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Detection and Clinical Usefulness of a Biphasic Response During Exercise Echocardiography Early After Myocardial Infarction

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OBJECTIVES The aim of this study was to determine the accuracy of exercise echocardiography (EE) for detecting infarct-related artery (IRA) stenosis and predicting functional recovery early after acute myocardial infarction (AMI).

BACKGROUND Dobutamine stress echocardiography is widely used for identifying jeopardized myocardium. The clinical usefulness of a biphasic response detected during EE has never been investigated.

METHODS A total of 114 consecutive patients with a first AMI and ≥2 dyssynergic segments in the infarct-related territory underwent semi-supine continuous EE 6 ± 2 days after AMI. Quantitative coronary angiography was performed in all patients after EE. A follow-up echocardiogram was obtained one month later.

RESULTS Ninety-seven patients had significant (≥50%) IRA stenosis, and 26 had multivessel disease. Residual ischemia was identified in 77 patients (biphasic response in 62 and worsening response in 15). The sensitivity and specificity of ischemia during EE for predicting IRA stenosis were 75% and 76%, respectively. The sensitivity of a biphasic response was higher than the sensitivity of a worsening response (61% vs. 14%, $p < 0.0001$). Wall motion abnormalities induced in other vascular territories were specific (97%) and moderately sensitive (62%) for the detection of multivessel disease. Functional recovery was observed in 75 patients. Two independent variables predicted contractile recovery: contractile reserve during EE ($p < 0.0001$) and elective angioplasty of the IRA ($p = 0.002$). A biphasic response, but not sustained improvement, predicted reversible dysfunction (73% vs. 9%, $p < 0.0001$).

CONCLUSIONS A biphasic response can be detected during exercise. Exercise echocardiography is an accurate tool for detecting IRA stenosis and predicting functional improvement early after AMI. (J Am Coll Cardiol 2003;41:1142–7) © 2003 by the American College of Cardiology Foundation

Predischarge detection of residual ischemia in the infarct zone and in remote zones after acute myocardial infarction (AMI) has prognostic and therapeutic implications (1). In patients with viable, jeopardized myocardium, timely revascularization of the culprit lesion improves left ventricular function and reduces the risk of further cardiac events (2,3). Several noninvasive methods can be performed for detecting viable and ischemic myocardium (4). Pharmacologic stress echocardiography is widely used in this setting. Contractile reserve of viable, akinetic myocardium can be recruited with low-dose dobutamine infusion (5), but also during low-level exercise echocardiography (EE) (6). At high dobutamine doses, jeopardized myocardium in the affected area can be identified by a biphasic response—that is, deterioration of regional thickening after initial improvement (7). The possibility of detecting a biphasic response during exercise and the potential clinical usefulness of this response have never been investigated. This study was undertaken to evaluate EE in detecting significant infarct-related artery (IRA) stenosis and predicting reversible dysfunction after a first AMI.

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METHODS

Study patients. A total of 114 consecutive patients with a first uncomplicated AMI who had at least two dyssynergic left ventricular segments on the baseline echocardiogram were prospectively enrolled in this study. Acute MI was suspected on the basis of chest pain lasting >30 min, with acute ≥1 mm ST-segment deviation in two or more leads on the initial electrocardiogram (ECG) and confirmed by a typical increase and decrease in serum creatine kinase (CK) and CK-MB fraction levels. None of these patients had an intraventricular conduction defect, valvular heart disease, cardiomyopathy, heart failure, or contraindications to exercise testing, including post-infarction angina, major ventricular arrhythmias, and severe systemic hypertension. No patient was excluded because of a technically inadequate echocardiogram. The infarct location was anterior in 54 patients and inferior or lateral in 60. Q-waves evolved in 90 patients. Eighty patients (69%) received thrombolytic therapy. Peak serum levels of CK and CK-MB were 1,939 ± 902 and 205 ± 109 IU/l. All patients underwent EE at 6 ± 2 days after AMI and before coronary angiography. The study protocol was approved by the institutional Research Ethics Committee, and all patients gave informed consent.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
CK-MB	= creatine kinase-MB fraction
ECG	= electrocardiogram/electrocardiographic
EE	= exercise echocardiography
IRA	= infarct-related artery

Exercise echocardiography. Beta-adrenergic blocking agents were withdrawn 48 h before the study. Exercise echocardiography was performed in semi-supine position on a tilting exercise table, with the table tilted up to 45° in the left lateral decubitus position. The exercise test was started at 25 W during 3 min, followed by a 25-W increase every 2 min. Echocardiographic imaging was continuous during exercise. End points for the stress test included the target heart rate (≥85% of the maximal age-predicted heart rate), limiting chest pain, >1-mm ST-segment depression compared with baseline in two or more ECG leads, significant arrhythmias (supraventricular tachyarrhythmias or ventricular tachycardia), severe hypertension (systolic blood pressure >230 mm Hg), and hypotension (fall in systolic blood pressure >30 mm Hg). The ECG was continuously monitored throughout the test and recorded at each stage. Blood pressure was measured at each stage by an arm-cuff sphygmomanometer. The low-level stage was recorded during the first work load, when the heart rate was 10 to 20 beats/min higher than at baseline.

Echocardiographic imaging and analysis. Baseline and exercise images were digitized with the same equipment (General Electric VingMed CFM 800 or System Five, Horten, Norway) and reviewed on a side-by-side cine-loop display. Left ventricular wall motion and thickening were evaluated with a 16-segment, 4-grade scale model: 1 = normal wall thickening; 2 = hypokinesia; 3 = akinesia; and 4 = dyskinesia. Regional dyssynergy was defined when a score ≥2 was assigned to a myocardial segment. Four different echocardiographic responses were identified: 1) sustained improvement, when improvement in contractility was observed in dyssynergic segments throughout stress, without deterioration; 2) a biphasic response, defined as an initial improvement of contractility by ≥1 score in the infarct area at low-level exercise, followed by subsequent worsening at a high level; 3) development of new dyssynergy adjacent to the infarct zone or deterioration of rest dyssynergic segments in the infarct zone by 1 score and in two or more segments, corresponding to a worsening response; and 4) akinesia without change, defined as no change in basal asynergy throughout the test. A patient was considered to have contractile reserve if wall thickening improved in two or more contiguous segments. The echocardiographic criterion for residual stenosis of the IRA was the induction, during exercise, of new or worsened regional dyssynergy in two or more contiguous segments in the affected region and/or in the adjacent area. The criterion for multivessel disease was abnormal wall thickening in two or more contiguous segments in one or more remote vascular territory (8). Follow-up rest echocardiograms were obtained 30 ± 3 days after the acute event in all patients, and functional recovery was defined as an increase in wall thickening of ≥1 grade at follow-up in two contiguous segments of the affected area. All echocardiograms were reviewed by two observers who were unaware of the clinical data. In case of disagreement, the judgment of a third observer was obtained. Interobserver agreements regarding the presence of contractile reserve and ischemia in segmental analysis were 89% (κ = 0.87) and 86% (κ = 0.84), respectively. For segmental biphasic response, the interobserver agreement was 85% (κ = 0.81).

Coronary angiography. Quantitative coronary angiography was performed in all patients within one week after the exercise test. Quantitative measurements of coronary stenoses were performed using the Cardiovascular Angiography Analysis System (CAAS, Philips Integris-Medical System, The Netherlands). Significant stenosis of the IRA (≥50%) was observed in 97 patients. Persistent occlusion of the IRA was found in 15 patients. Mean residual stenosis of the patent IRA was 68 ± 19%. Elective angioplasty of the IRA was performed in 68 patients. No patient underwent surgical revascularization. The results of stress testing were not used for the decision to perform the procedure. Twenty-six patients had multivessel disease (double-vessel disease in 18 and triple-vessel disease in 8).

Statistical analysis. Data are expressed as the mean value ± SD. Quantitative variables were tested by the Student *t* test, and nominal findings by the chi-square test. To detect independent variables associated with functional recovery, a multivariate logistic regression procedure was performed (STATISTICA, version 5). Statistical significance was defined as a two-tailed p value ≤0.05. The sensitivity, specificity, positive and negative predictive values, and accuracy of EE findings for the detection of significant IRA residual stenosis and multivessel disease and for the prediction of functional recovery were calculated with standard formulas.

RESULTS

Exercise stress echocardiography. Heart rate and systolic blood pressure increased significantly from rest to peak exercise (76 ± 14 vs. 130 ± 11 beats/min and 131 ± 23 vs. 165 ± 20 mm Hg, respectively; $p < 0.001$ for both). There were no complications as a result of the exercise test. Angina developed in 22 patients (19%), ST-segment depression in 31 (27%), and ST-segment elevation in 34 (29%). Sixty-eight patients (60%) reached the target heart rate, and 93 reached ≥120 beats/min. The test was interrupted before reaching the target heart rate because of angina (n = 3), ST-segment depression (n = 12), significant arrhythmias (n = 3), muscular fatigue or leg pain (n = 11), and severe ischemia (e.g., low ischemic threshold, multiple inducible wall motion abnormalities, ischemia in the affected area,

Table 1. Accuracy of Clinical, Electrocardiographic, and Exercise Echocardiographic Findings for the Detection of Significant Infarct-Related Artery Stenosis

Data	Sensitivity (n = 97)	Specificity (n = 17)	Accuracy (n = 114)
Chest pain (n = 18)	15 (15%)	82 (14%)	25%
ST-segment depression (n = 31)	28 (27%)	76 (13%)	35%
ST-segment elevation (n = 34)	32 (31%)	82 (14%)	39%
Biphasic response (n = 62)	61 (59%)	82 (14%)	64%
Worsening in adjacent area (n = 15)	14 (14%)	94 (16%)	26%
Residual infarct-zone ischemia (n = 77)	75 (73%)	76 (13%)	76%

Data are presented as the number (%) of true-positive (sensitivity column) and true-negative (specificity column) values.

severe angina) (n = 17). During EE, contractile reserve was observed in 73 patients, and residual ischemia in the infarct zone was seen in 77. Sustained improvement was identified in 11 patients, a biphasic response in 62, a worsening response in 15, and akinesia without change in 26. Remote ischemia was observed in 19 patients.

Detection of residual IRA stenosis and multivessel disease. Table 1 presents the sensitivity, specificity, predictive value, and accuracy of EE findings for the prediction of ≥50% stenosis of the IRA. Both worsening and biphasic responses were more sensitive than the occurrence of exercise-induced chest pain or ECG changes ($p < 0.0001$). Specificities were not significantly different for all stress parameters. Progressive ischemia (worsening) was associated with more severe angiographic severity of the infarct stenosis than was a biphasic response (79 ± 14% vs. 63 ± 22%; $p = 0.028$). The involved vascular territory did not influence the sensitivity and specificity (Table 2). Submaximal stress defined as <85% of predicted heart rate did not affect the sensitivity or specificity, whereas a peak heart rate <120 beats/min significantly reduced the sensitivity (50% vs. 80%; $p = 0.038$). The baseline wall motion score index did not influence the accuracy of the test. The sensitivity and accuracy of EE were higher in patients with improved wall motion at low-level exercise (92% vs. 42% and 89% vs. 51%, respectively; $p < 0.0001$). Wall motion abnormalities developing in one or more of the other coronary territories were highly specific (85/88 [97%]) and moderately sensitive (16/26 [62%]) for detecting multivessel disease (Table 3). Sensitivity tended to be higher when the peak heart rate was ≥120 beats/min compared with <120 beats/min ($p = 0.06$). The sensitivity of EE for detecting remote vascular disease was lower when ischemia was induced in the affected zone (36% vs. 92%; $p = 0.005$).

Table 2. Effects of Heart Rate, Infarct Size, and Location on the Accuracy of Exercise Parameters for Detecting Infarct-Related Artery Stenosis

	Sensitivity (n/N)	Specificity [n′/N′]	Accuracy
Target heart rate not reached (n = 46)	67% (24/36)	80% [8/10]	70%
Target heart rate reached (n = 68)	80% (49/61)	71% [5/7]	79%
Peak heart rate <120 beats/min (n = 21)	50% (7/14)*	86% [6/7]	62%
Peak heart rate ≥120 beats/min (n = 93)	80% (66/83)*	70% [7/10]	78%
Baseline WSI <1.5 (n = 62)	75% (40/53)	67% [6/9]	74%
Baseline WSI ≥1.5 (n = 52)	75% (33/44)	88% [7/8]	77%
Anterior infarction (n = 54)	83% (39/47)	71% [5/7]	81%
Infero-lateral infarction (n = 60)	68% (34/50)	80% [8/10]	70%
No contractile reserve at low-level EE (n = 41)	42% (14/33)†	88% [7/8]	51%†
Contractile reserve at low-level EE (n = 73)	92% (59/64)†	67% [6/9]	89%†

*$p < 0.05$. †$p < 0.0001$. Data in parentheses and brackets are presented as the number of patients with (n) or without (n′) ischemia in the infarct zone and the number of patients with (N) or without (N′) significant stenosis of the infarct-related artery.
EE = exercise echocardiography; WSI = wall motion score index.

Table 3. Effects of Heart Rate and Ischemia in the Infarct Zone on the Accuracy of Exercise Parameters for Detecting Multivessel Disease

	Sensitivity (n/N)	Specificity [n′/N′]	Accuracy
Target heart rate not reached (n = 46)	50% (5/10)	92% [33/36]	83%
Target heart rate reached (n = 68)	69% (11/16)	100% [52/52]	93%
Peak heart rate <120 beats/min (n = 21)	29% (2/7)	100% [14/14]	76%
Peak heart rate ≥120 beats/min (n = 93)	74% (14/19)	96% [71/74]	91%
No ischemia during EE (n = 37)	92% (11/12)*	92% [23/25]	92%
Ischemia during EE (n = 77)	36% (5/14)*	98% [62/63]	87%

*$p < 0.05$. Data in parentheses and brackets are presented as the number of patients with (n) or without (n′) remote ischemia and the number of patients with (N) or without (N′) multivessel disease.
EE = exercise echocardiography.

Predictors of functional recovery. Table 4 presents the clinical, echocardiographic, and angiographic findings in patients with and without segmental improvement in left ventricular systolic function. Recovery of contraction was observed in 75 patients (66%). There were no significant differences between the groups in terms of age, gender, site of infarction, proportion of Q-wave infarction, use of thrombolytic therapy, and baseline wall motion score index. The peak level of CK was lower in patients who recovered (1,758 ± 816 vs. 2,288 ± 966 IU/l; $p = 0.0026$). Elective coronary angioplasty of the IRA was more frequently performed in patients with reversible dysfunction (54/75 vs. 14/39; $p = 0.0002$). Contractile improvement during EE and the development of residual ischemia in the affected area were also more frequent in those patients ($p < 0.0001$ for both). In contrast to sustained improvement, a biphasic response was closely associated with recovery ($p < 0.0001$). On multivariate analysis, two independent variables predicting functional recovery were selected stepwise: contractile reserve (chi-square = 29; p = < 0.0001) and elective angioplasty of the IRA (chi-squared = 10; $p = 0.002$). The

Table 4. Comparison Between Patients With and Without Functional Recovery

Data	Recovery (n = 75)	No Recovery (n = 39)	p Value
Clinical			
Age (yrs)	59 ± 11	61 ± 10	NS
Gender (% male)	69 (92%)	31 (74%)	NS
Anterior infarction	38 (51%)	16 (41%)	NS
Thrombolytic therapy	51 (68%)	29 (74%)	NS
Peak CK (IU/l)	1,758 ± 816	2,288 ± 966	0.0026
Q waves	62 (83%)	28 (71%)	NS
Echocardiography			
Baseline score index	1.41 ± 0.20	1.40 ± 0.22	NS
Score index at low-level EE	1.18 ± 0.19	1.35 ± 0.27	0.00029
Score index at high-level EE	1.44 ± 0.23	1.42 ± 0.24	NS
Contractile reserve	62 (83%)	11 (30%)	<0.0001
Ischemia during EE	63 (84%)	14 (36%)	<0.0001
Sustained improvement	7 (9%)	4 (10%)	NS
Biphasic response	55 (73%)	7 (18%)	<0.0001
Ischemia in adjacent area	8 (11%)	7 (18%)	NS
Akinesia without change	5 (7%)	21 (54%)	0.0001
Angiography			
Residual stenosis of IRA (%)	70 ± 20	64 ± 19	NS
Occluded IRA	11 (15%)	4 (10%)	NS
Elective angioplasty of IRA	54 (72%)	14 (36%)	0.0002

Data are presented as the mean value ± SD or number (%) of patients.
CK = creatine kinase; EE = exercise echocardiography; IRA = infarct-related artery; NS = not significant.

sensitivity, specificity, and accuracy of contractile reserve (83%, 72%, and 79%, respectively) and biphasic response (73%, 82%, and 76%) for predicting functional recovery are shown in Figure 1.

DISCUSSION

Residual stenosis of the IRA is common after AMI and is associated with a worse outcome, but only in patients with viable, jeopardized myocardium and inducible ischemia (1,9). Early identification of these patients is therefore of clinical importance for selecting those who may benefit the most from early revascularization of the IRA. To the best of our knowledge, this is the first study demonstrating the usefulness of continuous echocardiographic monitoring of regional wall thickening during a semi-supine exercise test early after AMI. The main findings can be summarized as follows: 1) a biphasic response can be identified during EE; 2) a biphasic response in the affected zone is the most sensitive stress finding for the detection of significant IRA stenosis; 3) remote ischemia is highly specific and moderately sensitive for predicting multivessel disease; 4) a biphasic response has the highest predictive value for predicting reversible dysfunction, as compared with sustained improvement; and 5) elective percutaneous transluminal coronary angioplasty was also an independent variable predicting recovery.

Biphasic response. Several experimental and clinical studies have demonstrated that a biphasic response of wall thickening with incremental doses of dobutamine—initial improvement followed by subsequent deterioration—is a marker of viable, jeopardized or hibernating myocardium perfused by a severely flow-limiting coronary stenosis (10–13). The initial improvement is transient and occurs at the expense of metabolic deterioration of myocardial ischemia. If the inotropic challenge is prolonged, wall thickening deteriorates, with increases in lactate production and development of myocardial acidosis (10). We have previously demonstrated that contractile reserve can be observed during low-level exercise and that its accuracy is similar to that of low-dose dobutamine echocardiography for predicting reversible dysfunction. No study has evaluated whether a

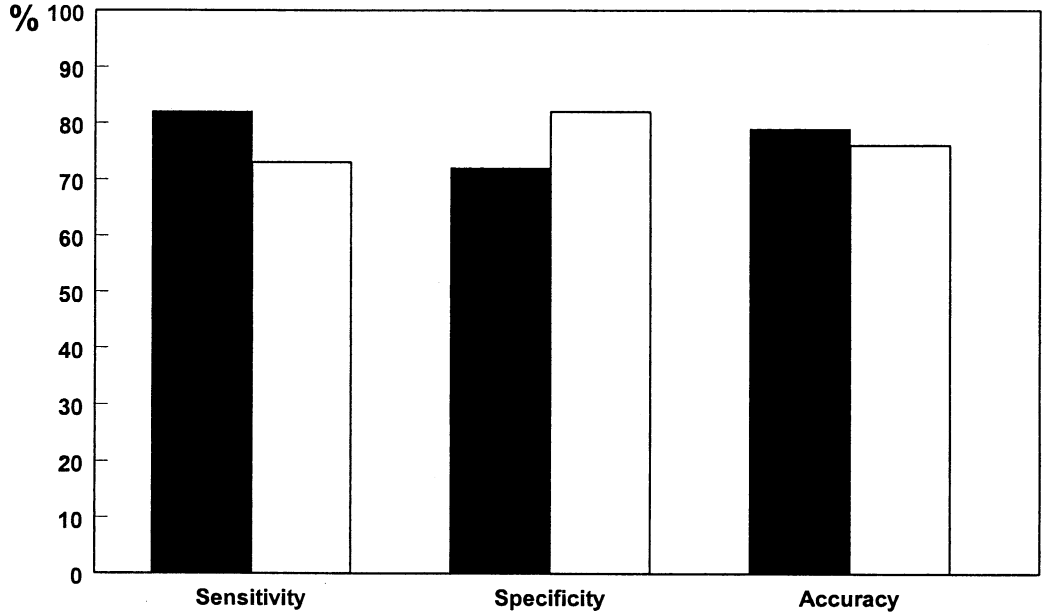

Figure 1. Bar graph showing sensitivity, specificity, and accuracy of contractile reserve **(solid bars)** and biphasic response **(open bars)** during exercise echocardiography for predicting functional recovery.

biphasic response can be identifiable during exercise. The detection of a transient improvement in regional wall thickening rapidly followed by reworsening requires continuous monitoring of echocardiographic images, an initial low work load, and recording of the low-level exercise images before an excessive increase in heart rate. In the present study, a biphasic response was observed in 62 patients, with high interobserver agreement.

Detection of significant IRA stenosis and multivessel disease. After AMI, the ischemic myocardium usually reflects the presence of a significant residual stenosis of the IRA. Ischemia (biphasic response and ischemia in the adjacent area) during EE was sensitive and specific for detecting IRA. A biphasic response enhanced the sensitivity of ischemia in an adjacent area, without a significant change of specificity. The diagnostic accuracy of EE was not affected by the location of the affected region or the extent of baseline wall motion abnormalities. The sensitivity of EE was higher in patients reaching a peak heart rate ≥120 beats/min than in those with a peak rate <120 beats/min. False-negatives studies were also found in patients with unchanged wall motion at low-level exercise. Thus, the accuracy of EE is dependent on the transmural extent of necrosis. Our results are comparable with previous studies using dobutamine stress echocardiography after AMI (4,7). The specificity of EE for detecting residual IRA stenosis was higher than that recently reported by Nishioka et al. (14). In their study, treadmill EE was performed late after AMI, and image acquisition was obtained only after exercise, which precludes the possibility of detecting a biphasic response. The specificity of EE for identifying patients with multivessel disease in our study was similar to that reported recently with post-exercise and dobutamine stress tests, although the sensitivity was lower (4,7,15,16). Several factors may contribute to the absence of myocardial ischemia in some patients with remote vascular disease: a submaximal stress test, vascular overlap, ischemic threshold, and a discrepancy between coronary anatomy and function (17). In the present study, the sensitivity for detecting multivessel disease was lower in patients with inducible ischemia in the infarct zone and in those reaching a peak heart rate <120 beats/min.

Functional recovery. In the present era of early intervention, the incidence of transmural infarction has largely decreased. Most patients develop an incomplete infarction, with an admixture of subendocardial necrosis and salvaged subepicardium (6,18). Low-dose dobutamine or low-level exercise echocardiography may identify viable but noncontractile myocardium early after AMI. The detection of myocardium at jeopardy, rather than simply viable myocardium, is more important for clinical decision-making. The observation of a biphasic response during dobutamine stress testing has been found to be needed for optimal prediction of reversible dysfunction after revascularization in patients with chronic coronary artery disease or a recent AMI (11,12,19). In the present study, contractile reserve was detected with low-level exercise in 62 (83%) of the 75 patients in whom improved regional function was observed at one-month follow-up. A biphasic response was observed in 55 of these patients and had the highest predictive value for recovery. Elective angioplasty of the IRA was performed in 43 (78%) of 55 of these patients. Although the results of stress testing were not used for deciding early revascularization, elective percutaneous transluminal coronary angioplasty emerged as an independent predictor of functional recovery. Contractile improvement in patients not submitted to revascularization can result from spontaneous recovery of stunned myocardium or progressive improvement in perfusion in the infarct area as a result of collateral recruitment (20).

Study limitations. Several limitations of the present study deserve consideration. The patients enrolled were consecutive patients without contraindications to an early stress test, and the hospital treatment was not standardized. Myocardial ischemia detected during EE was used to predict the presence or absence of significant coronary stenosis. However, coronary angiography does not always reflect the functional significance of stenosis. Wall motion analysis was done by a semi-quantitative method rather than by quantitative techniques, but this method remains the standard. New ultrasonic modalities such as Doppler myocardial imaging could potentially provide more quantitative information in the future. Coronary angiography was not repeated at follow-up. Thus, restenosis or reocclusion cannot be excluded; this could have resulted in a lack of recovery in some patients. However, repeat catheterization is not indicated in an asymptomatic patient. It should also be acknowledged that our observations pertain only to patients with a small or moderate infarct size. Whether a biphasic response can be accurately identified during exercise in other clinical settings, such as chronic coronary artery disease and heart failure, remains to be investigated

Conclusions. Continuous echocardiographic examination during semi-supine exercise allows the observation of contractile reserve and a biphasic response early after AMI. Inducible ischemia, as detected by EE, predicts the presence of IRA stenosis and multivessel disease. It represents an attractive tool, more physiologic than pharmacologic stress testing, for identifying viable, jeopardized myocardium and predicting reversible dysfunction early after AMI.

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