Risk stratification and prognosis of patients with known or suspected coronary artery disease by use of supine bicycle exercise stress echocardiography

Antonello D'Andrea, Sergio Severino*, Pio Caso*, Angela Fusco*, Rosalia Lo Piccolo*, Biagio Liccardo*, Alberto Forni*, Giovanni Di Salvo, Marino Scherillo**, Nicola Mininni*, Raffaele Calabrò

*Department of Cardiology, Second University of Naples, *Department of Cardiology, Monaldi Hospital, Naples, **Department of Interventional Cardiology, G. Rummo Hospital, Benevento, Italy*

Key words:
Coronary artery disease; Exercise; Prognosis; Stress echocardiography.

Background. **The aim of this study was to assess the long-term predictive values of supine bicycle exercise stress echocardiography (ESE), and the ESE additional role compared to other traditional clinical and rest echocardiographic variables, in 607 patients with low, intermediate and high pretest risk of cardiac events.**

Methods. **Clinical status and long-term outcome were assessed for a mean period of 46 months (range 12-60 months). ESE was performed for the diagnosis of suspected coronary artery disease (CAD) in 267 patients (43.9%), and for risk stratification of known CAD in 340 patients (56.1%). At baseline, the mean value of wall motion score index (WMSI) was 1.22 ± 0.36, and the mean left ventricular ejection fraction was 58.5 ± 10.9%.**

Results. **ESE was positive for ischemia in 210 patients (34.9%), while ECG was suggestive for ischemia in 157 patients (25.8%). During the test only 97 patients (15.9%) experienced angina. At peak effort, the mean WMSI was 1.38 ± 0.46. A low workload was achieved by 158 patients (26.1%). During the follow-up period there were 222 events, including 82 hard events (36.9%), 48 deaths (21.6%) and 34 acute non-fatal myocardial infarction (15.3%). At stepwise multivariate model, cigarette smoking ($p < 0.01$), peak WMSI ($p < 0.001$), ESE positive for ischemia ($p < 0.001$) and low workload ($p < 0.01$) were the only independent predictors of cardiac death, while positive ESE, peak WMSI, angina during the test and hypercholesterolemia were the only independent determinants of hard cardiac events. The cumulative 5-year mean survival rate according to ESE response was 95.9% in patients with negative ESE, and 83.7% in patients with positive ESE (log rank 13.6; $p < 0.00001$).**

Conclusions. **ESE yields prognostic information in known or suspected CAD, especially in patients with intermediate pretest risk level. The combined evaluation of clinical variables and other ESE variables, such as peak WMSI and exercise capacity, may further select patients at greatest risk of cardiac death in the overall population.**

(Ital Heart J 2005; 6 (7): 565-572)

Received November 29, 2004; revision received February 22, 2005; accepted February 24, 2005.

Address:
Dr. Antonello D'Andrea
Via G. Martucci, 35
80121 Napoli
E-mail:
adandrea@synapsis.it

Stress echocardiography, either with pharmacologic or exercise protocol, is a routinely accepted tool both for the diagnosis of coronary artery disease (CAD) and the evaluation of cardiac risk in different clinical settings[1].

In patients unable to perform exercise, pharmacologic stress echocardiography is widely used for the diagnosis of CAD, and its efficacy for cardiac risk stratification has been tested in patients undergoing major vascular surgery, with impaired left ventricular (LV) function, with diabetes mellitus, and early after uncomplicated acute myocardial infarction[2-9]. On the other hand, exercise stress echocardiography (ESE) is a routine test in patients able to perform a physical stress but with repolarization abnormalities that make exercise ECG uninterpretable, or when treatment decisions may be dependent on the site or the extent of ischemia[10-14].

Although several recent studies have reported an excellent outcome in patients without evidence of stress-induced wall motion abnormalities, the ESE capacity to effectively identify patients at higher risk of cardiac events is less definite. In fact, many of the studies on this topic differ in follow-up duration, cardiac events considered (revascularization sometimes included), analysis of stress echo variables (often limited to stress-induced ischemia) and modalities (exercise, pharmacological)[10-14].

In addition, no study on the long-term prognostic value of supine bicycle ESE in a large population of patients has been reported to date, since most of previous studies used post-treadmill stress echo analysis.

On this ground, the present study was undertaken to assess the long-term prognostic significance of ESE, and the ESE additional role compared to other traditional clinical and rest echo variables, in a large population of patients with low, intermediate and high pretest risk of cardiac events, followed up for ≥ 46 months.

Methods

Study population. The initial cohort included 640 consecutive patients who underwent ESE clinically indicated from July 1997 to December 2003 for the evaluation of chest pain symptoms or for cardiac risk stratification. Twenty-two patients who underwent coronary artery revascularization within 3 months of ESE procedure, and 8 patients who were lost to follow-up (0.9%), were censored. Non-cardiac death occurred in 3 patients: 2 for malignant cancer and 1 for a car accident.

Patient outcome and clinical status were finally assessed in 607 patients, for a mean period of 46.9 months (range 12-60 months). Exercise echo was performed for the diagnosis of suspected CAD in 267 patients (43.9%), and for risk stratification of known CAD in 340 patients (56.1%). Medical treatment if present was discontinued 3 days before the test.

Follow-up data were obtained from September 2003 to March 2004 through a review of patient hospital records, by periodical follow-up visit at our institution, or by phone interview with the patient. In case of death, data were collected by phone contact with the same household family member.

Exercise stress echocardiography. In our study patients performed ESE by bicycle ergometer in a supine position, using a standard Bruce protocol. After recording a resting two-dimensional echocardiogram, the heart rate was continuously monitored and 12-lead ECG, echocardiographic images and blood pressure were recorded at every step. Criteria for test interruption were: maximal heart rate achievement, onset of new or worsening wall motion abnormalities, severe chest pain, horizontal or down-sloping 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, supraventricular or ventricular tachyarrhythmias.

Two-dimensional images were obtained in four standard views (parasternal long-axis, parasternal short-axis, apical 4- and 2-chamber views) using Acuson Sequoia ultrasuond systems (Mountain View, CA, USA) at baseline, at each exercise step and during recovery, and 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 LV wall motion analysis, standard 16-segment LV model of the American Society of Echocardiography was used[15], and wall motion was scored as 1 = normal; 2 = hypokinetic; 3 = akinetic; 4 = dyskinetic. LV wall motion score index (WMSI) was calculated at baseline and at peak effort dividing the sum of individual segment scores by the number of considered segments. LV ejection fraction was measured at baseline and at peak effort, using a commercially available software program that applied Simpson's rule on the 2-chamber and 4-chamber views.

In patients with normal rest wall motion, the test was considered positive for myocardial ischemia in case of development of a transient regional dyssinergy. In case of development of regional dyssinergy limited to a single segment, the test was considered positive only in case of 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 a new or a worsening wall motion abnormality, including a deterioration of wall motion after improvement at low workload, was considered indicative of residual myocardial ischemia. Furthermore, rest akinesia becoming dyskinesia was not considered a positive result[1].

A low workload was defined as an achievement of < 7 metabolic equivalents (METS) for males and < 5 METS for females, because the expected treadmill time for males is, on average, 2-3 min longer than that for females (Bruce protocol)[11,12]. ECG was indicative of myocardial ischemia if a horizontal or downsloping ST depression > 1 mm, 80 ms after J point, developed with stress. However, electrocardiographic changes and chest pain were not considered *per se* as a positive response to stress test in 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 due to congestive heart failure or myocardial infarction in absence of any other precipitating factors.

Non-fatal myocardial infarction was defined as a cardiac event requiring admission to the hospital, with elevation of biochemical markers of myocardial necrosis (troponin) and with at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on ECG; c) ECG changes indicative of ischemia (ST-segment elevation or depression); d) coronary artery intervention (coronary angioplasty).

Statistical analysis. Descriptive statistics procedures were used to analyze the distribution of each variable. Patient groups were compared by Student's t-test for continuous variables and the χ^2 test for categorical variables. Independent predictors of late cardiac events (death, hard events) were identified at 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. At multivariate analysis an automatic backward stepwise procedure was adopted. The cumulative probability of freedom from cardiac events was calculated by Kaplan-Meier life-table analysis and compared between groups by the use of the log-rank test.

Results

Study population. The final study population included 607 patients. An extensive analysis of cardiac risk factors was performed in all patients (Table I). The pretest cardiovascular risk was determined using an algorithm based on previous studies[11,12,16] (Table II). We classified chest pain using the three categories of Diamond[16]: typical angina, atypical angina, and non-anginal chest pain. Risk factors included the following: current or prior cigarette smoking, history of hypertension (on antihypertensive therapy), history of insulin- or non-insulin-requiring diabetes, history of high cholesterol or on cholesterol-lowering therapy, family history of premature (< 60 years of age) CAD (infarction, coronary artery bypass or angioplasty, sudden death) in first-degree relatives, and obesity defined as a body mass index > 27 kg/m^2. Females were estrogen status negative if they were in post-menopause and not receiving estrogen replacement therapy. If they were in pre-menopause or receiving estrogen replacement therapy, they were considered as estrogen status positive.

On these bases, in our population we identified three subgroups of patients: low-risk (116 patients), intermediate-risk (410 patients), and high-risk (81 patients) groups.

Table I. Clinical findings in the study population.

No. patients	607
Age (years)	58.5 ± 10.9
Males	470 (77.4%)
Family history of CAD	455 (75.8%)
Diabetes mellitus	91 (14.9%)
Hypercholesterolemia	361 (59.4%)
Arterial hypertension	394 (64.9%)
Smokers	355 (58.4%)
Angina	520 (85.6%)
Previous AMI	260 (42.8%)
Previous PTCA	61 (10.1%)
Previous CABG	19 (3.2%)

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

Table II. Variables included in our pretest cardiovascular risk evaluation.

Variable	Score
Age (years)	
Males	
< 40	3
40-54	6
≥ 55	9
Females	
< 50	3
50-64	6
≥ 65	9
Angina history	
Typical	5
Atypical	3
Non-anginal	1
Diabetes	2
Hypercholesterolemia	1
Arterial hypertension	1
Cigarette smoking	1
Family history of CAD	1
Obesity	1
Estrogen status	
Positive	-3
Negative	+3
Total	

CAD = coronary artery disease. Pretest score: low, 0 to 8 points; intermediate, 9 to 15 points; high, > 15 points.

Rest and exercise echocardiography. During ESE test, 9 tests (1.4%) were prematurely stopped because of the appearance of limiting side effects: non-sustained ventricular tachycardia in 3 patients, severe chest pain in the absence of new wall motion abnormalities in 3, severe hypertension in 3. All side effects reversed by the administration of methoprolol.

At baseline, the mean value of WMSI was 1.22 ± 0.36, and the mean ejection fraction was 58.2 ± 10.9%. Wall motion abnormalities were present in 365 patients (60.1%). ESE was positive for ischemia in 210 patients (34.9%), while ECG was suggestive for ischemia in 157 patients (25.8%). During the test only 97 patients (15.9%) experienced angina. At peak effort, the mean WMSI was 1.38 ± 0.46, and ejection fraction was 62.3 ± 9.8%. A low workload was achieved by 158 patients (26.1%).

Interobserver agreement was 95% for the assessment of LV WMSI and 92% for analysis of positive response for ischemia. Intraobserver reproducibility was 96 and 94%, respectively.

Cardiac events. During the follow-up period there were 222 events, including 82 hard events (36.9%), 48 deaths

(21.6%) and 34 acute non-fatal myocardial infarction (15.3%). The other cardiac events were: angina pectoris in 30 patients (15.5%), acute heart failure in 16 (7.2%), percutaneous transluminal coronary angioplasty in 72 (31.4 %), coronary artery bypass graft in 20 (9%).

At univariate analysis, the following variables resulted significantly predictive for cardiac death (in descending order): ESE positive for ischemia, peak WMSI, low workload, rest WMSI, cigarette smoking and age (Table III). At multivariate analysis, utilizing an automatic stepwise procedure, the combination of clinical, rest and stress test variables identified ESE positive for ischemia, peak WMSI, low workload, and cigarette smoking as strongest independent predictors of cardiac death. The global χ^2 of this combined clinical and stress test model was 37.9 ($p < 0.00001$) (Table IV).

As for hard events (death + myocardial infarction), at univariate analysis the following variables resulted significantly predictive: positive stress test, peak WMSI, angina during the test, rest WMSI, hypercholesterolemia and cigarette smoking (Table III). However, multivariate analysis identified positive ESE, peak WMSI, angina during the test and hypercholesterolemia as only independent determinants of hard cardiac events. The global χ^2 of this combined clinical

Table III. Univariate predictive value of clinical risk factors and exercise stress echocardiography (ESE) results for cardiac events

	Cardiac death			Hard events		
	p	HR	95% CI	p	HR	95% CI
Clinical data						
Age	< 0.01	1.9	1.5-4.8	NS	1.2	1.1-5.2
Hypercholesterolemia	NS	1.3	0.7-4.4	< 0.001	4.7	3.3-6.0
Cigarette smoking	< 0.001	4.1	2.3-4.8	NS	1.3	1.2-4.6
Rest echocardiographic data						
Rest WMSI	< 0.01	3.6	2.3-6.1	< 0.01	3.8	2.4-5.8
ESE data				< 0.0001	5.3	4.9-5.6
Positive ESE	< 0.0001	5.1	4.8-5.8			
Peak WMSI	< 0.0001	4.8	4.2-5.7	< 0.0001	5.0	4.8-6.1
Low workload	< 0.001	4.1	3.5-5.1	NS	2.3	1.4-4
Angina during ESE	NS	2.2	1.9-3.6	< 0.001	4.1	2.8-4.9

CI = confidence interval; HR = hazard ratio; WMSI = wall motion score index.

Table IV. Multivariate predictive value of clinical risk factors and exercise stress echocardiography (ESE) results for cardiac events.

Variables	χ^2	p	Variables selected (partial χ^2; 95% CI; p)
Cardiac death			
Clinical	9.3	0.01	Cigarette smoking (2.8; 1.8-4.1; < 0.01)
Clinical + Rest echo	11.8	0.001	Rest WMSI (3.0; 2.1-4.1; < 0.01)
Clinical + Rest echo + ESE	37.9	0.00001	Positive ESE (4.1; 3.6-4.4; < 0.0001) Peak WMSI (3.5; 2.8-4.1; < 0.0001) Low workload (3.1; 2.7-3.7; < 0.01)
Hard events			
Clinical	9.6	0.01	Hypercholesterolemia (2.5; 1.6-3.3; < 0.01)
Clinical + Rest echo	12.5	0.001	Rest WMSI (3.1; 2.4-3.8; < 0.01)
Clinical + Rest echo + ESE	39.6	0.00001	Positive ESE (4.5; 3.6-5.3; < 0.0001) Peak WMSI (3.7; 2.6-4.4; < 0.0001) Angina during ESE (2.9; 2.3-3.8; < 0.01)

CI = confidence interval; WMSI = wall motion score index.

and stress test model was 39.8 ($p < 0.00001$) (Table IV).

The cumulative 5-year mean survival time free of cardiac events in patients with negative stress echo was 56.8 vs 43.2 months in patients with positive test. The cumulative 5-year mean survival rate according to ESE response was 95.9% in patients with negative ESE, and 83.7% in patients with positive ESE (log rank 13.6; $p < 0.00001$) (Fig. 1).

On the other hand, receiver operating characteristic curve analyses selected cut-off values of peak workload < 7 METS (area under the curve 0.79; $p < 0.0001$) as powerful predictor of cardiac mortality, in accordance with previous reports[11,12] (Fig. 2).

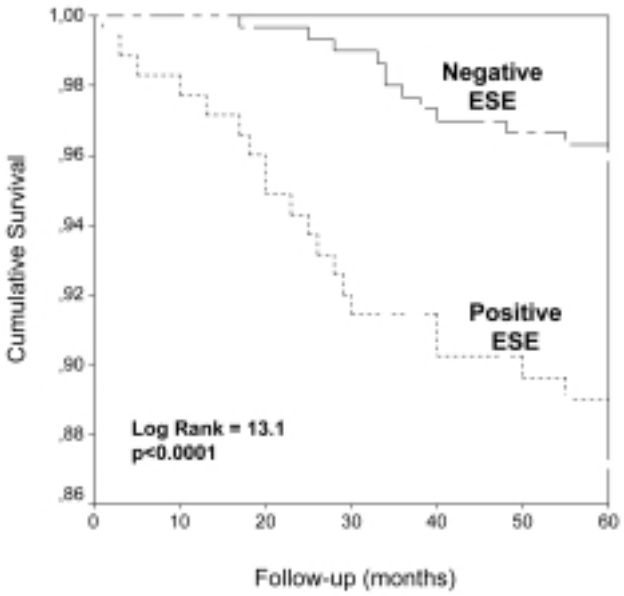

Figure 1. *Kaplan-Meier curves for cardiac death during follow-up obtained by the results of exercise stress echocardiography (ESE) in the overall population. Cumulative survival rate according to the ischemic response to ESE.*

Subgroup analysis. Although 28 out of 116 patients (24.5%) at low risk of cardiac events showed an ESE positive for ischemia, in this subset of patients there were only 4 deaths (3.4%) during the follow-up ($p = NS$ vs patients with negative ESE). Conversely, either in 410 patients with intermediate risk or in 81 patients at high risk, an ischemic result of ESE (occurring in 30 and 75% of patients, respectively) allowed to identify patients with significantly higher risk of death than in patients with negative ESE (15.1 vs 3.3%, $p < 0.0001$, and 21.3 vs 9.6%, $p < 0.0001$, respectively).

Discussion

Our study confirms that the absence of ESE-induced myocardial dyssinergy provides a good long-term prognosis in a population with proven or suspected CAD and normal LV global systolic function. Conversely, an ischemic pattern at ESE predicts a 4-fold higher cardiac mortality rate over a 5-year follow-up. Moreover, our results emphasize that information obtained by ESE is additional and independent to that provided by clinical and rest echocardiographic data (Fig. 3).

Previous reports on exercise stress echocardiography in patients with coronary artery disease. To the best of our knowledge, our study is the first to provide data regarding the long-term prognostic usefulness of supine bicycle ESE to stratify patients with known or suspected CAD into high- and low-risk subsets for car-

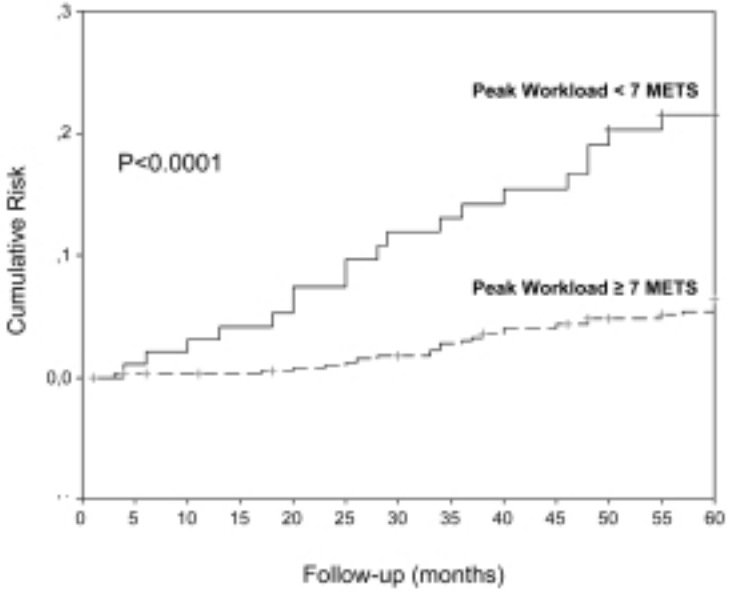

Figure 2. *Cumulative risk of cardiac death at follow-up among subjects who achieved a peak exercise capacity during exercise stress echocardiography (ESE) < 7 or ≥ 7 METS.*

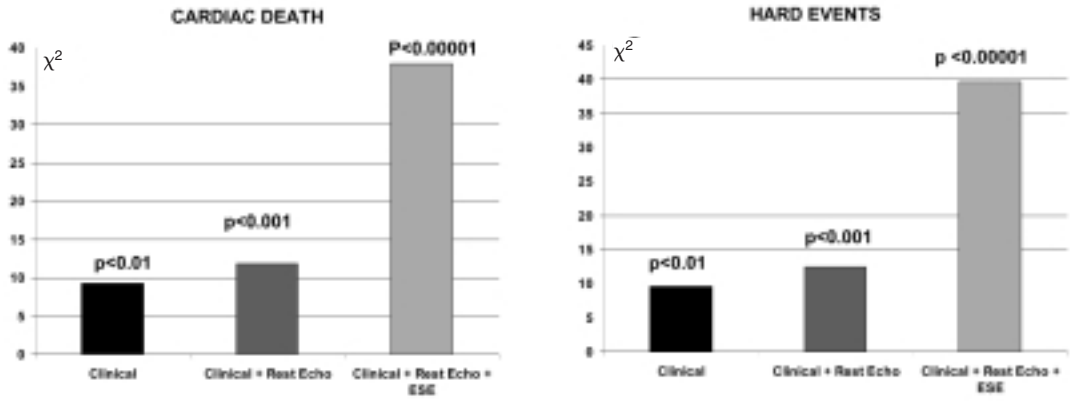

Figure 3. *Incremental values of exercise stress echocardiography (ESE) in predicting late cardiac events.*

diac events. In fact, most of the previous studies are based on post-treadmill stress echo results, an approach which relies on imaging within a short time after the stress, a period when ischemia is resolving[10-14,16]. In comparison, supine bicycle ESE has the advantage of imaging at baseline, at each exercise step and during recovery, and therefore during the development of ischemia and at its peak. As a result, according to previous reports, supine bicycle ESE could detect even small, quickly reversible wall motion abnormalities, while post-treadmill testing could loose important information about the existence, extension, and location of CAD[17-19]. Furthermore, ESE allows to accurately determine the location of wall motion abnormalities during exercise[20].

Current exercise testing guidelines state that a standard exercise ECG should be the first investigation in patients with a diagnostic ECG who are able to perform exercise. However, recent studies with ESE have indicated that the imaging component of this test adds incremental and independent information to the results of standard ECG testing[10-14].

When performed by experienced operators, ESE is a low-cost, easy-repeatable diagnostic technique, with high safety and feasibility (in our study 98.6%), and therefore well tolerated by the patient[20-23].

Several recent reports have also performed cost-effectiveness analyses of alternative strategies to investigate patients with chest pain. In particular, Kuntz et al.[21] evaluated different protocols including no testing versus pharmacologic echocardiography versus exercise echocardiography versus exercise single-photon emission computed tomography versus coronary angiography. The conclusion of the study was that, for patients with intermediate risk of CAD (the risk profile of our population), ESE represented the best cost-effective proposal. Also Marwick et al.[22] confirmed that, using decision analysis, ESE was associated with a greater incremental life expectancy and a lower use of additional diagnostic procedures when compared with exercise ECG (especially in lower risk patients).

Prognostic value of exercise stress echocardiography in our study population. In our study, at multivariate analysis, a positive ESE result for ischemia appeared to be the strongest independent predictor of cardiac-related death and of hard events. Even if ESE offers incremental prognostic information in the group as a whole, this is of limited value in patients who are at low pretest risk, while in the remaining patients at intermediate level of risk it is able to further stratify risk and therefore reduce the cost of subsequent investigations.

Among other stress echo variables, also indexes of the extent and the severity of stress-induced myocardial ischemia (peak WMSI) and of exercise capacity (low workload) appeared to be the significant predictors of cardiac death, while angina during the test resulted as a powerful predictor when hard cardiac events were considered. This fact may be the consequence of the different physiological mechanisms involved in the determination of different cardiac endpoints. In fact, some parameters (i.e. angina during stress) seem to be related to the degree of a single coronary stenosis, whereas other variables (i.e. impaired exercise capacity, high peak WMSI) presume an impaired global LV function secondary to a multivessel CAD, which is more frequently related to the risk of cardiac death[24].

Our findings are in accordance with the conclusions of the previous studies on the long-term prognostic value of exercise testing. In fact, poor exercise capacity, usually a consequence of a multivessel involvement of the atherosclerotic process, showed a greater effect on survival than ST depression during exercise, while several studies have shown that patients who can perform exercise into stage 4 of the Bruce protocol (> 10 METS) have a favorable outcome[12,25-28].

In addition, peak WMSI, an integrated expression of both the amount and the severity of wall motion abnormalities, carried out in our study a strong predictive value of the same cardiac events, as previously pointed out in patients undergoing ESE for known or suspected CAD or with recent uncomplicated myocardial infarction[15].

Of note, multiple studies have emphasized the prognostic role of indexes of global systolic function (rest and peak LV ejection fraction)[5,7,29] while in our population these parameters were not predictive of cardiac events. This was most likely due to the fact that most of the patients in our study group had normal LV systolic function, no significant valvular disease and the capability of performing exercise.

Our findings, therefore, confirmed the usefulness of additional features of an ESE test in depicting the cardiac risk profile better than the sole use of the ischemic response to the stress.

Although extensive outcome literature surrounds the use of pharmacological stress echocardiography[2-9], patients who are unable to perform exercise may have a particularly high event rate, which may not be representative of patients submitted to exercise testing. Moreover, the additional cost of pharmacological stress imaging techniques is more difficult to rationalize in patients who are able to perform exercise, since physical stress is an excellent tool for assessing risk in patients with known or suspected CAD[21,22].

As a result, in patients who are able to perform exercise, an exercise stress test is always desirable, as the stress may be correlated to the patient's symptoms, useful ST segment data may be obtained and exercise data are prognostically important.

Study limitations. As currently performed, exercise echocardiography is interpreted subjectively. An unsatisfactory intra and interobserver variability in stress echo interpretation has been previously reported[30]. Although we sought to replicate "real life" by studying the performance of the test in a referral center and a large independent laboratory, the tests were interpreted in a single center by experts who have a similar approach to test interpretation, reflecting previous collaborative teaching and training activities. It is hoped that the development of a quantitative echocardiographic approach may facilitate a subtler means of assessing disease extent in the future.

The routine implementation of second harmonic imaging, of modern ultrasound systems, with and without contrast enhancement, improved the ability to detect mild form of CAD. This fact would have further increased the negative prognostic power of the stress echo[31].

There is controversy whether percutaneous transluminal coronary angioplasty and coronary artery bypass graft 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 by itself an adverse outcome. As a consequence, we preferred to not include these events among the endpoints of our study.

In conclusion, the findings of the present study apply to patients with known or suspected CAD who are able to perform exercise and whose symptom status does not require revascularization. In these patients, the first step is to exclude individuals at low risk on clinical grounds and by the application of the treadmill test, which is able to identify almost 50% of the patients who are either at low risk (in which case, further intervention would not be necessary) or at high risk (in which case, further stratification would in most instances be deemed inappropriate). The remaining patients, together with patients with uninterpretable exercise ECG, deserve further evaluation by exercise echocardiography, which is able to stratify patients at higher risk of death or non-fatal myocardial infarction, avoiding any additional cost of pharmacological stress imaging techniques. However, only the evaluation of clinical variables, as well as of other stress echo variables, such as peak WMSI and exercise capacity, may better select patients at greatest risk of cardiac events. This investigative approach may potentially reduce the performance of coronary angiography, at the same time identifying patients at risk of subsequent cardiac events.

Acknowledgments

The authors are grateful to Miss Maria Bocchetti, Mr. Antonio Capone and Mr. Franco Vitiello for excellent nursing and technical support in the study protocol.

References

1. Roger VL, Pellikka PA, Oh JK, Miller FA, Seward JB, Tajik AJ. Stress echocardiography. Part I. Exercise echocardiography: techniques, implementation, clinical applications, and correlations. Mayo Clin Proc 1995; 70: 5-15.
2. Chuah SC, Pellikka PA, Roger VL, McCully RB, Seward JB. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. Circulation 1998; 97: 1474-80.
3. Krivokapich J, Child JS, Walter DO, Garfinkel A. Prognostic value of dobutamine stress echocardiography in predicting cardiac events in patients with known or suspected coronary artery disease. J Am Coll Cardiol 1999; 33: 708-16.
4. Poldermans D, Fioretti P, Boersma E, et al. Long-term prognostic value of dobutamine-atropine stress echocardiography in 1737 patients with known or suspected coronary artery disease. Circulation 1999; 99: 757-62.
5. Severino S, D'Andrea A, Caso P, et al. Long-term prognostic value of dipyridamole and dobutamine stress echocardiography in patients with known or suspected coronary artery disease. Ital Heart J 2001; 2: 256-64.
6. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol 1995; 26: 648-53.
7. D'Andrea A, Severino S, Caso P, et al. Prognostic value of pharmacological stress echocardiography in diabetic patients. Eur J Echocardiogr 2003; 4: 202-8.
8. Sicari R, Picano E, Landi P, et al. Prognostic value of dobutamine-atropine stress echocardiography early after acute myocardial infarction. Echo dobutamine International Cooperative (EDIC) Study. J Am Coll Cardiol 1997; 29: 254-60.

9. Salustri A, Ciavatti M, Seccareccia F, et al. Prediction of cardiac events after uncomplicated acute myocardial infarction by clinical variables and dobutamine stress test. J Am Coll Cardiol 1999; 34: 435-40.
10. Krivokapich J, Child JS, Gerber RS, et al. Prognostic usefulness of positive or negative exercise stress echocardiography for predicting coronary events in ensuing 12 months. Am J Cardiol 1993; 71: 646-51.
11. Marwick TH, Mehta R, Arheart K, Lauer MS. Use of exercise echocardiography for prognostic evaluation of patients with known or suspected coronary artery disease. J Am Coll Cardiol 1997; 30: 83-90.
12. Marwick TH, Case C, Vasey C, Allen S, Short L, Thomas JD. Prediction of mortality by exercise echocardiography: a strategy for combination with the duke treadmill score. Circulation 2001; 103: 2566-71.
13. Arruda AM, McCully RB, Oh JK, Mahoney DW, Seward JB, Pellikka PA. Prognostic value of exercise echocardiography in patients after coronary artery bypass surgery. Am J Cardiol 2001; 87: 1069-73.
14. Elhendy A, Arruda AM, Mahoney DW, Pellikka PA. Prognostic stratification of diabetic patients by exercise echocardiography. J Am Coll Cardiol 2001; 37: 1551-7.
15. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography (American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms). J Am Soc Echocardiogr 1989; 2: 358-67.
16. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979; 300: 1350-8.
17. Dagianti A, Rosanio S, Penco M, et al. Clinical and prognostic usefulness of supine bicycle exercise echocardiography in the functional evaluation of patients undergoing elective percutaneous transluminal coronary angioplasty. Circulation 1997; 95: 1176-84.
18. Dagianti A, Penco M, Bandiera A, Sgorbini L, Fedele F. Clinical application of exercise stress echocardiography: supine bicycle or treadmill? Am J Cardiol 1998; 81: 62G-67G.
19. Badruddin SM, Ahmad A, Mickelson J, et al. Supine bicycle versus post-treadmill exercise echocardiography in the detection of myocardial ischemia: a randomized single-blind crossover trial. J Am Coll Cardiol 1999; 33: 1485-90.
20. Elhendy A, Mahoney DW, Khandheria BK, et al. Prognostic significance of the location of wall motion abnormalities during exercise echocardiography. J Am Coll Cardiol 2002; 40: 1623-9.
21. Kuntz KM, Fleischmann KE, Hunink MG, et al. Cost-effectiveness of diagnostic strategies for patients with chest pain. Ann Intern Med 1999; 130: 709-18.
22. Marwick TH, Shaw L, Case C, Vasey C, Thomas JD. Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. Eur Heart J 2003; 24: 1153-63.
23. Yao S, Qureshi E, Sherrid MV, Chaudhry FA. Practical applications in stress echocardiography: risk stratification and suspected ischemic heart disease. J Am Coll Cardiol 2003; 42: 1084-90.
24. Fuster V, Badimon L, Badimon JJ, Chesebro J. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992; 326: 242-50.
25. Morris CK, Morrow K, Froelieher VF, et al. Prediction of cardiovascular death by means of clinical and exercise test variables in patients selected for cardiac catheterization. Am Heart J 1993; 125: 1717-26.
26. Weiner DA, Ryan TJ, Parson L, et al. Long-term prognostic value of exercise testing in men and woman from the Coronary Artery Surgery Study (CASS) registry. Am J Cardiol 1995; 75: 865-70.
27. Panza J, Curiel R, Laurienzo JM, Quyyumi AA, Dilsizian V. Relation between ischemic threshold measured during dobutamine stress echocardiography and known indices of poor prognosis in patients with coronary artery disease. Circulation 1995; 92: 2095-103.
28. McCully RB, Roger VL, Mahoney DW, et al. Outcome after abnormal exercise echocardiography for patients with good exercise capacity: prognostic importance of the extent and severity of exercise-related left ventricular dysfunction. J Am Coll Cardiol 2002; 39: 1345-52.
29. Coletta C, Galati A, Ricci R, et al. Prognostic value of left ventricular volume response during dobutamine stress echocardiography. Eur Heart J 1997; 18: 1599-605.
30. Hoffmann R, Lethen H, Marwick T, et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. J Am Coll Cardiol 1996; 27: 330-6.
31. Spencer K, Bednarz J, Rafter P, Korcarz C, Lang RM. Use of harmonic imaging without echocardiographic contrast to improve two-dimensional image quality. Am J Cardiol 1998; 82: 794-9.