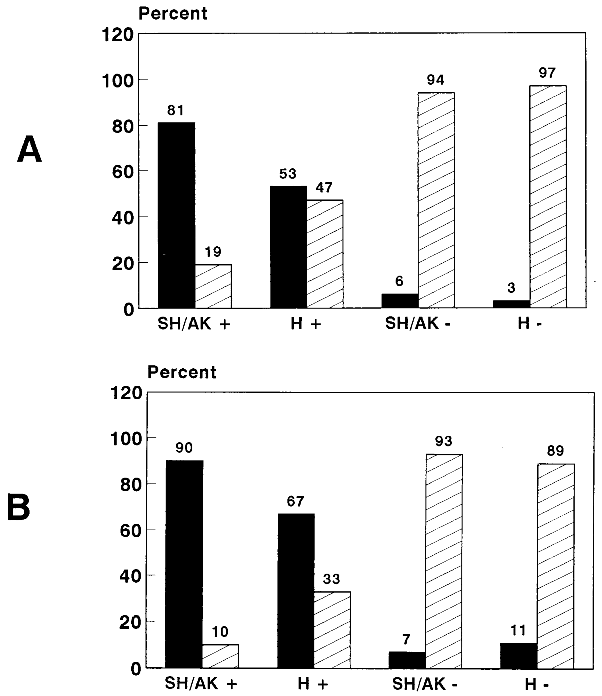


Figure 4. Bar graph demonstrating prediction of recovery of regional ventricular function 3 months (**A**) and 14 months (**B**) after surgical revascularization, related to the preoperative degree of wall motion abnormality and different types of responsiveness to dobutamine infusion. SH/AK+ = severely hypokinetic or akinetic segments with a biphasic response; SH/AK− = severely hypokinetic or akinetic segments without a biphasic response, including sustained improvement; H+ = mildly hypokinetic segments with a biphasic response; H− = mildly hypokinetic segments without a biphasic response. Symbols as in Figure 3.

creased significantly after the operation from 343 to 20 segments ($p < 0.0001$, ≥2 segments in five patients).

Of a total of 537 revascularized segments with abnormal wall motion, 186 (35%) segments exhibited a biphasic response, 58 (11%) demonstrated sustained improvement, 68 (12%) showed worsening (without improvement), and 225 (42%) showed no change in regional wall motion during dobutamine challenge.

Predictive accuracy of dobutamine stress echocardiography for functional recovery. The different types of response to dobutamine infusion in relation to the functional outcome of all dyssynergic segments after revascularization at 3 months and at late follow-up are depicted in Figure 3.

At 3 months, 118 (63%) of 186 segments with a biphasic response showed recovery of wall motion, whereas the other three patterns were not predictive of functional recovery. At late follow-up, 140 (75%) of 186 segments with a biphasic response showed recovery of wall motion. Also, segments with sustained improvement showed a trend toward recovery at late follow-up (22%). When considering only the low dose phase, a positive inotropic response (n = 244) showed a positive predictive value of 63% for recovery at late follow-up. This underscores the added value of the biphasic pattern in predicting functional recovery. Assuming a biphasic response as indicative of recovery and the other three predefined patterns as indicative of no recovery, the sensitivity, specificity and positive and negative predictive values for functional recovery are 87% (95% CI 81% to 93%), 83% (95% CI 79% to 87%), 63% (95% CI 56% to 70%) and 95% (95% CI 93% to 97%) at 3-month follow-up and 83% (95% CI 77% to 89%), 88% (95% CI 85% to 91%), 75% (95% CI 69% to 81%) and 92% (95% CI 89% to 95%), at late follow-up, respectively.

Figure 4 shows the influence of severity of segmental LV dysfunction at baseline on the predictive value of dobutamine echocardiography and the timing of the follow-up study. It clearly demonstrates a much less accurate prediction of functional recovery in mildly hypokinetic segments compared with severely hypokinetic/akinetic segments. In addition, it shows that the positive predictive value improves when late follow-up is considered (mild hypokinesia: 67% [95% CI 59% to 75%] vs. 53% [95% CI 44% to 62%]; severe hypokinesia/akinesia: 90% [95% CI 83% to 97%] vs. 81% [95% CI 72% to 90%]). At late follow-up, both the specificity (74% [95% CI 67% to 81%] vs. 97% [95% CI 95% to 99%]) and positive predictive value (67% [95% CI 59% to 75%] vs. 90% [95% CI 83% to 97%]) were significantly better in segments with the most severe wall motion abnormalities at baseline. In contrast, neither the sensitivity (86% [95% CI 79% to 93%] vs. 79% [95% CI 70% to 88%]) nor negative predictive value (89% [95% CI 84% to 94%] vs. 93% [95% CI 90% to 96%]) differed significantly

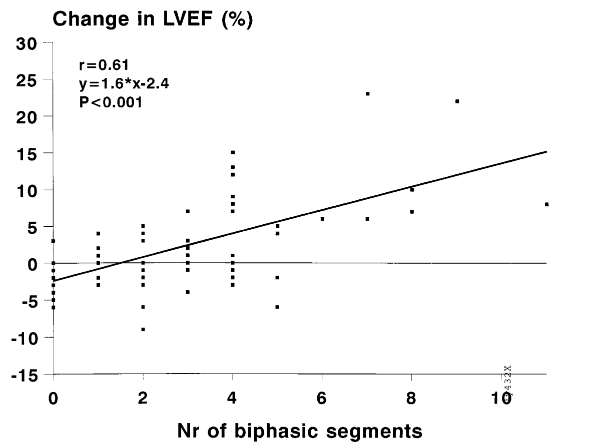


Figure 5. Postoperative change in LVEF at late follow-up, related to the number (Nr) of segments with a biphasic response in 61 patients.

between mildly hypokinetic and severely hypokinetic/akinetic segments.

To provide more insight into the relation between the number of segments showing a biphasic response per patient and the magnitude of change in LVEF at late follow-up, linear regression analysis was performed (Fig. 5). It showed that most patients (17 of 25) with four or more jeopardized but viable segments had improved global LV function after revascularization (r = 0.61).

The sensitivity and specificity for the detection of functional improvement of global LV function (≥5% increase of LVEF) at late follow-up were determined in all patients and in two subsets with either somewhat preserved or diminished LV function (Table 2). In patients with ≤35% LVEF, the diagnostic accuracy of the test seems similar compared with that in the patients with mild LV dysfunction (positive predictive value 63% vs. 71%; negative predictive value 93% vs. 95%).

Univariate analysis identified the preoperative use of beta-blockers and a global biphasic response during dobutamine infusion as the only predictors of improvement of LVEF at late follow-up. Multivariate analysis showed that a global biphasic response was the only independent predictor.

Discussion

Few studies have addressed the time course of recovery of contractile function of chronically dysfunctional myocardium after successful revascularization (27,28). In the present study, we have tried to evaluate potential factors that may influence the diagnostic accuracy of dobutamine stress echocardiography in predicting the effects of revascularization on contractile function in patients with chronic ischemic LV dysfunction. Radionuclide ventriculography was used to verify changes in global LV function. The main findings are as follows:

Table 2. Sensitivity and Specificity for the Presence of Four or More Segments With a Biphasic Response on the Preoperative Dobutamine Echocardiogram to Predict ≥5% Improvement in Left Ventricular Ejection Fraction Late After Revascularization

	Sensitivity	Specificity
All pts (n = 61)	89% (17/19)	81% (34/42)
Pts with LVEF ≤35% (n = 39)	92% (12/13)	81% (21/26)
Pts with LVEF >35% (n = 22)	83% (5/6)	81% (13/16)

LVEF = left ventricular ejection fraction; Pts = patients.

1. In one-third of our patients, as well as in the subset with ≤35% LVEF, global LV function significantly improved after revascularization. Serial postoperative follow-up studies demonstrated gradual improvement with incomplete improvement at 3 months. The frequency and time course of improvement of LVEF were similar in patients with mild and severe LV dysfunction.
2. This study confirms that a biphasic response to dobutamine is highly predictive of postoperative recovery of regional contractile function (75% at late follow-up). The other patterns of dobutamine responsiveness are predictors of nonrecovery (92% at late follow-up). The diagnostic accuracy of dobutamine responsiveness is best in segments with the most severe wall motion abnormalities at baseline, reaching sensitivity, specificity and positive and negative predictive values of 79%, 97%, 90% and 93%, respectively.
3. Dobutamine stress echocardiography in the aforementioned clinical setting, including segments with mild dysfunction, has a sensitivity of 89% and a specificity of 81% to predict a ≥5% improvement in LVEF.

All previous studies using dobutamine echocardiography have also used echocardiography to assess recovery of wall motion, without an independent technique to verify these data (12–20,29). In the present study, we have circumvented this shortcoming by using serial radionuclide ventriculographic studies for the assessment of changes in global LV function. Our study is unique in that it reports the effects of sequential follow-up studies on the diagnostic accuracy of the test for postrevascularization improvement of both regional and global LV function. Furthermore, this study adds to the accumulating evidence that high dose dobutamine stress testing, even with the addition of atropine, can be performed safely without serious complications in patients with poor LV function (30).

Timing of follow-up. The optimal timing for the assessment of functional recovery after revascularization is essential for the correct interpretation of the diagnostic accuracy of a given test. Currently, functional follow-up studies in chronic coronary artery disease are performed within 3 months after the revascularization procedure (12,14–20,29,31). In individual patients all types of reversible and irreversible contractile dysfunction may coexist, including repetitive myocardial stunning and hibernation. However, chronic ischemic myocardium does not represent a uniform morphologic appearance, but varies from slight changes to severe ultrastructural damage (23). In addition, the degree of damage does not correlate with the severity of the wall motion abnormalities (23). Nonetheless, myocardium with severe ultrastructural changes (21,22) is likely to show delayed recovery of contractile function after revascularization. Therefore, because a time dependence of structural remodeling is likely, recovery may appear gradually (28), and its completion should not be expected before 4 to 8 months after revascularization in patients with chronic coronary artery disease. Our data support these concepts, because 7 of the 19 patients with improvement at late follow-up did not show improvement of global LV function at 3 months. Such delayed improvement after CABG has been described earlier (27,28,32) and underlines the importance of late follow-up studies after revascularization procedures in this clinical setting.

A similar time course of improvement of LVEF was found in patients with mild and severe LV dysfunction. This is not surprising, because it has been reported that the severity of LV dysfunction is not correlated with the degree of ultrastructural damage (23).

Biphasic response. Several studies, experimental or clinical, using a head to head comparison between dobutamine stress echocardiography and myocardial perfusion scintigraphy, describe a relation between a biphasic response to dobutamine and myocardial scintigraphic ischemia (33–35). This relation can be explained by the presence of viable tissue in a dyssynergic segment subtended by a critically stenotic coronary artery, exhibiting an inotropic response to low dose dobutamine and ischemia at high dose dobutamine provoked by the increased rate–pressure product and flow maldistribution. In the present study, the majority of segments demonstrating such a biphasic response recovered in contractile function after revascularization. Our findings are in accordance with data reported by Afridi et al. (16). Reversible, chronic ischemic LV dysfunction is associated with ultrastructural alterations, including minimal fibrosis, loss of myofilaments and an accumulation of intracellular glycogen (21,23,36). These morphologic changes have been correlated with recruitable inotropic reserve, perfusion–metabolism mismatch and nearly normal absolute myocardial blood flow in combination with reduced coronary flow reserve (36,37). Repetitive stunning as an alternative to myocardial hibernation has been postulated to explain these findings. It is likely that after successful revascularization, high energy phosphate stores are ensured through adequate myocardial perfusion at rest and during stress. Under these circumstances, by rebuilding cellular contractile material, dyssynergic myocardium may recover over time.

Other responses to dobutamine challenge. In dyssynergic segments demonstrating a sustained improvement during dobutamine, it is likely that there is sufficient coronary flow and metabolic reserve to maintain enhanced contractility until the final stage of the test. Functional recovery after revascularization was demonstrated in 22% of these segments. The presence of myocardial stunning without substantial subendocardial fibrosis in segments showing functional recovery could explain the findings. The remaining segments, which did not demonstrate functional recovery, may have contained a mixture of predominantly normal, nonjeopardized myocardium and subendocardial necrosis leading to wall motion abnormalities at rest with preserved inotropic reserve (31). Segments with direct worsening in wall motion during dobutamine challenge rarely recovered after revascularization. It is conceivable that these segments contain a mixture of a considerable amount of scar tissue and some normal myocardium, becoming ischemic during dobutamine infusion. Although Afridi et al. (16) reported a higher recovery rate of these segments (35%), one should bear in mind that in absolute terms this represents only six segments. Finally, the lack of change in wall thickening during dobutamine infusion is a very specific marker for the prediction of a lack of functional recovery after surgical revascularization. This echocardiographic pattern of not responding to dobutamine is therefore in agreement with the diagnosis of scar with no clinically relevant amount of residual viable myocardium. This observation is quite relevant, because it suggests that further tests for the assessment of the potential reversibility of dysfunction in segments with this specific echocardiographic pattern are redundant.

Diagnostic accuracy. Previous studies using low dose dobutamine echocardiography have concentrated on the prediction of regional recovery after revascularization. They show sensitivities ranging from 71% to 97% (weighted mean 85%) and specificities ranging from 63% to 95% (weighted mean 89%) (12,14–20). Our results add to the accumulating evidence that the test is an accurate method for the evaluation of myocardial viability in patients with chronic dysfunctional myocardium due to coronary artery disease. In our study, both the specificity and positive predictive value improved when only severely dyssynergic segments were evaluated, similar to previous studies (14,15,18,31). Mildly hypokinetic segments are likely to contain normal myocardium, subendocardial scar or viable but dysfunctional myocardium, or a combination of these. If relatively little viable tissue is present, hypokinesia is caused by the presence of subendocardial scar, and then dobutamine challenge may stimulate normal myocardium to a hyperkinetic response, simulating a positive test for viability. In contrast, if a substantial amount of viable myocardium is present (without substantial scar tissue), a similar test result may appear. However, only in the latter example should one expect functional recovery to occur after revascularization. False positive tests occur less often in severe dyskinesia, because the presence of normal myocardial tissue is minimal in segments with severe contractile dysfunction.

In the present study we showed that patients with four or more jeopardized but viable segments (25% of the myocardium) are likely to have improved global LV function. The data confirm earlier studies (17,38–42) employing different techniques to assess myocardial viability, and indicate that a substantial amount of viable but jeopardized myocardium needs to be present to result in improved global LV function. This observation implies, if confirmed in larger series, that dobutamine stress echocardiography is a reliable technique to predict functional outcome after revascularization, even in patients with poor LV function.

Study limitations. Incomplete revascularization may prohibit viable segments to recover, thereby underestimating the diagnostic accuracy of a diagnostic technique. Because we did not perform repeat angiography after the operation to assess graft patency, we do not know about the success of coronary revascularization. However, repeat dobutamine stress echocardiographic studies performed 3 months after CABG revealed a decrease in inducible myocardial ischemia from 343 to 20 segments. Because we did not study patients at 6 months, we do not know about the completeness of improvement at 6 months. Therefore, we cannot comment on this issue regarding the optimal timing of follow-up studies for the detection of complete recovery of contractile function after CABG in the aforementioned clinical setting. Detailed and larger studies are needed to answer this question.

Regional wall thickness has not been measured. Normal end-diastolic thickness has been described as marker of myocardial viability and a predictor of recovery after revascularization (43,44). In contrast, dyssynergic segments with severely reduced thickness rarely show recovery of contractile function after revascularization. Further studies are needed to answer the question of what is the additional value of dobutamine challenge on top of wall thickness measurements. In addition, LV volumes may provide important prognostic information (45). Unfortunately, these variables were not assessed in the current study.

Patients with poor LV function may potentially benefit most from myocardial viability studies, given the condition that viability leads to improvement of global LV function. Because only a small number of patients with poor LV function were studied, we cannot draw firm conclusions about the diagnostic accuracy of dobutamine stress echocardiography for the prediction of functional improvement in these patients.

Conclusions. Serial postoperative follow-up studies demonstrate incomplete recovery of contractile function at 3 months. Dobutamine stress echocardiography is a useful method to predict improvement of regional and global LV function after CABG. Its diagnostic accuracy depends on 1) combining low and high doses of dobutamine infusion; 2) the severity of regional dyssynergy; and 3) the timing of evaluation. This study contributes to the increasing clinical experience with dobutamine stress echocardiography in patients with stable ischemic LV dysfunction.

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