

Prediction of Cardiac Events After Uncomplicated Acute Myocardial Infarction by Clinical Variables and Dobutamine Stress Test

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- OBJECTIVES** We sought to determine the relative prognostic power of several clinical and dobutamine stress test variables in patients after a first uncomplicated acute myocardial infarction (AMI).
- BACKGROUND** The value of dobutamine echocardiography (DE) for determining prognosis after AMI is not yet defined. In particular, the influence of dobutamine stress test response on the outcome of these patients is unknown.
- METHODS** A graded predischarge DE (from 5 to 40 $\mu\text{g}/\text{kg}/\text{min}$, plus atropine if needed) was performed in 245 patients (mean age 60 ± 10 years) with a first uncomplicated AMI.
- RESULTS** At follow-up (17 ± 13 months), an adverse outcome occurred in 40 patients: cardiac death in 7, nonfatal myocardial infarction in 9 (hard events = 16) and unstable angina requiring hospital readmission in 24. Significant predictors of adverse outcome by univariate analysis were positive DE, ischemic wall motion score index (WMSI), angina during DE and diabetes for all events, and positive DE, ischemic WMSI and age for hard events. At multivariate analysis, the only independent predictors of adverse outcome were positive DE, diabetes and angina during DE for all events, and positive DE and age for hard events. The presence of both age >60 years and a history of diabetes identified patients at high risk of cardiac events (event rate 37%), compared with patients <60 years and no diabetes (event rate 11%). In patients with intermediate risk (only one clinical risk factor, event rate 18%), DE added prognostic information (event rate 10% in the negatives, 25% in the positives and 35% in the positives with angina).
- CONCLUSIONS** After uncomplicated AMI, dobutamine stress test variables offer additional prognostic information to clinical data. (J Am Coll Cardiol 1999;34:435-40) © 1999 by the American College of Cardiology

Prognostication of patients after acute myocardial infarction (AMI) is still under debate. Clinical evaluation during hospital stay allows identification of high-risk patients who have complications and probably benefit from early angiography. Patients at low risk can be identified from simple clinical characteristics that include no evidence of heart failure, no recurrent ischemia and a preserved left ventricular (LV) function. Such patients have an overall good prognosis, with an expected one-year mortality of $<4\%$, and usually undergo a predischarge stress testing to refine risk assessment and to provide guidance for future management (1).

Over the last few years, dobutamine echocardiography (DE) has been increasingly proposed for the diagnosis and prognosis of patients with suspected or proven coronary artery disease (2). We have recently found that dobutamine-

induced wall motion abnormalities provide similar prognostic information to exercise induced S-T segment depression in patients evaluated early after an uncomplicated AMI (3). However, the additional information of DE beyond that obtained by clinical data has not been explored. Furthermore, complementary information regarding LV function, presence of myocardial viability, extent and severity of myocardial ischemia, symptoms and electrocardiographic (ECG) changes during dobutamine infusion can be obtained during the dobutamine stress test, possibly enhancing the diagnostic and prognostic capability of the test.

Accordingly, the purpose of this study was: 1) to analyze the power of dobutamine stress test variables for predicting cardiac events after an uncomplicated AMI; and 2) to evaluate the additional prognostic information of dobutamine stress test beyond those obtained by clinical data only.

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METHODS

Study group. This prospective study was carried out in 342 patients who were consecutively admitted to the coronary

Abbreviations and Acronyms

AMI	= acute myocardial infarction
DE	= dobutamine echocardiography
ECG	= electrocardiogram, electrocardiographic
LV	= left ventricular
WMSI	= wall motion score index

care unit at our institution for a first AMI. Diagnosis of myocardial infarction was based on a consistent history, ECG changes and cardiac enzyme level elevations. Patients with early postinfarction angina (n = 44), left ventricular failure (n = 38) or important cardiac arrhythmias (n = 12) were excluded from the study. Of the 248 patients fulfilling the selection criteria, three had low-quality baseline echocardiographic images making the DE unfeasible. Therefore, the final study population consisted of 245 patients (mean age 60 ± 10 years; 210 males) with a clinically uncomplicated first AMI who were enrolled in a follow-up program. Sixty-eight (28%) patients had a history of hypertension and 26 (11%) were diabetic. Thrombolysis was performed in 118 (48%) patients. The site of myocardial infarction was anterior in 103 (42%), inferior in 114 (47%) and non-Q in 28 (11%) patients. After written informed consent, DE was performed 1 to 2 days before hospital discharge (range 6 to 14 days after admission). Antianginal drugs were discontinued (beta-adrenergic blocking agents for 36 h, nitrates and calcium channel antagonist for 24 h).

Dobutamine echocardiography. Each patient underwent DE using a standard protocol that has been described in detail previously (3). Briefly, a two-dimensional trans-thoracic echocardiogram in standard views was recorded at rest and then dobutamine was infused, at dosages of 5 and 10 $\mu\text{g}/\text{kg}/\text{min}$ for 5 min at each dose (these two steps were considered as low-dose). Subsequently, three other steps from 20 to 40 $\mu\text{g}/\text{kg}/\text{min}$ for 3 min were added. Finally, in patients not achieving 85% of their gender- and age-predicted maximal heart rate and with no symptoms or signs of myocardial ischemia, atropine (starting with 0.25 mg increasing to a maximum of 1 mg) was injected, while dobutamine was continued.

The test was prematurely terminated in the presence of horizontal or downsloping S-T segment depression >0.2 mV 80 ms after the J point, S-T segment elevation in non-Q wave leads, serious cardiac arrhythmias, significant chest pain, reduction in systolic blood pressure >40 mm Hg from that at rest, a systolic blood pressure <90 mm Hg, hypertension (systolic blood pressure >220 mm Hg) or any side effect regarded as being due to dobutamine. A new wall motion abnormality was considered an interruption criteria only if it occurred in more than two segments. Atenolol was available and used (1 to 5 mg intravenously) to reverse the effects of dobutamine or dobutamine-atropine combination if these did not revert spontaneously and quickly.

A commercially available imaging system equipped with a 2.5-MHz probe was used for imaging. Left ventricular wall motion was continuously monitored and the images were recorded on video tape at rest and during the final minute of each stage.

Echocardiographic images were analyzed off-line and a consensus was achieved by two cardiologists blinded to clinical data. For the wall motion analysis, the left ventricle was divided into 16 segments (4) and each segment was scored using a four-point scale, where: 1 = normal, 2 = hypokinesis, 3 = akinesis and 4 = dyskinesis. A global wall motion score index (WMSI) was calculated at baseline, at low and at high doses of dobutamine, dividing the sum of each segments by the number of the segments. Infarct zones for anterior and inferior infarcts were constructed according to the theoretic maximal area at risk (5). The apical inferior and apical lateral segments were considered to be overlapping. Thus, each infarct zone comprised nine segments. An infarct zone WMSI was calculated at baseline and during low- and high-dose dobutamine, averaging the sum of the individual scores in segments in the infarct zone by the number of the segments. An infarct zone was judged to have contractile reserve (comparing baseline WMSI with WMSI at low dose dobutamine) when infarct zone WMSI decreased by ≥ 0.22 (5). An ischemic response was defined by an increase in WMSI ≥ 0.22 in the infarct region (homozonal ischemia) or in the noninfarcted region (remote ischemia) in comparison with WMSI during low-dose dobutamine. Ischemia was not considered when akinetic segments at rest became dyskinetic at stress without improvement during low-dose infusion (6).

Electrocardiograms during dobutamine were reviewed by an observer who was unaware of the results of DE; S-T segment depression >1 mm was considered as a positive ECG response.

Follow-up. Follow-up data were obtained in all patients from routine follow-up visits in the outpatient cardiac clinic at the Sandro Pertini Hospital or from a telephone interview with the patient conducted by a staff cardiologist. We determined the specific occurrence of cardiac events defined as cardiac death, nonfatal recurrent infarction and readmission to the coronary care unit for control of unstable angina. Description of causes and circumstances of death and the definition of a new cardiac event have been described elsewhere (3). Only the first event was considered for each patient. Referral for cardiac catheterization and subsequent therapeutic decisions were made by the patient's physician based on the results of exercise testing and/or because the patients were symptomatic, and were independent of the DE results. Follow-up of patients undergoing elective revascularization procedures was concluded at the time of revascularization, which was not considered a cardiac event because the decision to perform these procedures might be subjective.

Statistical analysis. Results are expressed as mean value \pm SD for continuous variables and as percent for categorical variables.

The predictive role of certain variables on event-free survival was evaluated by the Cox proportional hazard model using the forward selection stepwise procedure available in BMDP 2L statistical package (7). The clinical variables consisted of age, gender, thrombolysis, Q-wave myocardial infarction, anterior AMI, hypertension and diabetes. The stress test variables included WMSI at rest, WMSI at low dose, WMSI at peak stress, ischemic WMSI (stress/rest WMSI variation), viability at low-dose dobutamine, positive DE, remote ischemia, dobutamine time (the interval from the beginning of the test to the onset of myocardial ischemia), S-T segment depression during dobutamine and angina during dobutamine. In tests giving negative results, the dobutamine time was arbitrarily assumed to be 26 min.

Continuous variables were compared by the unpaired *t* test. Proportions were compared by using the zeta test by Remington. For multivariate analysis, data are expressed as relative risk with 95% confidence intervals (CI). A *p* value <0.05 was considered significant.

RESULTS

Dobutamine stress test. No serious complications were noted during dobutamine infusion. Atropine was added to dobutamine in 130 patients. The test was inconclusive (negative echocardiogram at submaximal stress, i.e., peak heart rate <85% of maximal age predicted heart rate) in four patients. The test results of these patients were included in the analysis. The rate-pressure product at peak stress was $19,422 \pm 3,469$.

Myocardial viability was present at low dose of dobutamine in 73 patients (30%). Dobutamine echocardiography was positive for myocardial ischemia in 115 patients (47%). Among the patients with a positive result, 57 (50%) had a positive finding after atropine administration. In 70 (61%) patients, a worsening of wall motion appeared within the infarct zone (homozonal ischemia), in 53 of these after an improvement at low dose of dobutamine (biphasic response). These 53 patients were similar in terms of clinical or baseline echocardiographic findings to the 17 patients with a direct worsening of wall motion. In the remaining 45 patients, new wall motion abnormalities were found in the remote zone (remote ischemia). The mean time of echocardiographic positivity was 20.1 ± 4.1 min.

Significant S-T segment depression occurred in 70 patients (29%) and angina in 47 (19%). Considering wall motion abnormalities, S-T segment depression and angina during dobutamine stress test as markers of myocardial ischemia, 20 patients had 3 markers, 53 patients had 2 markers, 61 patients had 1 marker and 111 patients had no marker of myocardial ischemia. The number of markers of

Table 1. Event Rate Occurrence in Relation to Dobutamine Echocardiographic Results

	DE+ (n = 115)	DE- (n = 130)
No events (n = 205)	89 (77%)	116 (89%)
All events (n = 40)	26 (23%)*	14 (11%)
Hard events (n = 16)	13 (11%)+	3 (2.3%)
Death (n = 7)	5 (4%)	2 (1.5%)
Myocardial infarction (n = 9)	8 (7%)+	1 (0.8%)
Unstable angina (n = 24)	13 (11%)	11 (8%)

**p* = 0.05; †*p* < 0.01.

DE = dobutamine echocardiography; + = positive; - = negative.

ischemia observed was not related to the peak dobutamine dose or the dobutamine time.

Follow-up data. During the follow-up (mean 17 ± 13 months, range 1 to 44 months), a total of 40 events occurred: 7 deaths, 9 nonfatal AMIs (hard events, *n* = 16) and 24 unstable angina requiring hospital admission.

In Table 1, the results of DE are correlated with the spontaneous events that occurred at follow-up evaluation. A positive DE increases the risk of all and hard cardiac events by 2.1- and 4.8-fold, respectively. Sensitivity, specificity and positive and negative predictive values for all events were 65%, 57%, 23% and 89%, and for hard events, 81%, 55%, 11% and 98%, respectively.

The univariate prognostic factors for spontaneous events are shown in Table 2. The most important predictors for all events was the ischemic WMSI, and for hard events, the positivity at DE. The event rate was similar in patients with homozonal versus remote ischemia (24% vs. 20% for all events; 13% vs. 9% for hard events).

By stepwise analysis, the predictors for all events were a history of diabetes, DE positivity and the occurrence of angina during DE. Considering hard events, the only independent prognostic factors were age and DE positivity (Fig. 1).

Predictive value of dobutamine stress test. The incidence of cardiac events according to the number of ischemic markers (wall motion abnormalities, angina and S-T segment changes) during dobutamine stress test is reported in Figure 2. The results indicate that the higher the number of ischemic markers during dobutamine stress test, the worse the outcome of the patients. In particular, cardiac events occurred in 19 of 73 patients with two or three markers of myocardial ischemia, and in 21 of 171 patients with zero or one marker of myocardial ischemia. The event rate was 26% versus 12% (*p* < 0.01).

DISCUSSION

Dobutamine stress test after AMI. We have already evaluated the relative merit of DE and exercise testing for risk stratification early after AMI (3), and we found that the presence of dobutamine-induced wall motion abnormalities

Table 2. Comparison of Patients With and Without Cardiac Events (Univariate Analysis)

Variable	All			Hard		
	Events (n = 40)	No events (n = 205)	p-value	Events (n = 16)	No events (n = 229)	p-value
Age	61 ± 7	59 ± 10	NS	64 ± 5	59 ± 10	0.032
Gender	31 (77%)	179 (87%)	NS	12 (75%)	198 (86%)	NS
Hypertension	10 (25%)	58 (28%)	NS	2 (12%)	66 (29%)	NS
Diabetes	8 (20%)	18 (9%)	0.035	2 (12%)	24 (10%)	NS
Thrombolysis	20 (50%)	98 (48%)	NS	6 (37%)	112 (49%)	NS
Site of infarction	17 (42%)	86 (42%)	NS	6 (37%)	97 (42%)	NS
Rest WMSI	1.41 ± 0.28	1.41 ± 0.30	NS	1.47 ± 0.21	1.41 ± 0.30	NS
Peak WMSI	1.59 ± 0.28	1.54 ± 0.34	NS	1.65 ± 0.20	1.54 ± 0.33	NS
Ischemic WMSI	0.11 ± 0.17	0.20 ± 0.22	0.004	0.12 ± 0.18	0.25 ± 0.17	0.005
Viability	15 (37%)	58 (28%)	NS	5 (31%)	68 (30%)	NS
Positive DE	26 (65%)	89 (43%)	0.005	13 (81%)	102 (44%)	0.0009
Dobutamine time	23 ± 4	23 ± 4	NS	23 ± 4	22 ± 5	NS
Remote ischemia	9 (22%)	36 (18%)	NS	4 (25%)	41 (17%)	NS
Angina during DE	12 (30%)	35 (17%)	0.057	4 (25%)	43 (19%)	NS
ECG during DE	13 (32%)	57 (28%)	NS	6 (37%)	64 (28%)	NS

DE = dobutamine echocardiography; ECG = electrocardiogram; WMSI = wall motion score index.

gives prognostic information similar or even better than exercise-induced S-T segment depression. However, complementary information can be obtained from other variables that can be monitored during dobutamine stress testing, the presence of myocardial viability at a low dose of dobutamine and the occurrence of ECG changes or angina.

The results of the present study can be summarized as follows:

- 1) dobutamine-induced wall motion abnormalities are predictors of cardiac events at follow-up;
- 2) the presence of contractile reserve at a low dose of dobutamine is not associated with a worse outcome, unless further deterioration of wall motion does occur at higher doses (biphasic response); and
- 3) patients with two or more markers of myocardial ischemia during dobutamine stress test have a higher incidence of cardiac events compared with patients with more than two ischemic markers.

In this group of patients with a first uncomplicated AMI and preserved LV function, the presence of residual myocardial ischemia as documented by worsening of wall motion during DE emerged as the most important prognostic factor of adverse outcome. This is in agreement with the findings from the Echocardiography Persantine International Cooperative study, where dipyridamole echocardiography added significant prognostic information on top of clinical and exercise ECG test data (8). In the present study, the prognostic value of DE was similar in patients with homozonal compared with remote ischemia. Remote ischemia at DE is a marker of multivessel disease (9) and, at least in a recent study, was found to be a predictor of poor

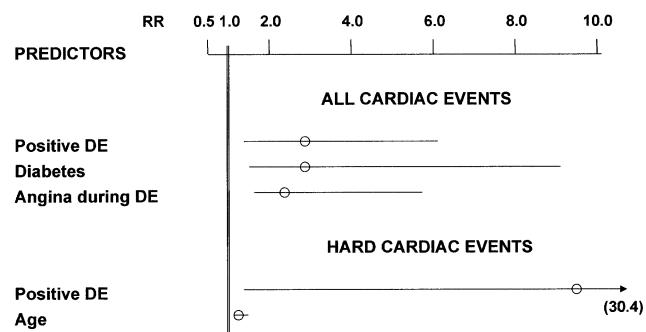


Figure 1. Multivariate predictors of all cardiac events (death, myocardial infarction or unstable angina) and hard cardiac events (death or myocardial infarction) after uncomplicated AMI. The risk associated with a given variable is expressed by a relative risk (RR) with corresponding 95% confidence intervals. DE = dobutamine echocardiography.

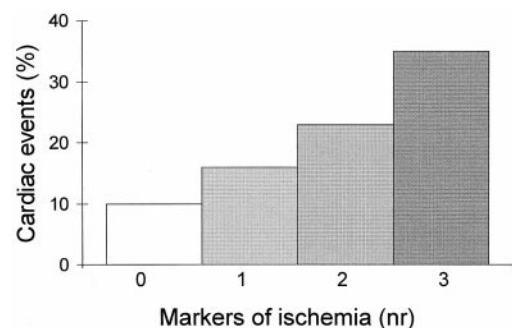


Figure 2. Incidence of cardiac events (death, myocardial infarction or unstable angina) during follow-up as a function of the number (no, one, two or three) of ischemic markers (wall motion abnormalities, S-T segment depression or angina) during dobutamine stress test.

Dobutamine Stress Test After Myocardial Infarction

prognosis after AMI (10). However, we considered dobutamine-induced wall motion abnormalities as an end point, thus limiting the power of the test for detecting multivessel disease.

The prognostic value of viable myocardium after an AMI has been questioned. Previous reports suggested that the evidence of dysfunctioning but viable myocardium after AMI might be an adverse prognostic factor, acting as an “unstable substrate” for recurrent myocardial ischemia or life-threatening arrhythmias (11-13). Recently, and in contrast with this observation, lack of functional viability has been associated with adverse outcome (10,14). In the present study, myocardial viability did not show an independent prognostic value. These controversial results can be explained by the following considerations: 1) the different echocardiographic criteria of myocardial viability and clinical end points adopted in the different studies; 2) the high prevalence of biphasic response and the findings at multivariate analysis in the present study indicate that, in patients with a well-preserved LV function, the prognostic importance of myocardial viability can be obscured by the impact of ischemia; this is also reported in a recent study in patients with a first AMI treated with thrombolysis, where myocardial viability did not show an independent prognostic value (15); 3) remote ischemia may offset the prognostic significance of myocardial viability within the infarct zone; and 4) the beneficial effect of myocardial viability can be more evident in patients with global LV dysfunction (16) rather than in patients with a preserved LV function as those represented in the present study.

In stress echocardiography, the typical marker of myocardial ischemia is considered to be the deterioration of wall motion, with S-T segment depression or angina as nonspecific and neglectable markers. The results of the present study indicate that considering all the markers enhances the prognostic power of dobutamine stress test, with a two-fold increase in cardiac events at follow-up in patients with two or more markers compared with patients with one or no markers. This finding is consistent with previous data demonstrating the prognostic importance of chest pain and ECG changes during pharmacologic stress echocardiography (8,15,17). However, whether the test should be continued beyond one significant marker end point is reached has not been investigated either in terms of safety or prognostic power.

Risk stratification after AMI. In patients with an AMI, a set of clinical findings are used as a signal of increased risk for recurrent cardiac events. These findings include clinical evidence of pump dysfunction, recurrent ischemia and high-risk arrhythmias, which dictate for prompt cardiac catheterization. Patients with intermediate/low risk (that is, patients who lack these features) are usually referred for predischARGE stress testing, with the challenge to distinguish the few patients at higher risk from the many relatively low-risk patients.

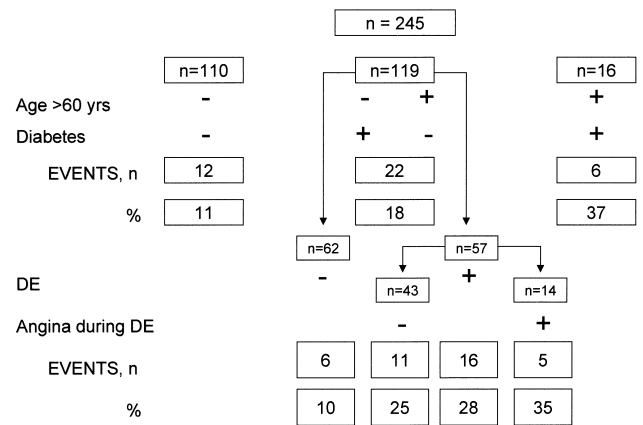


Figure 3. Incidence of cardiac events (death, myocardial infarction or unstable angina) in patients after uncomplicated acute myocardial infarction, according to the presence of clinical risk factors and the response at dobutamine stress test. DE = dobutamine echocardiography.

In the present study, we assessed the prognostic value of the predischARGE dobutamine stress test to establish whether it provides additional information beyond the known clinical information in patients with an uncomplicated AMI. When multivariate analysis was applied to the different clinical data, the only independent prognostic variables were age and diabetes. These factors have been already recognized as “not low-risk factors” in a previous study (18).

Our results point out that in a group of patients recovering from an AMI with an uncomplicated course and with an overall a priori good outcome, this clinical information alone can efficiently identify low- (no clinical risk factor) and high- (both clinical risk factors) risk patients. In patients with an intermediate risk at clinical judgment (only one clinical risk factor), a dobutamine stress test can be applied as an adjunctive useful risk stratification tool (Fig. 3). Based on the results of multivariate analysis, age and diabetes were considered for risk stratification on clinical ground: patients >60 years with a history of diabetes had a 3.4-fold increase of cardiac events at follow-up compared with patients <60 years with no history of diabetes (37% vs. 11%). The presence of only one of the two clinical risk factors identified a group of patients with an intermediate risk (18%). In this subgroup of patients, the response at dobutamine stress test can be used to distinguish patients at different risk of future cardiac events (10% in patients with negative DE; 25% in patients with positive DE and no angina during the test; 35% in patients with positive DE and angina during the test).

Clinical implications. The optimal risk stratification of patients after an AMI is still uncertain (19,20). We believe that in patients without contraindications and who can exercise, predischARGE exercise testing is still the test of choice, due to its large availability and the solid prognostic data obtained so far. In patients who are not able to exercise,

with nondiagnostic or inconclusive exercise test, DE is an attractive and useful alternative, which should be implemented in all echocardiographic laboratory. In our experience, careful selection of patients with AMI and adaptation of simple criteria for interruption of the test make predischarge DE a safe procedure.

In the present study, age and a history of diabetes emerged as important clinical predictors of adverse outcome; dobutamine stress test added independent and prognostically more important variables through the presence of wall motion abnormalities and angina during dobutamine infusion. Thus, the integration of the echocardiographic results with simple clinical (age, diabetes) and dobutamine stress test variables (angina) refines the interpretation of the test and may guide cardiologists to optimal clinical decision making.

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