IMAGING TECHNIQUES

Prognostic Value of Treadmill Exercise Echocardiography

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Introduction and objectives. Exercise echocardiography (EE) is useful for diagnosing coronary disease, but little is known about its value for risk stratification. We aimed to determine: *a)* whether data from EE supplemented clinical data and data from exercise testing and resting echocardiography in predicting cardiac events; and *b)* whether the number and location of abnormal regions and their responses to exercise influenced risk stratification.

Patients and method. The 2,436 patients referred for EE were followed up for 2.1±1.5 years. Some 120 serious cardiovascular events (i.e., non-fatal myocardial infarction or cardiovascular death) occurred before revascularization.

Results. In 1203 patients (49%), EE gave abnormal results. There were 89 events in patients with an abnormal result (7.3%) and 31 in those with a normal result (2.5%; $P<.0001$). Multivariate analysis of clinical data, and data from exercise testing, resting echocardiography, and EE showed that male sex (RR=1.7; 95% CI, 1.1-2.8; $P=.02$), metabolic equivalents or METs (RR=0.9; 95% CI, 0.86-0.98; $P=.01$), peak heart rate × blood pressure (RR= 0.9; 95% CI, 0.9; $P=.002$), resting wall motion score index (RR=2.5; 95% CI, 1.5-4.1; $P<.0001$), and number of abnormal regions at peak exercise (RR=1.4; 95% CI, 1.2-1.7; $P<.0001$) were independently associated with the risk of a serious event (final model χ^2, 170; incremental $P<.0001$). The same variables, excluding sex, were independently associated with cardiovascular death (final model χ^2, 169; incremental $P =.01$).

Conclusions. Exercise echocardiography supplements clinical data and data from exercise testing and resting echocardiography in patients with known or suspected coronary artery disease.

Key words: *Exercise echocardiography. Prognostic value. Treadmill.*

SEE EDITORIAL ON PAGES 891-4

Valor pronóstico de la ecocardiografía de ejercicio en cinta rodante

Introducción y objetivos. Aunque la ecocardiografía de ejercicio es útil para el diagnóstico de la enfermedad coronaria, hay menos datos referentes a su valor pronóstico. El objetivo de este estudio fue esclarecer: *a)* si hay un valor incremental de la ecocardiografía en el pico del ejercicio respecto a las variables clínicas, la prueba de esfuerzo y la ecocardiografía en reposo, y *b)* si el número y la localización de los territorios afectados, así como el tipo de respuesta al ejercicio, influyen en la estratificación.

Pacientes y método. En 2.436 pacientes referidos para ecocardiografía de ejercicio se realizó un seguimiento de 2,1 ± 1,5 años. Hubo 120 eventos (infarto no fatal o muerte cardiovascular) antes de la revascularización.

Resultados. La ecocardiografía fue anormal en 1.203 pacientes (49%). Hubo 89 eventos en pacientes con resultado anormal (7,3%) frente a 31 con resultado normal (2,5%; p < 0,001). Mediante un análisis multivariable de variables clínicas, de la prueba de esfuerzo y de la ecocardiografía en reposo y ejercicio encontramos que las variables asociadas de manera independiente con el riesgo de eventos eran: ser varón (riesgo relativo [RR] = 1,7; intervalo de confianza [IC] del 95%, 1,1-2,8; p = 0,02), los equivalentes metabólicos o MET (RR = 0,9; IC del 95%, 0,9-1,0; p = 0,01), el producto frecuencia cardíaca × presión arterial (RR = 0,9; IC del 95%, 0,9-1,0; p = 0,02), el índice de motilidad segmentaria basal (RR = 2,5; IC del 95%, 1,5-4,1; p < 0,0001) y el número de territorios afectados (RR = 1,4; IC del 95%, 1,2-1,7; p < 0,0001) (χ^2 final = 170, valor incremental de la ecocardiografía en el máximo esfuerzo; p < 0,0001). Las mismas variables, excepto el sexo, estaban asociadas con la muerte (χ^2 final = 169, valor incremental de la ecocardiografía de ejercicio; p = 0,01).

Conclusiones. La ecocardiografía en el máximo ejercicio incrementa el valor pronóstico de las variables clínicas, la prueba de esfuerzo y la ecocardiografía de reposo.

Palabras clave: *Ecocardiografía de ejercicio. Valor pronóstico. Cinta rodante.*

INTRODUCTION

Exercise echocardiography (EE) has advanced significantly from the diagnostic point of view, and several recent studies (most carried out at the same center) have shown that the extent of resting or exercise- induced ventricular dysfunction is a robust predictor of cardiac death and myocardial infarction.[1-10]

The purpose of this study was to investigate whether the number and location of diseased territories during the exercise peak, as well as the type of response to exercise (ischemia, necrosis or remote ischemia) influenced risk stratification more than clinical, stress test, and resting echocardiography variables in patients with known or suspected coronary artery disease (CAD). We also investigated whether EE supplemented resting echocardiography in patients with a history of acute myocardial infarction (AMI) as recorded in the medical history.

PATIENTS AND METHODS

Patients

We studied 2479 patients who had undergone treadmill EE at our institution during a 4.2-year period from December 1997 to March 2002. Patients with significant valve disease (n=13) or with proven hypertrophic or dilated cardiomyopathy (n=30) were excluded, with the final group composed of 2436 patients who were followed until 31 December 2002. The patients' medical history revealed a history of myocardial infarction in 741 patients (30%), that was acute in 386 (16%) with elevation of ST segment in 276; of these, 176 had undergone fibrinolysis (7%) and 38, primary angioplasty (1.5%). A total of 385 patients had been previously revascularized (16%), with coronary angioplasty in 199 (8%), surgery in 167 (7%), or both in 19 (1%). There was atrial fibrillation in 130 patients (5%), complete left bundle branch block or pacemaker rhythm in 218 (9%), and left ventricular hypertrophy according to echocardiographic criteria (wall thickness ≥1.1 cm) in 1340 (55%). At the time of EE, 24% of the patients were taking nitrates;

8%, calcium antagonists; 4%, beta-blockers; 22%, angiotensin-converting enzyme inhibitors; 9%, diuretics, and 4%, digoxin.

Exercise Echocardiography

Data on heart rate and blood pressure were obtained and a 12-lead electrocardiogram (ECG) was recorded at rest and at each stage of the exercise protocol. The patients were encouraged to reach peak exercise according to the protocols adjusted to the characteristics of each patient (Bruce 90%, modified Bruce 7%, Naugthon 2%, Bruce for athletes 1%) until exhaustion or until reaching a specific criterion for termination. The termination criteria were suppression or elevation of >2 mm in ST segment, significant arrhythmia, severe hypertension (systolic blood pressure >240 mm Hg or diastolic blood pressure >110 mm Hg) and hypotensive response (decrease ≥20 mmHg from baseline). The ECG was considered positive in the case of horizontal or downsloping elevation or depression of ST segment ≥1 mm at 80 ms after the J point, and nondiagnostic when the baseline ECG was abnormal or the patient was receiving digoxin.

Two-dimensional echocardiography with fundamental or harmonic imaging was performed in the standard apical and parasternal views at baseline, at the exercise peak,[11,12] and immediately after exercise. Peak EE was done when there were signs or symptoms of exhaustion or some criterion for termination had been reached. All images were acquired on-line and saved to optical disc for subsequent analysis.

Image Analysis

The images were analyzed using a quad screen format to compare the same views at baseline and exercise peak. The left ventricle was divided into 16 segments,[13] with each segment assigned to 1 of the 3 coronary arterial territories.[14] The onset of regional dysfunction (hypokinesia, akinesia, or dyskinesia) or worsening from hypokinesia to akinesia or dyskinesia was considered an ischemic response. The persistence of baseline regional dysfunction affecting at least one segment or worsening from akinesia to dyskinesia was considered necrosis with no ischemia, except in the case of isolated hypokinesia of the posterobasal segment,[15] and septal hypokinesia in patients with complete left bundle branch block, pacemaker, or recent heart surgery. In these cases, hypokinesia was considered normal. In patients with global ventricular dysfunction of unknown origin, a response of progressive improvement was considered normal and a diagnosis of dilated cardiomyopathy was suggested.[16] In all other patients, EE positive for CAD was defined as ischemia or necrosis in 1 coronary arterial territory.[17-19] The following types of

response were considered for each patient: normal (same or greater thickening and systolic wall motion with exercise), isolated ischemia (normal thickening/systolic motion at baseline and appearance of regional or global dysfunction with exercise), necrosis (persistence of baseline regional dysfunction with exercise or worsening from akinesia to dyskinesia), necrosis with remote ischemia (presence of baseline regional dysfunction and onset of new dysergia in a different territory), and ischemia and necrosis affecting the same territory (presence of baseline regional dysfunction that worsens in the same territory due to worsening from hypokinesia to akinesia or dyskinesia, or greater extension of dysergia but without affecting territories other than the one affected at baseline). Patients were classified according to the number of abnormal territories (0, 1, 2, or 3) during exercise. Regional wall motion (RWM) was calculated at rest and during exercise, scoring normal motion as 1, hypokinesia as 2, akinesia as 3, and dyskinesia as 4. The resting and exercise ejection fraction (EF) was measured through visual estimation[20] by an observer. Data are provided for between-observer variability in the visual estimation of EF at our center from an analysis of 60 studies selected at random (20 with fundamental imaging, 40 with harmonic) and assessed on 2 occasions 36 months apart.

Follow-up

Events were followed up and assessed through a review of the medical histories and death certificates. We had access to hospital admissions, out-of-hospital consultations, and emergency room services of all SERGAS centers; no patients were lost during follow-up. If no data were available for a patient at the end of the study (31 December 2002), the health card database was consulted to determine whether the patient had died or moved to a location outside the autonomous community. In the event of death of unknown origin, precise information on the cause (cardiovascular, neoplasm, etc) was obtained from the Death Register of Galicia. Only hard events were considered, with these defined as death of cardiovascular origin or nonfatal AMI. Sudden death occurring with no other explanation was considered of cardiac origin. Revascularization procedures during follow-up were recorded. Patients who were revascularized before an event were excluded at the time of the event.

Statistical Analysis

Continuous variables are described as mean ± standard deviation (SD), with the comparison between patients with and without events based on the Mann-Whitney U-test. Categorical variables are described as

percentages and the between-group comparison was done using χ^2. Event-free survival was estimated by Kaplan-Meier using time to first event. Patients who died due to noncardiovascular events and those who were revascularized before an event were excluded at the time of death or revascularization.

Univariate associations of clinical variables, ECG, and EE with hard events were measured with the Cox proportional hazards model. Significance was set at a *P* value of less than .05 and the 95% confidence intervals (CI) were calculated. The incremental value of EE with respect to clinical and ECG variables was measured step-by-step, considering for entry into each step those variables that were significant in the univariate analysis, in which the first step only included clinical data; the second step consisted of hemodynamic and ECG data in response to exercise; afterwards, the resting echocardiography data were entered; in the final step, the EE variables were included. The χ^2 values and the incremental value of adding the subsequent variables were calculated for each step.

Variability in the calculation of visual EF is expressed as the quotient between the difference of the 2 measurements and the mean value of both ×100.

RESULTS

The mean patient age was 62±12 years. There were 1584 men (65%) and 852 women (35%). Diabetes mellitus was observed in 449 patients (18%), hypertension in 1325 (54%), smoking in 688 (28%), hypercholesterolemia in 1272 (52%), and family history of CAD in 376 (15%). The reasons for performing EE were precordial pain or dyspnea in 1582 patients (65%), history of AMI in 725 (30%), positive or non-diagnostic ECG in 111 (5%), and evaluation of risk factors in 18 (0.7%). The stress test was discontinued because of exhaustion in 2212 patients (91%), angina in 63 (3%), lower limb pain in 148 (6%), and arrhythmias in 3 patients (0.1%).

Exercise Echocardiography Data

The EE was considered normal in 1233 patients (51%) and abnormal in 1203 (49%). There were baseline alterations in regional motion in 652 patients (27%). Among the 1203 patients with an abnormal EE, 282 had only necrosis (23%); 547, ischemia (45%); 284, remote ischemia (24%), and 90, ischemia and necrosis in the same territory (7%). In the patients with normal EE, involvement of 1 territory was found in 566 (47%), 2 territories in 230 (19%), and 3 territories in 407 patients (34%). Among patients with abnormal EE, the EE was positive for disease in the left anterior descending artery territory in 870 (72%) and positive for disease in the

right coronary artery or circumflex artery territory in 913 (76%).

In patients with a history of AMI as recorded in the medical history, EE was normal in 97 (13%) and abnormal in 644 (87%). Abnormal EE was categorized as necrosis in 30%, ischemia in 22%, remote ischemia in 24%, and necrosis associated with ischemia in the same territory in 10%. Multi-territory disease was reported in 311 patients (42%).

Revascularization Procedures

A total of 454 patients (20%) were revascularized during follow-up, 152 surgically and 302 by angioplasty. Of these, 427 patients who were revascularized before a hard event were excluded. The reasons for revascularization were coronary event in 89 patients (20%) and EE result in 365 (80%). Early revascularization (≤3 months) was done in 279 patients and late revascularization (>3 months) in 175. In most cases of early revascularization, the reason was the EE result (89%), whereas late revascularization was carried out because of the EE result in 66% of the cases and onset of acute coronary syndrome in 34%. The revascularized patients had a higher prevalence of angina during exercise (38% vs 9%; $P<.0001$), positive ECG (37% vs 12%; $P<.0001$), abnormal EE (87% vs 41%; $P<.0001$), ischemia on EE (79% vs 28%; $P<.0001$), and involvement of more than 1 territory (56% vs 19%; $P<.05$).

Events

Over a mean follow-up of 2.1±1.5 years (median, 2.0 years; maximum, 5 years) there were 167 cardiovascular events: cardiovascular death in 112 patients and nonfatal AMI in 55. There were significant differences in baseline characteristics between the 2269 patients who had no events during follow-up and the 167 who had some event: age (61±11 vs 64±10 years; $P<.001$), male sex (64% vs 81%; $P<.001$), diabetes (18% vs 24%; $P=.05$), smoking (28% vs 35%; $P<.05$), previous revascularizations (15% vs 22%; $P=.01$), precordial pain or dyspnea as reason for request (66% vs 54%; $P<.01$), history of AMI as reason for request (29% vs 42%; $P<.0001$), and patients revascularized during follow-up (17% vs 44%; $P<.05$). Table 1 contains the exercise data for patients with and without

TABLE 1. **Exercise Echocardiography and Echocardiographic data in Patients With and Without Hard Cardiovascular Events in the Follow-up***

	Patients Without Events (n=2269)	Patients With Events (n=167)	*P*
Baseline HR, bpm	79±14	80±13	NS
Maximum HR, bpm	145±21	136±21	<.0001
Baseline SBP, mm Hg	138±19	135±18	NS
Maximum SBP, mm Hg	174±29	163±31	<.0001
Change in SBP, mm Hg	36±24	28±23	<.0001
HR × maximum SBP×1000	25 440±5912	22 264±5768	<.0001
METs	9.4±3.1	7.7±3.2	<.0001
Theoretical maximum HR, %	0.92±0.12	0.87±0.13	<.0001
Angina during test	307 (14%)	34 (20%)	.02
ECG			
Positive	357 (16%)	41 (25%)	.005
Negative	1217 (53%)	50 (30%)	<.0001
Nondiagnostic	695 (31%)	76 (45%)	<.0001
Baseline EF, %	57±10	50±13	<.0001
Peak EF, %	60±14	47±17	<.0001
Δ in EF	2.9±8.4	−2.7±9.3	<.0001
Abnormal EE	1069 (47%)	134 (80%)	<.0001
EE response			
Normal	1200 (53%)	33 (20%)	<.0001
Ischemia	491 (22%)	56 (34%)	<.001
Necrosis	253 (11%)	29 (17%)	.03
Remote ischemia	239 (11%)	45 (27%)	<.0001
Ischemia + necrosis in the same territory	86 (4%)	4 (2%)	NS
Baseline RWM	1.15±0.29	1.38±0.42	<.0001
Peak RWM	1.27±0.37	1.62±0.46	<.0001
Δ of RWM	0.12±0.23	0.24±0.30	<.0001

*AMI indicates acute myocardial infarction; ECG, electrocardiogram; EE, exercise echocardiography; EF, ejection fraction; HR, heart rate; METs, metabolic equivalents; NS, nonsignificant; RWM, regional wall motion; SBP, systolic blood pressure.

events. Of the 167 cardiovascular events, 120 occurred before any revascularization procedure was done and were used to estimate event-free survival by Kaplan-Meier and to construct survival curves. The causes of these 120 hard events were nonfatal AMI in 45 patients (38%) and death in 75 (62%). The causes of cardiovascular death were proven fatal AMI in 6, fatal deterioration of heart failure in 8, sudden death in 6, stroke in 6, and gangrene in 2. Out-of-hospital cardiovascular death was considered to have occurred in 39 patients after excluding other causes of noncardiovascular death from the death certificates. Heart transplantation in 4 patients and first discharge of defibrillator in another 4, were also considered hard events. The EE was positive in 89 of the 120 patients with events (74%), in 24 (20%) of the patients with necrosis, in 29 (20%) of those with ischemia, in 33 (28%) of those with remote ischemia, and in 3 (3%) patients with ischemia and necrosis in the same territory. Multi-territory disease was detected in 59 of these patients (49%).

Clinical, Stress Test, and Resting and Exercise Echocardiography Variables for Prediction of Cardiovascular Events

Table 2 shows the clinical, stress test, and echocardiography variables associated with the risk of cardiovascular events. Event-free survival and number of events in patients with normal EE versus those with involvement of 1, 2, and 3 territories are shown in Figure 1. Figure 2 shows event-free survival and number of events in patients with normal EE versus patients with EE who had necrosis, ischemia, or remote ischemia and Figure 3 indicates event-free survival according to RWM during exercise.

Predictors of Cardiovascular Death and AMI by Multivariate Analysis

Table 3 contains the result of the four steps of the incremental model, including independent predictors for each step. In the final model, the independent pre-

TABLE 2. **Risk of Hard Cardiovascular Events (Cardiovascular Death and Nonfatal Infarction) in Univariate Analysis of Clinical Variables, Stress Test, and Exercise Echocardiography***

Variables	Wald	P	RR	95% CI
Baseline clinical characteristics				
Age†	10	.002	1.34	1.12-1.60
Male sex	16	<.0001	2.45	1.58-3.81
Diabetes mellitus	6	.02	1.65	1.09-2.48
History of AMI	20	<.0001	2.27	1.59-3.26
History of revascularization	9	.003	1.85	1.23-2.79
Stress test				
Angina	4	.05	1.64	0.99-2.71
Change in ST segment‡	10	.002	1.46	1.15-1.86
Theoretical maximum HR, %	18	<.0001	0.05	0.01-0.20
METs$	37	<.0001	0.84	0.79-0.89
HR × maximum SBP×1000‖	45	<.0001	0.90	0.87-0.93
EE variables				
Abnormal EE	44	<.0001	4.00	2.64-6.00
Ischemia	32	<.0001	2.82	1.97-4.04
Remote ischemia	50	<.0001	4.28	2.86-6.40
Baseline ejection fraction$	79	<.0001	0.95	0.93-0.96
Peak ejection fraction$	100	<.0001	0.95	0.94-0.96
Δ in ejection fraction$	47	<.0001	0.94	0.93-0.96
Baseline RWM$	90	<.0001	6.63	4.50-9.88
Peak RWM$	116	<.0001	7.14	4.91-10.37
Δ in RWM$	21	<.0001	4.52	2.37-8.60
Number of territories affected	78	<.0001	1.92	1.66-2.22
Multivessel disease	61	<.0001	4.19	2.92-6.00
Involvement of ADA territory (± other territories)	53	<.0001	3.90	2.70-5.63
Involvement of RCA/Cx territory (± other territories)	43	<.0001	3.42	2.37-4.94

*AMI indicates acute myocardial infarction; CI, confidence interval; Cx, circumflex artery; EE, exercise echocardiography; HR, heart rate; LAD, left anterior descending artery; METs, metabolic equivalents; RCA, right coronary artery; RR, risk relative; RWM, regional wall motion; SBP, systolic blood pressure.
†According to decade.
‡According to mm of change.
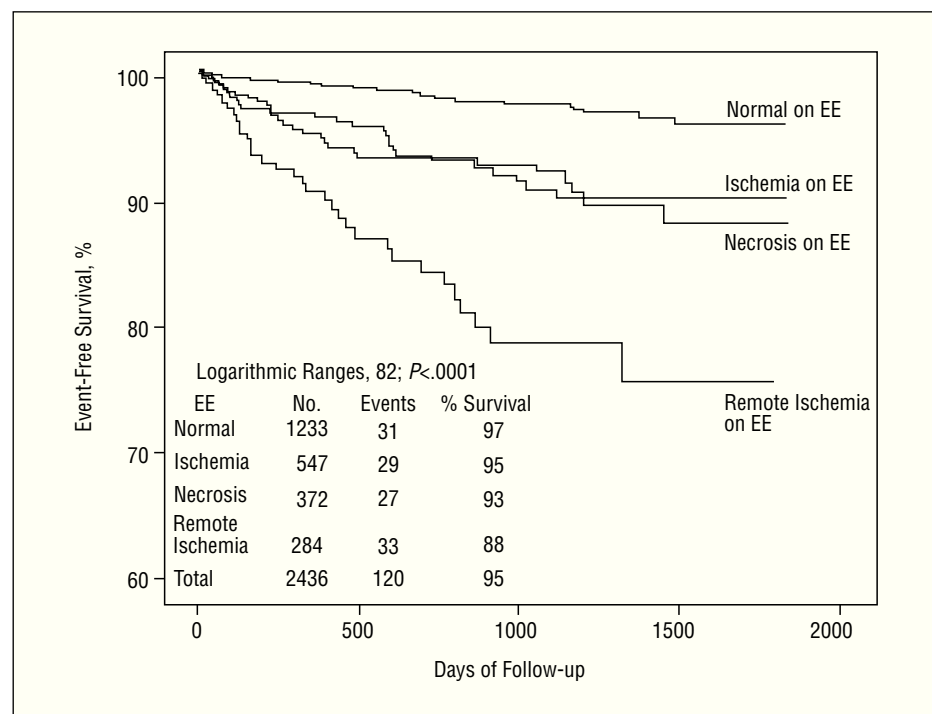$According to 1 U.
‖According to 1000 U.

Figure 1. Kaplan-Meier survival curves and number of events in patients with involvement of 0, 1, 2, and 3 territories on exercise echocardiography. 0 versus 1 territory, $P<.001$; 0 versus 2 and 3 territories, $P<.00001$; 1 versus 2 territories, P=NS; 1 versus 3 territories, $P<.00001$; 2 versus 3 territories, $P<.01$.
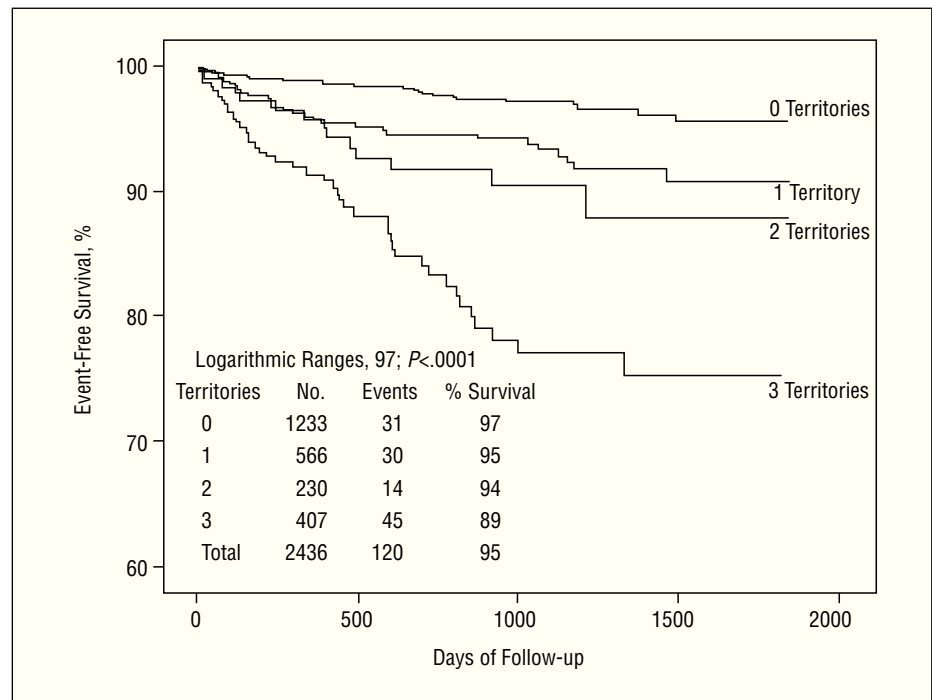
dictors of hard cardiovascular events were: male sex, METs achieved, heart rate × maximum blood pressure, baseline RWM, and number of territories affected at exercise peak. The independent predictors of cardiovascular death were METs achieved (relative risk [RR]=0.88; 95% CI, 0.80-0.96; P=.004), heart rate ×

blood pressure (RR=0.93; 95% CI, 0.89-0.98; P=.003), baseline RWM (RR=3.8; 95% CI, 2.1-7.0; $P<.0001$), and number of territories affected in the exercise peak (RR=1.5; 95% CI, 1.1-1.7; P=.015), but not sex (χ^2 of the final model =169; added value of exercise echocardiograph; P=.015).

Figure 2. Kaplan-Meier survival curves and number of events in patients with normal results on exercise echocardiography, compared to patients with evidence of ischemia, necrosis, and remote ischemia. The necrosis subgroup includes patients with only necrosis in at least 1 territory, as well as patients with necrosis and associated ischemia in the same territory. Normal on EE versus other type of response, $P<.0001$; necrosis on EE versus ischemia on EE, P=NS; necrosis on EE versus remote ischemia on EE, $P<.001$; ischemia on EE versus remote ischemia on EE, $P<.001$. EE indicates exercise echocardiography.
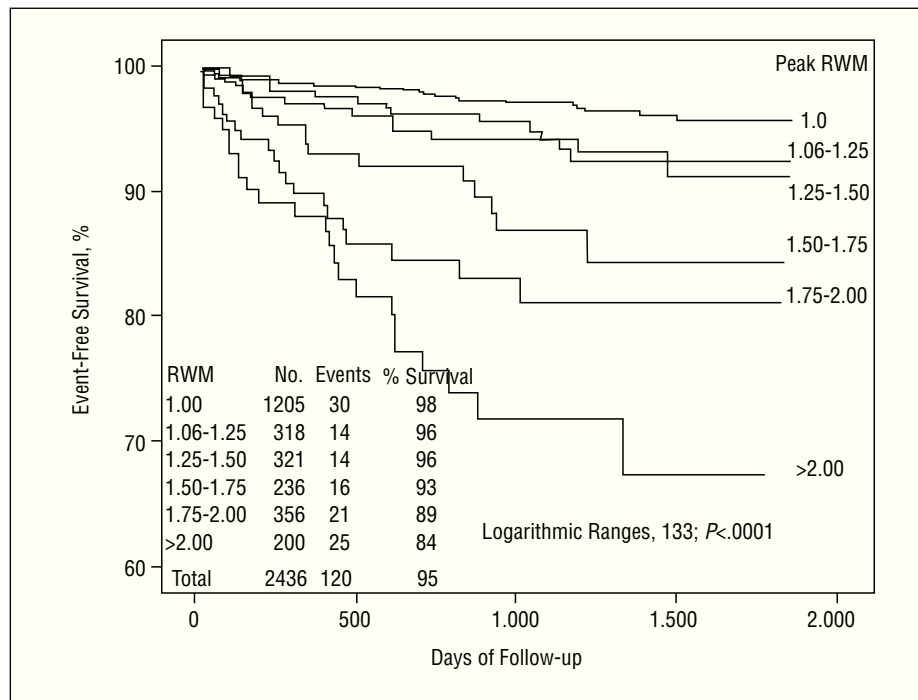
Figure 3. Kaplan-Meier survival curves and number of events according to regional wall motion during exercise. 1.00 versus 1.06-1.25, $P<.05$; 1.00 versus 1.25-1.50, 1.50-1.75, 1.75-2.00, and >2.00, $P<.00001$; 1.06-1.25 versus 1.25-1.50, P=NS; 1.06-1.25 versus 1.50-1.75, $P<.05$; 1.06-1.25 versus 1.75-2.00, $P<.001$; 1.06-1.25 versus >2.00, $P<.00001$; 1.25-1.50 versus 1.50-1.75, P=NS; 1.25-1.50 versus 1.50-1.75, $P<.001$; 1.25-1.50 versus >2.00, $P<.00001$; 1.50-1.75 versus 1.75-2.00, P=NS; 1.50-1.75 versus >2.00, $P<.05$; 1.75-2.00 versus > 2.00, P=NS.

Predictors of Events in Patients With History of AMI

Among the 741 patients with a history of AMI, there were 53 events (7%; 22 nonfatal infarctions, and 31 deaths of cardiovascular origin). The EE was abnormal in 93% of the patients with events, with necrosis in 19 (36%), ischemia in 10 (19%), remote ischemia in 18 (34%), and ischemia and necrosis in the same territory in 2 (4%). Exercise echocardiography indicated multivessel disease in 29 (55%). The independent predictive variables of hard events in the final model of patients with AMI were METs achieved, product of heart rate × blood pressure and peak EF (Table 4).

Between-Observer Variability in Ejection Fraction Calculation

The between-observer variation was 9%±9% for baseline EF calculation and 10%±10% for peak EF calculation.

TABLE 3. **Multivariate Analysis of: *a)* Clinical; *b)* Clinical and Stress Test; *c)* Clinical, Stress Test, and Resting Echocardiography; and *d)* Clinical, Stress Test, Resting Echocardiography, and Exercise Echocardiography Variables for Prediction of Events in 2436 Patients***

Variables	Clinical Model		Clinical Model + ST		Clinical Model + ST + Baseline Echo		Clinical Model + ST + Baseline Echo + Exercise Echo	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Age†	1.4 (1.2-1.7)	<.0001	1.0 (0.9-1.3)	.6	1.0 (0.9-1.3)	.7	1.0 (0.9-1.3)	.7
Male	2.2 (1.4-3.5)	.001	2.4 (1.5-3.9)	<.0001	2.0 (1.2-3.2)	.004	1.7 (1.1-2.8)	.02
History of AMI	1.9 (1.3-2.8)	<.001	1.7 (1.1-2.4)	.008	1.3 (0.9-1.9)	.2	1.2 (0.8-1.7)	.4
METs‡			0.87 (0.82-0.93)	<.0001	0.90 (0.84-0.97)	.003	0.92 (0.86-0.98)	.01
HR×SBP×1000$			0.94 (0.90-0.97)	<.0001	0.94 (0.91-0.98)	.002	0.4 (0.91-0.98)	.002
Baseline RWM‡					3.7 (2.4-5.8)	<.0001	2.5 (1.5-4.1)	<.0001
No. territories affected in EE							1.4 (1.2-1.7)	<.0001
Global χ^2	43		99		155		170	
Incremental P			<.0001		<.0001			<.0001

*AMI indicates acute myocardial infarction; CI, confidence interval; EE, exercise echocardiography; Echo, echocardiography; HR, heart rate; METs, metabolic equivalents; RWM, regional wall motion; SBP, systolic blood pressure; ST, stress test; RR, relative risk
†According to decade.
‡According to 1 U.
$According to 1000 U.

TABLE 4. **Multivariate Analysis of: a) Clinical; b) Clinical and Stress Test; c) Clinical, Stress Test, and Resting Echocardiography; and d) Clinical, Stress Test, Resting Echocardiography, and Exercise Echocardiography Variables for Prediction of Events in 741 Patients with a history of Acute Myocardial Iinfarction***

Variables	Clinical Model		Clinical Model + ST		Clinical Model + ST + Baseline echo		Clinical Model + ST + Baseline Echo + Exercise Echo	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Age†	1.9 (1.4-2.6)	<.0001	1.3 (0.9-1.8)	.1	1.3 (0.9-1.8)	.2	1.2 (0.9-1.7)	.2
METs‡			0.86 (0.78-0.95)	.002	0.88 (0.80-0.98)	.02	0.89 (0.81-1.0)	.04
HR×SBP×1000$			0.93 (0.88-0.99)	.02	0.94 (0.88-1.00)	.04	0.93 (0.88-0.94)	.03
Baseline EF‡					0.96 (0.94-0.99)	.004	1.00 (0.96-1.04)	1
Peak EF‡							0.96 (0.94-0.99)	.02
Global χ^2	17		45		58		62	
Incremental P			<.0001		.005		.02	

*CI indicates confidence interval; Echo, echocardiography; EE, exercise echocardiography; EF, ejection fraction; HR, heart rate; METs, metabolic equivalents RR: risk relative; SBP, systolic blood pressure; ST, stress test
†According to decade.
‡According to 1 U.
$According to 1000 U.

DISCUSSION

The most significant findings of this study were: *a)* EE supplements the clinical, exercise testing, and baseline echocardiography variables among a population with moderate-to-high pretest prevalence of CAD; *b)* a response of remote ischemia is significantly associated with poor prognosis, when compared to other types of response; and *c)* the added value of resting and exercise echocardiography is also observed in the subgroup of patients with a history of AMI.

Prognostic Value of Exercise Echocardiography

The incremental value of EE we found in our study has been previously demonstrated in recent studies,[1-10] although most were performed at the same center. However, the present study is the first to investigate this aspect in Spain and the first to use echocardiography during the exercise peak, instead of post-exercise or pharmacological echocardiography. We should mention that EE in general is a widely used technique in our setting,[21] and that EE at the exercise peak in particular is commonly used at various centers in Spain. The patients with three coronary territories affected during the exercise peak presented a high risk of events (11% of events at 2 years), when compared with those who had fewer territories affected. Nevertheless, there were no differences between 1 and 2 territories (5% vs 6% of events). Involvement of only 1 territory or even of 2 territories, if dependent on the right coronary or circumflex arteries, was not associated with significant risk in the univariate analysis.

Type of Response

The risk associated with the response of remote ischemia of a necrosis (12% events at 2 years) was significantly higher than the risk associated with other types of response. The risk associated with necrosis was found to be equal to the risk associated with ischemia. More patients with ischemia than with necrosis were excluded due to revascularizations, however, which may explain this lack of difference. Lastly, patients with RWM during the exercise peak >1.5 had a high risk of presenting events, with 10.5% of events in patients with RWM of 1.75-2.00 and 16% in those with RWM>2.0.

Exercise Echocardiography in Patients With a History of AMI

Since EE is particularly indicated in patients with a history of AMI due to the baseline alterations of repolarization that prevent an assessment of the ECG,[22] we were interested in analyzing these patients separately. In these patients we also found that an exercise imaging variable added significant value to the model above the resting echocardiography variables, which were not significant in the final model. However, the EE variable that enhanced the model was peak EF rather than RWM or ischemia, possibly reflecting the difficulty encountered for detecting pre-infarction ischemic areas and the prognostic value of the amount of necrotic myocardium with no contractility reserve.

Limitations

As mentioned above, EE was performed at the exercise peak instead of post-exercise since imaging at the

exercise peak has been shown to have greater sensitivity.[11,12,23] Nevertheless, the superiority of the echocardiography variables in the exercise peak over the clinical, ECG, and resting echocardiography variables we found in this study could be diminished if the EE is performed after exercise.

Since the EE results were used by the attending physician, the apparent prognostic information could be reduced, since most patients with severely positive tests who were revascularized might have presented serious events if they had not undergone revascularization.

The definition of nonfatal AMI was based on criteria from the pre-troponin era for most patients and therefore, although we have records on hospitalization for unstable angina, AMI was only considered to exist when it was specifically indicated in the medical reports. As a result, we are probably referring to infarctions of a certain entity in which, if the current, more sensitive criteria had been used, the number of events would be greater at the expense of nonfatal AMI. Nevertheless, we feel this does not diminish the value of our study, since EE continued to be associated with cardiovascular mortality.

Approximately 40% of the EEs were performed with fundamental imaging. The technology has dramatically improved since that time through the development of harmonic imaging and continuous image acquisition, which could result in greater sensitivity of the technique. Unfortunately, this is a common problem that affects continuous longitudinal studies conducted in this field.

Clinical Implications

Risk measurement with EE is superior to measurement with clinical, exercise testing, and baseline echocardiography variables. Patients who present involvement of 3 territories, remote ischemia, and peak RWM >1.75 on EE are at high risk for hard cardiovascular events.

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