Long-term prognostic value of dipyridamole and dobutamine stress echocardiography in patients with known or suspected coronary artery disease

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Coronary artery disease; Prognosis; Stress echocardiography.

Background. **Pharmacological stress echocardiography (PSE) is increasingly used for cardiac risk stratification. Our study was undertaken to assess the long-term prognostic significance of PSE in patients with known or suspected coronary artery disease.**

Methods. **We studied 622 consecutive patients who underwent PSE with either dobutamine or dipyridamole. Outcome was finally assessed in 448 patients for a mean period of 32.9 months. Death and hard events (death and myocardial infarction) were considered as endpoints.**

Results. **PSE was positive for ischemia in 192 patients (42.9%). During the follow-up, 53 hard events occurred, including 28 deaths and 25 acute non-fatal myocardial infarctions. With multivariate analysis, peak ejection fraction < 40% appeared to be the strongest predictor of cardiac-related deaths and of hard endpoints (χ^2 28.4 and 32.0, respectively). Peak wall motion score index revealed a strong predictive value of the same events (χ^2 8.6 and 16.3, respectively). An ischemic pattern at PSE predicted a 2.4 higher cardiac mortality rate over a 5-year follow-up (9.4 vs 3.9%, p < 0.01; log rank 5.68), while patients with a peak ejection fraction < 40% had a cardiac-related mortality 4 times higher (16.3 vs 4.1%, p < 0.00001; log rank 21.16). Hard events occurred in 6.7% of patients with a negative test vs 18.8% of patients with a positive test (p < 0.001; log rank 15.8), while hard event rate was 8.4% in patients with a peak ejection fraction > 40% vs 27.5% in patients with a peak ejection fraction < 40% (p < 0.00001; log rank 38.64).**

Conclusions. **The ischemic response to PSE showed a sustained prognostic value for cardiac events, especially in patients considered at either intermediate or high risk on the basis of recognized clinical risk factors. However, only the evaluation of both descriptors of global left ventricular performance and of the extension of induced ischemia may better help to select patients at higher risk of cardiac death.**

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Pharmacological stress echocardiography (PSE), with either dobutamine[1-3] or dipyridamole[4], is a widely accepted tool for both the diagnosis of coronary artery disease (CAD) and the evaluation of cardiac risk in different clinical situations.

Its efficacy for cardiac risk stratification has already been tested in patients with known or suspected CAD[5-9], early after uncomplicated myocardial infarction[10-13], and in patients undergoing major vascular surgery[14,15]. Although an excellent outcome in patients without evidence of stress-induced wall motion abnormalities has been reported[16], the PSE capacity to effectively identify patients at higher risk of cardiac events is less definite. Several recent studies on these topics reported an overall good negative prognostic power of stress echocardiography[7-13,16,17]. However, most of these studies are not directly comparable because they differ in follow-up duration (1 to 6 years), criteria of patient selection (chest pain, early after myocardial infarction, prior to major vascular surgery), cardiac events considered (sometimes including revascularization), analysis of stress echo variables (often limited to stress-induced ischemia) and modalities (exercise, pharmacological).

Our study was undertaken to assess the long-term prognostic significance of PSE for late cardiac events, and the PSE addi-

tional role compared to other traditional clinical and rest echo variables, in a large and heterogeneous patient population with proven or suspected CAD, followed up for ≥ 36 months.

Methods

Patient population. The initial cohort included 622 consecutive patients who underwent PSE clinically indicated from July 1994 to December 1998 for chest pain symptom evaluation or for cardiac risk stratification. Sixteen patients who underwent coronary artery revascularization within 3 months of PSE, and 8 patients who were lost to follow-up (1.8%) were censored. Moreover, 150 patients subjected only to low-dose dobutamine stress echo to assess myocardial viability were excluded from the study. Non-cardiac death occurred in 4 patients: 3 due to malignant cancer and 1 to a car accident.

Outcome and clinical status were finally assessed in 448 patients, for a mean period of 32.9 months (range 4-60 months). Stress echo was performed for diagnosis of suspected CAD in 192 patients (42.9%), and for risk stratification of known CAD in 256 patients (57.1%). If medical treatment had been administered it was not discontinued during the test.

Follow-up data were obtained from December 1998 to January 1999 through a review of the patient's hospital records, by periodical follow-up visits at our institution, or by phone interviews with the patient. In the case of death, data were collected by phone from a family member of the same household.

Pharmacological stress echocardiography. Patients who were unable to exercise underwent PSE when clinically indicated. In our echo laboratory we usually select the kind of stress on the basis of clinical findings and of known specific drug contraindications, such as uncontrolled hypertension or ventricular electrical instability in the case of dobutamine, and severe obstructive pulmonary disease in the case of dipyridamole.

In the present study we administered dobutamine in 330 patients and dipyridamole in 118 patients by using a standard protocol. After recording a resting two-dimensional echocardiogram, dobutamine was infused at a dose of 10, 20, 30 and 40 μg/kg/min in 3 min stages; the test started with a dose of 5 and 10 μg/kg/min over a 5 min period in patients with resting abnormal wall motion. The dipyridamole infusion included a low dose of 0.56 mg up to a high dose of 0.84 mg over 10 min. During the tests, heart rate was continuously monitored and 12-lead ECG and blood pressure were recorded at every step. Starting from January 1995, both protocols included atropine administration if the test was negative at the peak dose or if heart rate did not reach 85% of maximal age-predicted heart rate[18,19]. Criteria for test interruption were: achievement of maximal heart rate, onset of new or worsening wall motion abnormalities, severe chest pain, horizontal or downsloping ST-segment depression ≥ 2 mm, ST-segment elevation ≥ 1.5 mm, systolic blood pressure > 220 mmHg, diastolic blood pressure > 120 mmHg, reduction in systolic blood pressure ≥ 30 mmHg, and supraventricular or ventricular tachyarrhythmias.

Two-dimensional images were obtained in four standard views (parasternal long-axis, parasternal short-axis, apical 4- and 2-chamber view) using Acuson 128 XP-10 or Acuson Sequoia ultrasound systems (Mountain View, CA, USA) at baseline, at each dobutamine and dipyridamole dosage and during recovery, and recorded on a super-VHS videotape for subsequent analysis. In the last 300 patients images were also recorded using a quad-screen cine-loop system.

Echocardiographic analysis. All examinations were reviewed by two independent observers with extensive experience in interpretation of stress echocardiograms and blinded to the clinical data. Disagreements were resolved by consensus.

For left ventricular wall motion analysis, a standard 16-segment model of the left ventricle of the American Society of Echocardiography was used[20], and wall motion was scored as 1 = normal; 2 = hypokinetic; 3 = akinetic; 4 = dyskinetic. Left ventricular wall motion score index (WMSI) was calculated at baseline and at the peak of drug infusion dividing the sum of individual segment scores by the number of considered segments.

Left ventricular ejection fraction (EF) was measured at baseline and at peak pharmacological dosage using a commercially available software program that applied Simpson's rule on the 2- and 4-chamber views. Left ventricular dysfunction was considered prognostically significant if EF < 40%, which represents an optimal cut-off value for prediction of cardiac events[6]. Low-dose ischemic positivity was defined as an ischemic response occurring before the infusion of the high dose of dipyridamole or before the 30 γ/kg/min dobutamine infusion[11,21].

In patients with normal rest wall motion, the test was considered positive for myocardial ischemia in the case of development of a transient regional dyssynergy. In the case of development of regional dyssynergy limited to a single segment, the test was considered positive only if there was adequate visualization of the same segment in at least two different views. On the other hand, in patients with rest wall motion abnormalities the development of new or worsening wall motion abnormalities, including a deterioration of wall motion after improvement at low dose, was considered indicative of residual myocardial ischemia. Furthermore, rest akinesia becoming dyskinesia was not considered a positive result[22-26]. The ECG was indicative of myocardial ischemia if a horizontal or downsloping ST-segment depression > 1 mm, 80 ms after the J point, developed with stress. However, electrocardiographic changes and chest

pain were not considered *per se* as a positive response to stress test in the absence of induced or worsening wall motion abnormalities.

Follow-up. Cardiac-related death and non-fatal myocardial infarction were considered hard events. The definition of cardiac-related death required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. Non-fatal myocardial infarction was defined as a cardiac event requiring hospital admission, with development of new electrocardiographic changes and an increase in cardiac enzyme levels.

Statistical analysis. Descriptive statistical procedures were used to analyze the distribution of each variable. Patient groups were compared by Student's t-test for continuous variables and by the χ^2 test for categorical variables. Independent predictors of late cardiac events (death, hard events) were identified through univariate and multivariate Cox proportional-hazard regression models. The 0.05 probability level was adopted to consider the significance of the association between predictive variables and events. The risk associated with a given variable was expressed by a hazard ratio with corresponding 95% confidence intervals. On multivariate analysis an automatic backward stepwise procedure was adopted. The cumulative probability of freedom from cardiac events was calculated by Kaplan-Meier lifetable analysis and compared between groups by using the log rank test.

Results

Study population. The final study population included 448 patients (365 males and 83 females). An extensive analysis of both cardiac risk factors and rest echo characteristics was carried out in all patients (Tables I and II). Patients were considered to have hypercholesterolemia if their total cholesterol level was ≥ 200 mg/dl or if they were on cholesterol-lowering treatment. There were no differences in terms of clinical and resting echo parameters between patients undergoing either dobutamine or dipyridamole stress test.

On the basis of clinical data we identified in our population three subgroups of patients: low-risk (with neither diabetes nor previous myocardial infarction), intermediate-risk (with either diabetes or previous myocardial infarction), and high-risk (with both diabetes and previous myocardial infarction) patients. In addition, further separate analyses were carried out between patients with and without resting left ventricular wall motion abnormalities.

Stress echocardiography results. Dipyridamole was infused to a maximal dose of 0.84 μg/kg/min in 100 out of 118 patients. In the remaining 18 patients a low-dose ischemic positivity occurred. Dobutamine was infused to a mean peak dose of 32 ± 4 μg/kg/min. During dobutamine stress test, 54 tests were interrupted because of low-dose ischemic positivity, and 10 were prematurely stopped because of the appearance of limiting side effects: non-sustained ventricular tachycardia in 3, severe chest pain in the absence of new wall motion abnormalities in 5, and severe hypertension in 2. All side effects were reversed by antidote administration (metoprolol). Atropine was administered in 75 patients (31 dobutamine and 34 dipyridamole). No major complication occurred. The overall feasibility was 100% for dipyridamole and 97.8% for dobutamine stress echocardiography. Of the 448 tests, 38 patients failed to reach the endpoint target rate, in the absence of new wall motion abnormalities; 22 of them were on beta-blocker treatment. All these patients with submaximal or interrupted stress test were included in the analysis as negative.

Table I. Clinical findings in the study population.

	N.	%
Age (years)	66 ± 12	
Male sex	365	81.5
Family history of CAD	109	24.3
Diabetes	109	24.3
Hypercholesterolemia	136	30.4
Hypertension	178	39.7
Obesity	36	8.0
Cigarette smoking	211	47.1
Previous angina	209	46.7
Previous AMI	241	53.8
Previous PTCA	47	10.5
Previous CABG	40	9.0
Use of beta-blockers	65	14.5

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; PTCA = coronary angioplasty.

Table II. Rest echo variables and pharmacological stress echo results.

	N.	%
Rest echo variables		
Basal EF		48 ± 5
Basal WMSI		1.3 ± 0.3
Wall motion abnormalities	288	64
ECG abnormalities	62	19.8
PSE results		
Peak EF		45 ± 6
Peak WMSI		1.6 ± 0.6
Positive PSE	192	42.9
Angina during the test	76	17.0
ECG changes	89	19.8
Low-dose positivity	62	13.8

EF = ejection fraction; PSE = pharmacological stress echocardiography; WMSI = wall motion score index.

At baseline, the mean value of WMSI was 1.3, and the mean EF was 48%; wall motion abnormalities were present in 288 patients (64%). The stress echo test was positive for ischemia in 192 patients (42.9%). During the test 76 patients (17%) experienced angina. The ECG was suggestive of ischemia in 89 patients (19.8%). At the peak dosage, the mean WMSI was 1.6, and the mean EF was 45%. A low-dose ischemic response was present in 62 patients (19.8%).

Interobserver agreement (P.M., P.C.) was 95% for assessment of left ventricular WMSI and 92% for analysis of left ventricular EF. Intraobserver reproducibility was 96 and 94%, respectively.

Cardiac events. During the follow-up period there were 278 events (62.1%), including 53 hard events (11.8%), 28 deaths (6.3%), and 25 acute non-fatal myocardial infarctions (5.6%). The other cardiac events were: angina pectoris in 75 patients (16.7%), heart failure in 12 (2.7%), coronary angioplasty in 68 (15.2%), bypass surgery in 70 (15.6%).

Death. On univariate analysis the following variables resulted significantly predictive for cardiac death (in descending order): diabetes mellitus, peak and rest EF, peak and rest WMSI, low-dose ischemic positivity, previous myocardial infarction, positive stress test, and previous angina (Table III). On multivariate analysis, utilizing an automatic stepwise procedure, the combination of clinical, rest and stress test variables identified peak EF (χ^2 28.4, $p < 0.0001$), diabetes mellitus (χ^2 16.4, $p < 0.0001$), low-dose ischemic threshold (χ^2 9.6, $p < 0.002$), peak WMSI (χ^2 8.6, $p < 0.003$), and hypercholesterolemia (χ^2 4.1, $p < 0.04$) as the strongest independent predictors of cardiac death. The global χ^2 of this combined clinical and stress test model was 53.7 ($p < 0.00001$) (Table IV).

The annual survival rate at 1, 2 and 3 years was respectively 99.2, 98.2 and 94.8% in patients with negative test for ischemia vs 97.9, 91.2 and 87.5% in patients with positive test (Fig. 1). The cumulative 5-year survival rate was 96.1% in patients with negative stress echo vs 90.6% in patients with positive test (log rank 5.68, $p < 0.01$). The cumulative 5-year survival rate according to peak EF was 95.9% in patients with peak EF > 40%, and 83.7% if peak EF was < 40% ($p < 0.00001$, log rank 21.16).

Hard cardiac events (death, non-fatal myocardial infarction). On univariate analysis, among the different variables the following resulted significantly predictive of hard events (in descending order): peak and rest EF < 40%, positive stress test, peak WMSI, angina during the test, previous myocardial infarction, diabetes mellitus, family history for CAD (Table III). On multivariate analysis, the combination of clinical, rest and stress test variables identified peak EF (χ^2 32.0, $p < 0.0001$), diabetes mellitus (χ^2 9.2, $p < 0.003$), peak WMSI (χ^2 6.3, $p = 0.012$), male sex (χ^2 5.1, $p = 0.024$), and ischemic response to stress echo (χ^2 4.9, $p < 0.027$) as the strongest independent predictors of hard events. The global χ^2 of this model was 61.2 ($p < 0.0001$) (Table IV). The annual hard events-free rate at 1, 2 and 3 years of follow-up was 99.2, 96.9 and 92.5% respectively in patients with negative test for ischemia vs 97.9, 88.9 and 84.9% in patients with positive result (Fig. 2).

The cumulative 5-year survival rate free of hard cardiac events was 93.3% in patients with negative

Table III. Univariate predictive value of clinical risk factors and pharmacological stress echo results for cardiac events.

	Death			Hard events		
	p	HR	95% CI	p	HR	95% CI
Clinical data						
Age	NS	1.2	0.6-2.5	0.02	2.1	1.4-3.2
Family history of CAD	NS	1.6	0.7-3.4	0.006	2.2	1.3-4.0
Diabetes	0.0001	3.5	1.7-7.3	0.002	2.3	1.4-4.0
Previous angina	0.05	0.4	0.2-1.0	0.05	0.6	0.3-1.0
Previous AMI	0.01	3.2	1.3-8.0	0.002	2.7	1.4-5.0
Rest echocardiographic data						
Rest EF	0.03	2.3	1.1-4.7	0.0001	2.8	1.7-4.9
Rest EF < 40%	0.0008	3.6	1.7-7.5	0.0009	2.6	1.5-4.5
Rest WMSI	0.009	2.8	1.3-6.1	0.001	2.6	1.4-4.6
Stress echocardiographic data						
Positive PSE	0.02	2.5	1.1-5.3	0.0002	3.0	1.7-5.4
Peak EF	0.0001	0.9	0.9-1.0	0.0001	0.9	0.9-1.0
Peak EF < 40%	0.0009	4.8	2.3-10.2	0.0001	4.9	2.8-8.6
Peak WMSI	0.0001	0.9	0.9-1.0	0.0001	0.9	0.9-1.0
Low-dose ischemia	0.006	0.3	0.1-0.7	NS	0.7	0.3-1.5
Angina during PSE	NS	2.0	0.9-4.6	0.002	2.5	1.4-4.6

CI = confidence interval; HR = hazard ratio. Other abbreviations as in tables I and II.

Table IV. Multivariate predictive value of clinical risk factors and pharmacological stress echo results for cardiac events.

Variable considered	Model χ^2	p	Variables selected	Partial (χ^2; p value)
Death				
Clinical	26.4	0.0001	Diabetes mellitus	11.3; < 0.0001
			Previous AMI	6.4; < 0.0001
Clinical + rest echocardiography	38.3	0.0001	Rest EF	16.7; < 0.0001
			Diabetes mellitus	9.3; 0.002
			Hypercholesterolemia	4.1; 0.04
			Male sex	9.0; 0.05
Clinical + rest echocardiography + stress echocardiography	53.7	0.0001	Peak EF < 40%	28.4; < 0.0001
			Diabetes mellitus	16.4; < 0.0001
			Low-dose ischemia	9.6; 0.002
			Peak WMSI	8.6; 0.003
			Hypercholesterolemia	4.8; 0.029
Hard events				
Clinical	28.9	0.0001	Previous AMI	9.4; 0.002
			Diabetes mellitus	6.9; 0.009
			Male sex	4.7; 0.03
			Family history	4.1; 0.04
Clinical + rest echocardiography	35.4	0.0001	Rest EF	15.5; 0.033
			Diabetes mellitus	6.5; 0.03
			Family history	4.7; < 0.01
			Male sex	4.6; < 0.01
Clinical + rest echocardiography + stress echocardiography	61.2	0.0001	Peak EF < 40%	32.0; < 0.0001
			Diabetes mellitus	9.2; 0.003
			Peak WMSI	6.3; 0.012
			Male sex	5.1; 0.024
			Positive PSE	4.9; 0.027

Abbreviations as in tables I and II.

stress echo vs 81.2% in patients with positive test ($p < 0.001$, log rank 15.8). The cumulative 5-year survival rate according to peak EF was 91.6% if peak EF was > 40% and 72.5% in patients with peak EF < 40% ($p < 0.00001$, log rank 38.64).

Subgroup analysis. Although 48 out of 163 patients (29%) at low risk of cardiac events showed a PSE positive for ischemia, in this subset of patients there were only 3 deaths (2%) and 7 hard events (4%) during the follow-up (p = NS vs patients with negative PSE). Conversely, both in 220 patients at intermediate risk and in 65 patients at high risk, an ischemic result at PSE (occurring in 47 and 48% of patients, respectively) allowed us to identify patients with a significantly higher risk of cardiac death (12 vs 7% and 15 vs 9%, both $p < 0.01$) and of hard events (17 vs 9% and 19 vs 11%, respectively, both $p < 0.01$) than patients with negative PSE.

Among the 160 patients with normal left ventricular wall motion at rest, PSE was positive for ischemia in 57 cases (33%), and allowed us to select patients at higher risk (6%) of hard events ($p < 0.05$) but not of death (p = NS). Also in 128 out of 288 patients (44%) with rest wall motion abnormalities (baseline WMSI > 1) and ischemic response to PSE, we observed a significantly increased risk of hard events than in patients with negative PSE ($p > 0.01$). These findings are in agreement with previous studies reporting a higher risk of cardiac events in patients with both abnormal left ventricular rest wall motion and ischemic response to PSE, rather than either finding alone[5,7-8].

Discussion

Our study confirmed that the absence of stress echo-induced myocardial dyssynergy provides a good long-term prognosis in a population with proven or suspected CAD. Conversely, an ischemic pattern (i.e. new or worsening wall motion abnormalities) at PSE predicts a 2.4 higher cardiac mortality rate over a 5-year follow-up (9.4 vs 3.9%, $p < 0.01$, log rank 5.68). Furthermore, this conclusion becomes even more evident when analyzing EF at peak stress, a recognized and widely used parameter of global left ventricular function. In fact, car-

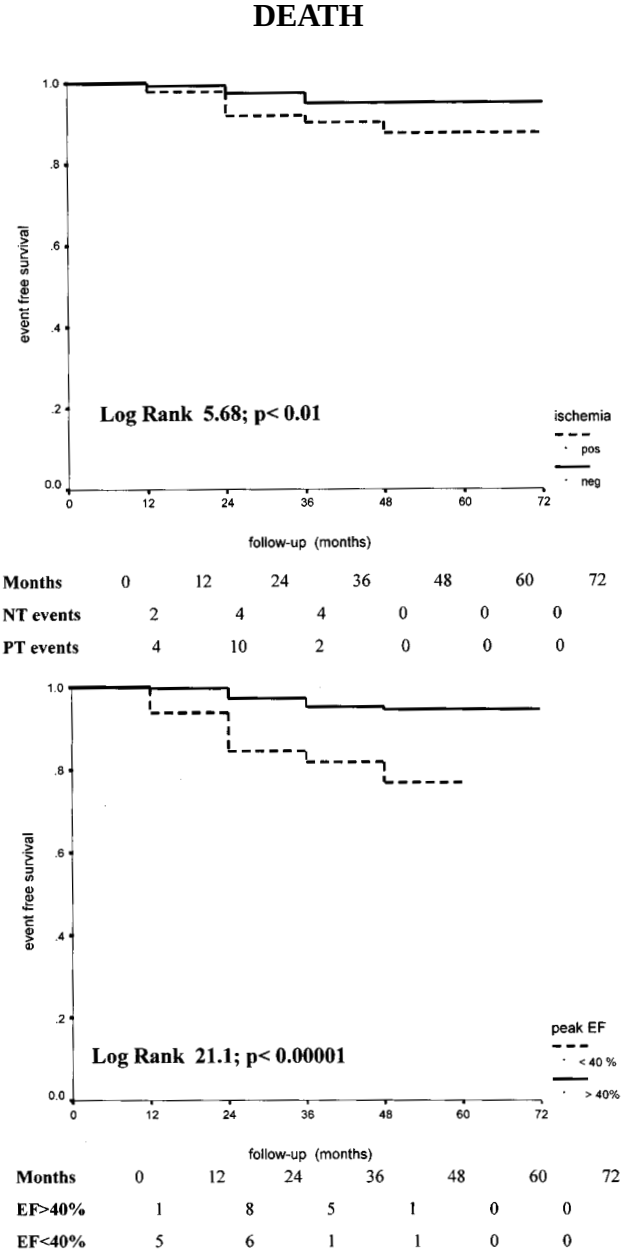

Figure 1. *Kaplan-Meier curves for cardiac death during follow-up by the results of pharmacological stress echocardiography and peak ejection fraction (EF).* Top: *cumulative survival rate according to the ischemic response to pharmacological stress echo.* Solid line: *negative test (NT);* dotted line: *positive test (PT).* Bottom: *cumulative survival rate according to the value of peak EF.* Solid line: *peak EF < 40%;* dotted line: *peak EF > 40%.*

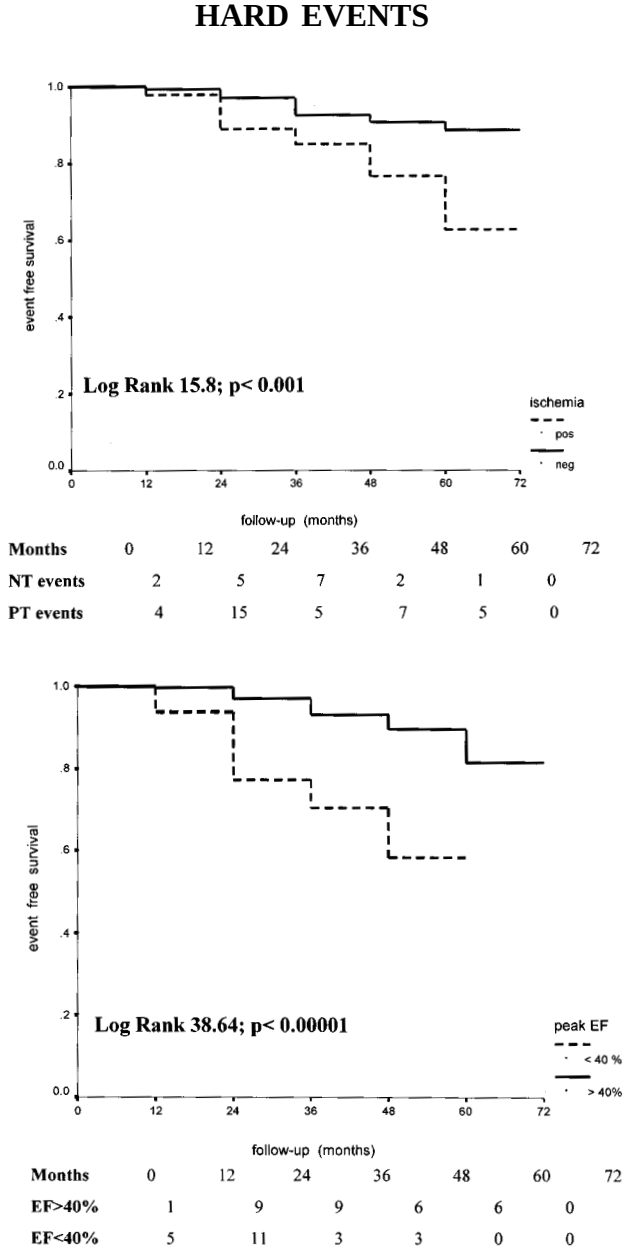

Figure 2. *Kaplan-Meier curves for hard cardiac events during follow-up by the results of pharmacological stress echocardiography and peak ejection fraction (EF).* Top: *cumulative survival rate free from hard events according to the ischemic response to pharmacological stress echo.* Solid line: *negative test (NT);* dotted line: *positive test (PT).* Bottom: *cumulative survival rate free from hard events according to the value of peak EF.* Solid line: *peak EF < 40%;* dotted line: *peak EF > 40%.*

diac-related mortality was 4 times higher in patients with a peak EF < 40% than in patients with a peak EF > 40% (16.3 vs 4.1%, p < 0.00001, log rank 21.16).

Considering both hard events, cardiac death and non-fatal myocardial infarction, the prognostic power of stress echocardiography remained evident. In fact, hard events occurred in 6.7% of patients with a negative test for ischemia vs 18.8% of patients with a positive test (p < 0.001, log rank 15.8). Furthermore, this difference was emphasized even more according to peak EF. Hard event rate was 8.4% in patients with a peak EF > 40% vs 27.5% in patients with a peak EF < 40% (p < 0.00001, log rank 38.64). Therefore, a reduced EF at peak stress seemed to better identify patients at higher risk of hard events.

On univariate analysis, among stress echo variables, descriptors of an impaired global left ventricular performance (peak EF < 40%: hazard ratio 4.8, 95% confidence interval 2.3-10.2) and indexes of the extent and severity of stress-induced myocardial ischemia (peak WMSI: hazard ratio 0.9, 95% confidence interval 0.9-1.0; low-dose positivity: hazard ratio 0.3, 95% confidence interval 0.1-0.7) appeared to be the best predic-

tors of cardiac death. On the other hand, angina during the test and induced myocardial ischemia resulted in being powerful predictors when hard cardiac events were considered. This fact may be the consequence of the different physiological mechanisms implicated in the determination of different cardiac endpoints[27]. In fact, some parameters (i.e. angina during stress) seem related to the degree of a single coronary stenosis, whereas other variables (i.e. reduced peak EF, low-dose positivity) presume there is an impaired global left ventricular function secondary to a multivessel CAD[21], which is more related to the risk of cardiac death. These results are in accordance with the conclusions of the Cass Registry on the long-term prognostic value of exercise testing. Poor exercise capacity, which is usually the consequence of a multivessel involvement of the atherosclerotic process, had a greater effect on survival than ST-segment depression during exercise[28,29].

On multivariate analysis, peak EF < 40% appeared to be the strongest predictor of cardiac-related death, and of hard endpoints (χ^2 28.4 and 32.0, respectively). The prognostic value of systolic function indices in dobutamine stress test has already been evaluated by Coletta et al.[30] who reported an abnormal end-diastolic volume response and baseline EF < 40% to be independent predictors of an unfavorable outcome. Furthermore, peak WMSI, an integrated expression of the amount of myocardium at risk, revealed a strong predictive value of the same events (χ^2 8.6 and 6.3, respectively), as previously pointed out by Sicari et al.[10] in patients with recent uncomplicated myocardial infarction.

In conclusion, our findings confirmed the prognostic role of recognized clinical risk factors and stress echo variables in cardiac events, emphasizing the role of the additional features of a pharmacological stress test in depicting the cardiac risk profile better than the sole use of the ischemic response to the stress.

Additive prognostic value of stress echocardiography. Our results, in keeping with Chuach et al.[7], showed that information obtained by stress echo was additional to and independent of that provided by clinical and rest echocardiographic data. In fact, considering cardiac death and hard events, the commonly considered clinical variables reached a global χ^2 of 26.4, with diabetes (partial χ^2 11.3) and previous myocardial infarction (partial χ^2 6.4) as the most powerful predictors. However, the addition of echo (rest abnormal wall motion abnormalities) and stress echo variables to this model increased the probability of events to 38.3 and 53.7 for death and to 35.4 and 61.2 for hard events, with peak EF as the best predictor of cardiac events (partial χ^2 28.4 and 32.0, respectively) (Fig. 3).

Considering the prognostic value of PSE in different subsets of patients, our findings underscored the incremental value of a positive PSE in identifying patients at higher risk of cardiac events, especially in patients considered at either intermediate or high risk on the basis of recognized clinical risk factors. Moreover, although not essential for further prognostication, an ischemic response to PSE in low-risk groups may be useful for diagnostic purposes since it may affect treatment plans.

Time allocation of cardiac events. In the overall population most of hard cardiac events were not concentrated in the first year of follow-up. In fact, cumulative survival rate and Kaplan-Meier curves became significantly different after the second year of follow-up. This fact could imply the need for a repetition of the test after the second year of follow-up in patients with high likelihood of CAD and negative stress echo.

Little is known of these topics. Our data are partially in accordance with Steinberg et al.[6], who found a clear

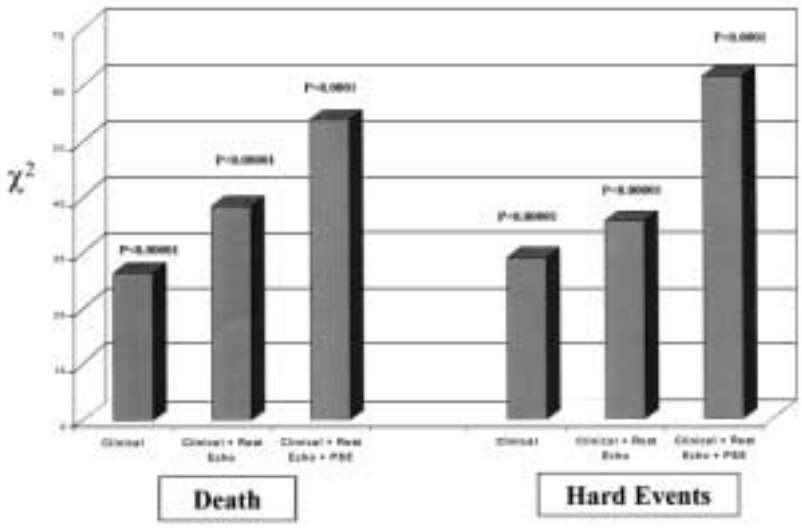

Figure 3. *Incremental value of pharmacological stress echocardiography (PSE) in predicting late cardiac events.*

difference in cumulative survival in the third year of follow-up, but this seems to be in contrast with the findings of Dhond et al.[16], who reported no significant change in event rate over a 5-year follow-up.

Stress test technique. We collected data from either dipyridamole or dobutamine stress echo, considering the identical diagnostic accuracy and prognostic power[12,30,31] of these two independent exercise stressors. At our institution we usually interchange this kind of test, although we prefer dobutamine echocardiography when assessing myocardial viability.

Atropine was only utilized in a percentage of patients reflecting the standard protocol at the time the study started. This fact does not seem to have affected the efficacy of the test, given the overall good prognosis connected with test negativity.

Study limitations. An unsatisfactory intra and inter-observer variability in stress echo interpretation has previously been reported[32]. However in our study all patients were evaluated in a single intensive coronary unit of our hospital, with the advantage of a homogeneous reading of stress echo in a single echo laboratory, which prevents the low inter-institutional agreement in the interpretation of stress echo findings.

In most patients wall motion analysis was qualitatively carried out from videotape and not in cine-loop fashion. Although representing a more valid form of stress testing storage, digital acquisition did not show an improved diagnostic value when compared to traditional videotape analysis[33].

The routine implementation of second harmonic imaging on modern ultrasound systems, with and without contrast enhancement, improved the ability to detect mild forms of CAD. This fact would have further increased the negative prognostic power of stress echocardiography[34,35].

There is controversy whether coronary angioplasty and bypass surgery have to be considered cardiac events. In fact, although they reflect the presence of a severe cardiac disease, the decision to undergo these procedures may be subjective and not in itself an adverse outcome. As a consequence, we preferred not to include these events among the endpoints of our study.

Clinical implications. The final report of a PSE performed for prognostic purposes should include both the assessment of the presence of induced dyssynergy and the evaluation of indexes of the extent and severity of myocardial ischemia (such as a low-dose ischemic response and peak WMSI). These analyses, together with descriptors of global left ventricular performance, such as peak EF, better identify a population at higher risk of late major cardiac events, especially in patients considered at either intermediate or high risk only on the basis of clinical data.

Conclusions. Absence of stress-induced myocardial ischemia at dipyridamole and dobutamine echocardiography determines a good prognosis over a 5-year follow-up. Evidence of ischemia at stress echocardiography may identify a population at risk of future cardiac events. However, only the evaluation of clinical variables, such as diabetes mellitus, as well as stress echo variables, such as low-dose positivity, peak EF < 40% and higher peak WMSI, may help to select patients at greatest risk of cardiac death.

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