Characteristics and Outcomes of Patients Who Achieve High Workload (≥10 Metabolic Equivalents) During Treadmill Exercise Echocardiography

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Abstract

Objective: To determine the frequency and prognostic significance of abnormal exercise echocardiographic results for patients achieving a workload of 10 or more metabolic equivalents during treadmill exercise echocardiography.

Patients and Methods: Patients who underwent treadmill exercise echocardiography from November 1, 2003, through December 31, 2008, and exercised for 9 or more minutes using the Bruce protocol (N=7236) were included. Clinical and exercise echocardiographic characteristics and outcomes were evaluated. Variables associated with abnormal exercise echocardiographic results and mortality were identified.

Results: Exercise echocardiographic results were positive for ischemia in 862 patients (12%). Extensive ischemia developed in 265 patients (4%). For patients with normal exercise echocardiographic results, all-cause and cardiovascular mortality rates were 0.30% and 0.05% per person-year of follow-up, respectively. For patients who had extensive ischemia, all-cause and cardiovascular mortality rates were 0.84% and 0.25% per person-year of follow-up, respectively. Patients at highest risk were those who had extensive and severe regional wall motion abnormalities at rest (n=58), and their all-cause and cardiovascular mortality rates were 2.65% and 0.76% per person-year of follow-up. Exercise echocardiographic variables did not identify sizable patient subgroups at risk for death and did not provide incremental prognostic information (C statistic was 0.74 compared with 0.73 for the clinical plus exercise electrocardiography model).

Conclusion: Patients achieving a workload of 10 or more metabolic equivalents during treadmill exercise testing do not often have extensive ischemic abnormalities on exercise echocardiography. Although exercise echocardiographic results provide some prognostic information, it is not of incremental value for these patients, whose short-term and medium-term prognosis is excellent.

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Functional capacity is an important predictor of cardiovascular events and survival for asymptomatic persons as well as for patients with cardiovascular disease who are referred for stress testing.[1-6] It has been reported that patients who achieve a high workload during treadmill exercise testing have a favorable prognosis even if they have marked electrocardiographic (ECG) ST-segment depression or multivessel coronary artery disease (CAD).[7,8]

Recently published studies have cast doubt on the usefulness of stress imaging in patients who achieve a high exercise workload, reporting that the presence of important ischemia, as measured by myocardial perfusion imaging (MPI), is an uncommon finding and of no added prognostic value for patients who achieve a workload of 10 or more metabolic equivalents (METs) during exercise testing.[9-11]

The prognosis of patients who have normal exercise echocardiographic results is good.[12-14] The outcomes of patients who have reduced exercise capacity and abnormal exercise echocardiographic results vary, but

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are often poor.[15] Prognoses in patients who have good exercise capacity but abnormal exercise echocardiographic results depend on the extent and severity of exercise-related regional wall motion abnormalities (RWMAs).[13,16-18] The prognostic implications of abnormalities seen on exercise echocardiography in patients who have excellent exercise capacity have not been extensively studied.[19]

The objectives of this study in patients who achieve a workload of 10 or more METs during treadmill exercise echocardiography were as follows: (1) to define the frequency of abnormal exercise echocardiographic results, (2) to identify any clinical or exercise ECG variables associated with the abnormalities seen on exercise echocardiography, (3) to ascertain all-cause and cardiovascular mortality rates, and (4) to identify any clinical or exercise echocardiographic predictors of outcome.

PATIENTS AND METHODS

Study Population

Patients who underwent treadmill exercise echocardiography using the Bruce protocol[20] from November 1, 2003, through December 31, 2008, and achieved a workload of 10 or more METs were eligible for this study. A total of 33,379 patients underwent stress echocardiography for clinical reasons at Mayo Clinic (Rochester, Minnesota) during the 62-month study period. Of these, 16,704 patients (50%) underwent dobutamine stress echocardiography and were excluded. Of the 16,675 patients who underwent treadmill exercise echocardiography, 83 (<1%) exercised using protocols other than the Bruce protocol. Of those remaining, 7636 (46%) exercised for 9 or more minutes using the Bruce protocol, achieving a workload associated with an approximate metabolic consumption equivalent of 10 or more METs. The following patients were excluded: 67 patients with dilated cardiomyopathy, 34 patients with at least moderate valvular heart disease, 3 patients with cardiac transplant, and 296 patients who did not consent to the use of their medical records for research purposes. The final study population comprised 7236 patients. This study was approved by the Mayo Clinic Institutional Review Board.

Clinical Information Collection

Patient data were abstracted at the time of exercise echocardiography by specially trained registered nurses and entered into a research database. Patients with a history of CAD, by definition, had a history of myocardial infarction (MI) or coronary revascularization. For patients who did not have a history of CAD, the pretest probability of CAD was estimated on the basis of previously published studies (see the Appendix).[21,22]

Exercise Echocardiography

Exercise testing was symptom-limited unless stopped according to the American College of Cardiology/American Heart Association Guidelines on exercise testing.[23] The maximal age-predicted heart rate (MAPHR) for each patient was calculated by subtracting his or her age from 220. The exercise ECG showed positive results for ischemia if there was 1 mm or more horizontal or downsloping ST-segment depression at 80 ms after the J point.[23] Two-dimensional echocardiographic images were acquired at rest and immediately after exercise by sonographers and analyzed by experienced echocardiologists on the basis of previously published protocols.[24,25] The overall change in left ventricular end-systolic volume (LVESV) was assessed visually by comparing digital images recorded at rest and immediately after exercise. The LVESV response was considered normal if it decreased in response to exercise and abnormal if it did not change appreciably or if it increased. Regional wall motion was assessed and graded on a scale of 1 to 5 at rest and immediately after exercise in each of the 16 left ventricular (LV) segments.[26] The segments were scored as follows: 1, normal; 2, mild to moderate hypokinesis; 3, severe hypokinesis or akinesis; 4, dyskinesis; and 5, aneurysm. The LV wall motion score index was calculated by adding the scores and then dividing by 16. Patients with normal exercise echocardiographic results had normal LV regional and global systolic function at rest and no exercise-induced RWMAs. Patients with abnormal exercise echocardiographic results, defined by imaging findings alone, had RWMAs at rest and/or exercise-induced RWMAs. Patients with abnormal exercise echocardiographic results were subclassified as

TABLE 1. Clinical Characteristics of the Study Population[a,b]

Variable	Study population (N=7236)	Normal exercise echo result (n=5961)	Abnormal exercise echo result (n=1275)	*P* value
Age (y)	54±12	52±12	60±10	<.001
Sex: male	5075 (70)	4062 (68)	1013 (79)	<.001
Hypertension	2717 (38)	2053 (34)	664 (52)	<.001
Diabetes	462 (6)	344 (6)	118 (9)	<.001
Hyperlipidemia	4253 (59)	3293 (55)	960 (75)	<.001
Smoking, current or past	2965 (41)	2332 (39)	633 (50)	<.001
Pretest probability of CAD				<.001
Low	3441 (48)	3055 (51)	386 (30)	
Intermediate or high	2884 (40)	2488 (42)	396 (31)	
History of CAD[c]	911 (13)	418 (7)	493 (39)	
History of MI	454 (6)	148 (2)	306 (24)	<.001
Previous revascularization	803 (11)	371 (6)	432 (34)	<.001
Chest pain	2915 (40)	2450 (41)	465 (36)	.002
Type of chest pain				<.001
Typical angina	289 (4)	204 (3)	85 (7)	
Atypical angina	2338 (32)	1993 (33)	345 (27)	
Nonanginal chest pain	288 (4)	253 (4)	35 (3)	
Dyspnea	1342 (19)	1109 (19)	233 (18)	.78
Medications				
Aspirin	2963 (41)	1946 (33)	747 (59)	<.001
β-Blockers	1454 (20)	958 (16)	496 (39)	<.001
ACE inhibitors or ARBs	1365 (19)	969 (16)	396 (31)	<.001
Statins	2351 (32)	1677 (28)	674 (53)	<.001

[a]ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; echo = echocardiographic; MI = myocardial infarction.
[b]Continuous data are expressed as mean ± SD and categorical data as No. (percentage).
[c]Patients with a history of MI or previous revascularization.

follows: patients who had RWMAs at rest that remained unchanged after exercise had a "fixed" abnormality; patients who had RWMAs at rest as well as new or worsening RWMAs after exercise had a "mixed" abnormality; and patients who had no RWMAs at rest but new RWMAs after exercise had an "ischemic" abnormality. Patients who had exercise echocardiographic results that were positive for ischemia were those with a mixed or an ischemic abnormality. Patients with abnormal exercise echocardiographic results were also stratified according to the extent of abnormality after exercise. Abnormal and ischemic segments were counted for each patient: 1 to 2 segments defined a mild abnormality, 3 to 4 segments defined a moderate abnormality, and 5 or more segments (>25% of LV segments) defined an extensive abnormality. A severely abnormal segment was one that was severely hypokinetic or worse (score ≥3).

Study End Points

Study end points included abnormal exercise echocardiographic results and all-cause and cardiovascular mortality rates. Mortality data were abstracted from the National Death Index. The cause of death was provided, and cardiovascular causes of death were subcategorized according to the American Heart Association categorization of the International Classification of Disease codes.[27]

Statistical Analyses

Data are expressed as mean ± SD for continuous variables and as frequency and percentage for categorical variables. Comparisons between groups were performed by using 2-tailed *t* tests for continuous variables and Pearson χ^2 test for categorical variables. A univariate logistic regression analysis of clinical (Table 1) and exercise ECG (Table 2) variables associated with abnormal exercise echocardiographic results was performed. Univariate variables with $P<.2$ were considered for the multivariate logistic regression model. Kaplan-Meier survival curves were constructed, and the log-rank test was used for comparison between groups. Patients undergoing early revascularization (performed within 30 days after exercise echocardiography) were censored at the time of the procedure. For time-to-event analyses, event time was calculated as time from exercise echocardiography to death for patients known to be deceased. Annualized mortality rates were calculated for the study population and various subgroups as percentage per person-year of follow-up. The 95% CIs were constructed for annualized mortality rates by calculating a Poisson CI on the observed number of events. Multivariate Cox proportional hazards regression modeling (using univariate variables with $P<.2$) was used to identify variables associated with outcome. Variables selected for this analysis were age, sex, diabetes, history of MI, previous revascularization, workload achieved, 85% or more of MAPHR achieved, exercise ECG result, final exercise echocardiographic result, LVESV response, exercise left ventricular ejection fraction (LVEF), extent of severe RWMAs at rest, extent of RWMAs after exercise, and extent of LV ischemia. Incremental models were constructed using clinical variables first and then

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TABLE 2. Exercise ECG and Echocardiographic Characteristics of the Study Population[a,b]

Variable	Total population (N=7236)	Normal exercise echo result (n=5961)	Abnormal exercise echo result (n=1275)	*P* value
Workload achieved (METs)	11.9±1.7	12.0±1.8	11.6±1.5	<.001
≥85% of MAPHR achieved	6066 (84)	5076 (85)	990 (78)	<.001
Peak heart rate−blood pressure product	26,597±4986	26,847±4893	25,433±5246	<.001
Angina during TMET	225 (3)	173 (3)	52 (4)	.03
Exercise ECG result				<.001
Positive	455 (6)	257 (4)	198 (16)	
Uninterpretable	349 (5)	216 (4)	133 (10)	
Negative	6432 (89)	5488 (92)	944 (74)	
LVEF at rest (%)[c]	61±5	61±4	57±8	<.001
LVEF immediately after exercise (%)[d]	70±7	72±4	62±10	<.001
WMSI at rest	1.04±0.15	1.00±0.03	1.21±0.30	<.001
WMSI immediately after exercise	1.06±0.19	1.00±0.01	1.36±0.31	<.001
Final exercise echocardiographic result				
Normal	5961 (82)	5961 (100)	0 (0)	
Fixed	413 (6)	...	413 (32)	
Mixed	315 (4)	...	315 (25)	
Ischemic	547 (8)	...	547 (43)	
Abnormal LVESV response	328 (5)	26 (<1)	302 (24)	<.001
No. of abnormal segments at rest				
1-2 (mild)	291 (4)	...	291 (23)	
3-4 (moderate)	224 (3)	...	224 (18)	
≥5 (extensive)	269 (4)	...	269 (21)	
No. of severely abnormal segments at rest				
1-2	165 (2)	...	165 (13)	
3-4	74 (1)	...	74 (6)	
≥5	58 (0.8)	...	58 (5)	
No. of abnormal segments immediately after exercise				
1-2 (mild)	379 (5)	...	379 (30)	
3-4 (moderate)	384 (5)	...	384 (30)	
≥5 (extensive)	512 (7)	...	512 (40)	
No. of severely abnormal segments immediately after exercise				
1-2	273 (4)	...	273 (21)	
3-4	140 (2)	...	140 (11)	
≥5	104 (1.4)	...	104 (8)	
No. of ischemic segments				
1-2 (mild)	308 (4)	...	308 (24)	
3-4 (moderate)	289 (4)	...	289 (23)	
≥5 (extensive)	265 (4)	...	265 (21)	

[a]Echo = echocardiographic; ECG = electrocardiographic; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MAPHR = maximal age-predicted heart rate; MET = metabolic equivalent; TMET = treadmill exercise test; WMSI = wall motion score index.
[b]Continuous data are expressed as mean ± SD and categorical data as No. (percentage).
[c]The LVEF at rest was <40% in 38 patients (0.5%).
[d]The LVEF immediately after exercise was <50% in 120 patients (1.7%).

exercise ECG variables, followed by exercise echocardiographic variables. The survival C statistic was calculated to show the discriminatory ability of the models.[28] To assess prognostic abilities of incremental models, the integrated discrimination improvement (IDI) measure was calculated at 5-year follow-up. The IDI measure evaluates the change in the differences of the mean predicted probabilities of death between persons dead and alive.[29] All *P* values were 2-tailed, and a *P* value of .05 or less was considered statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

RESULTS

Clinical and Exercise Echocardiographic Characteristics

The clinical characteristics of the study population are shown in Table 1. The mean age was 54±12 years, and 2161 (30%) were women. There were 3207 patients (44%) referred for symptoms of chest pain and/or dyspnea, 1707 (24%) for evaluation of CAD risk factors, 839 (12%) for an abnormal ECG, 727 (10%) for evaluation of known CAD, 473 (7%) for preoperative assessment, and 283 (4%) for abnormal computed tomography coronary calcium scores. Exercise ECG and echocardiographic characteristics are summarized in Table 2. Of the study population, 5961 patients (82%) had normal exercise echocardiographic results and 1275 patients (18%) had abnormal exercise echocardiographic results. Exercise echocardiographic results were positive for ischemia in 862 patients (12%).

The number of patients who had a low pretest probability of CAD was 3441. Among these patients, exercise echocardiographic results were abnormal in 386 (11%) and positive for ischemia in 282 (8%). The number of patients who had an intermediate or high pretest probability of CAD was 2884. Among these patients, exercise echocardiographic results were abnormal in 396 (14%) and positive for ischemia in 306 (11%). Of the 911 patients with a history of CAD, 493 (54%) had abnormal exercise echocardiographic results and 274 (30%) had positive results for ischemia. There were 462 patients with diabetes; exercise echocardiographic results were abnormal in 118 (26%) and positive for ischemia in 79 (17%). The corresponding results for the 6774 patients without diabetes were 1157 (17%) and 783 (12%), respectively.

Workload, Heart Rate, and Exercise ECG Variables

The average workload achieved was 11.9±1.7 METs. Most patients (5280) achieved a workload of 10 to 12.9 METs; 1956 patients achieved 13 or more METs. Fewer patients in the higher workload subgroup had abnormal exercise echocardiographic results (13% vs 19%, respectively; $P<.001$).

Of the 6066 patients who achieved an MAPHR of 85% or more, 871 (14%) were taking β-blockers. Of the 1170 patients who did not achieve an MAPHR of 85% or more, 583 (50%) were taking β-blockers. Sixteen percent of the patients who achieved an MAPHR of 85% or more had abnormal exercise echocardiographic results compared with 24% of those who did not achieve an MAPHR of 85% or more ($P<.001$).

The exercise ECG yielded positive results for ischemia in 455 patients. Of these, 257 (56%) had no exercise echocardiographic abnormality, 15 (3%) had a fixed abnormality, and 183 (40%) had exercise echocardiographic results that were positive for ischemia. Thus, the positive predictive value of the exercise ECG (for a positive exercise echocardiographic result) was 40%. Of the patients with a positive exercise ECG result, 210 patients (46%) had a low pretest probability of CAD, 160 (35%) had an intermediate or high pretest probability of CAD, and 85 (19%) had a history of CAD.

Extent and Severity of Abnormal Exercise Echocardiographic Results

Regarding the extent of abnormal exercise echocardiographic results, most were mild or moderate. There were extensive RWMAs after exercise in 512 patients (7%) and extensive ischemia in 265 (4%). Regional wall motion abnormalities that were both severe and extensive were seen in 58 patients at rest (0.8%) and 104 patients immediately after exercise (1.4%) (Table 2).

Predictors of Abnormal Exercise Echocardiographic Results

Following multivariate logistic regression analysis, variables (odds ratio [OR] and 95% CI) that were independently associated with abnormal exercise echocardiographic results were age, per 10 years (OR, 1.5; 95% CI, 1.4-1.6; $P<.001$); a history of MI (OR, 4.9; 95% CI, 3.8-6.4; $P<.001$); previous revascularization (OR, 2.6; 95% CI, 2.1-3.3; $P<.001$); current or past smoking (OR, 1.2; 95% CI, 1.0-1.4; $P=.02$); use of β-blockers (OR, 1.3; 95% CI, 1.1-1.5; $P=.006$), statins (OR, 1.2; 95% CI, 1.0-1.4; $P=.02$), and aspirin (OR, 1.2; 95% CI, 1.0-1.5; $P=.01$); workload achieved (OR, 0.94; 95% CI, 0.9-1.0; $P=.01$); and positive exercise ECG result (OR, 4.0; 95% CI, 3.2-5.0; $P<.001$).

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Survival of Study Population and Subgroups

The mean follow-up period was 4.8±1.7 years (maximum, 7.9 years). Nine patients had a follow-up of less than 6 months. After censoring for early coronary revascularization, 126 patients died during the follow-up period (all-cause mortality rate, 0.37% per person-year of follow-up; 95% CI, 0.30%-0.43%); of these, 28 patients died of cardiovascular disease (cardiovascular mortality rate, 0.08% per person-year of follow-up; 95% CI, 0.05%-0.12%) and 98 died of noncardiovascular disease. Among patients who died of cardiovascular disease, 18 died of coronary heart disease, 4 of stroke, 3 of hypertensive heart disease, 2 of heart failure, and 1 of aortic dissection. A total of 234 patients (3.2%) underwent coronary angiography within 30 days after exercise echocardiography, of whom 63 (27%) underwent coronary revascularization; 17 patients had coronary artery bypass graft operation, and 46 patients had percutaneous coronary intervention. Among patients undergoing early coronary revascularization, 34 (54%) had extensive ischemia. One patient died of cancer 5 years after early revascularization. Analysis was also performed for the occurrence of all-cause and cardiovascular mortality without censoring for early revascularization. This did not affect the survival estimates or predictors of outcome.

Selected patient characteristics and their effect on patient outcomes are shown in Figure 1. Age, sex, and a history of CAD were of small but significant prognostic importance, but diabetes was not. For patients without a history of CAD, there was no difference in outcome between those with a low pretest probability and those with an intermediate or high pretest probability of CAD (P=.80).

Exercise ECG variables of interest and patient outcomes are shown in Figure 2. Patients who achieved a workload of 13 or more METs had a slightly better prognosis than did patients who achieved 10 to 12.9 METs. Patients who achieved an MAPHR of 85% or more also had a slightly better prognosis than did those who did not. Patients who had a positive exercise ECG result had an outcome that was similar to those who had an uninterpretable or negative exercise ECG result.

Exercise echocardiographic variables and patient outcomes, including annualized all-cause and cardiovascular mortality rates, are shown in Figure 3. Patients who had normal exercise echocardiographic results had better survival than did those who had abnormal exercise echocardiographic results. Patients who had extensive RWMAs after exercise had a less favorable prognosis than did those who had mild to moderate RWMAs. Patients who had a normal compared with an abnormal LVESV response to exercise had slightly better survival, and patients who had an exercise LVEF of 50% or more compared with less than 50% had better survival. For patients who had extensive ischemia (n=265), the all-cause mortality rate was 0.84% (95% CI, 0.41%-1.55%), and the cardiovascular mortality rate was 0.25% (95% CI, 0.05%-0.74%) per person-year of follow-up. The subgroup of patients (n=58) who had extensive and severe RWMAs at rest had the least favorable prognosis, with an all-cause mortality rate of 2.65% (95% CI, 1.07%-5.46%) and a cardiovascular mortality rate of 0.76% (95% CI, 0.09%-2.74%) per person-year of follow-up. Of these, 51 (88%) had a history of MI or pathologic Q waves or left bundle branch block on the ECG.

Multivariate and Incremental Predictors of Outcome

After adjustment for age and sex, variables that were independently associated (hazard ratio [HR] and 95% CI) with all-cause mortality rates were a history of MI (HR, 1.8; 95% CI, 1.1-2.8; P=.02), failure to achieve an MAPHR of 85% or more (HR, 1.6; 95% CI, 1.1-2.4; P=.02), and exercise LVEF of less than 50% (HR, 2.7; 95% CI, 1.3-5.3; P=.004). The C statistic for the clinical model was 0.72 (95% CI, 0.68-0.77), and the addition of exercise ECG variables did not result in a significant addition of prognostic information (C statistic, 0.73; 95% CI, 0.69-0.78), with a gain of 0.2% in the IDI (P=.10). When evaluating the prognostic information provided by the exercise echocardiography model (C statistic, 0.74; 95% CI, 0.69-0.78), there was only a trivial gain (0.2%) in the IDI compared with that obtained by the clinical plus exercise ECG model and this gain did not reach statistical significance (P=.25).

DISCUSSION

In this large study of patients achieving a workload of 10 or more METs during treadmill

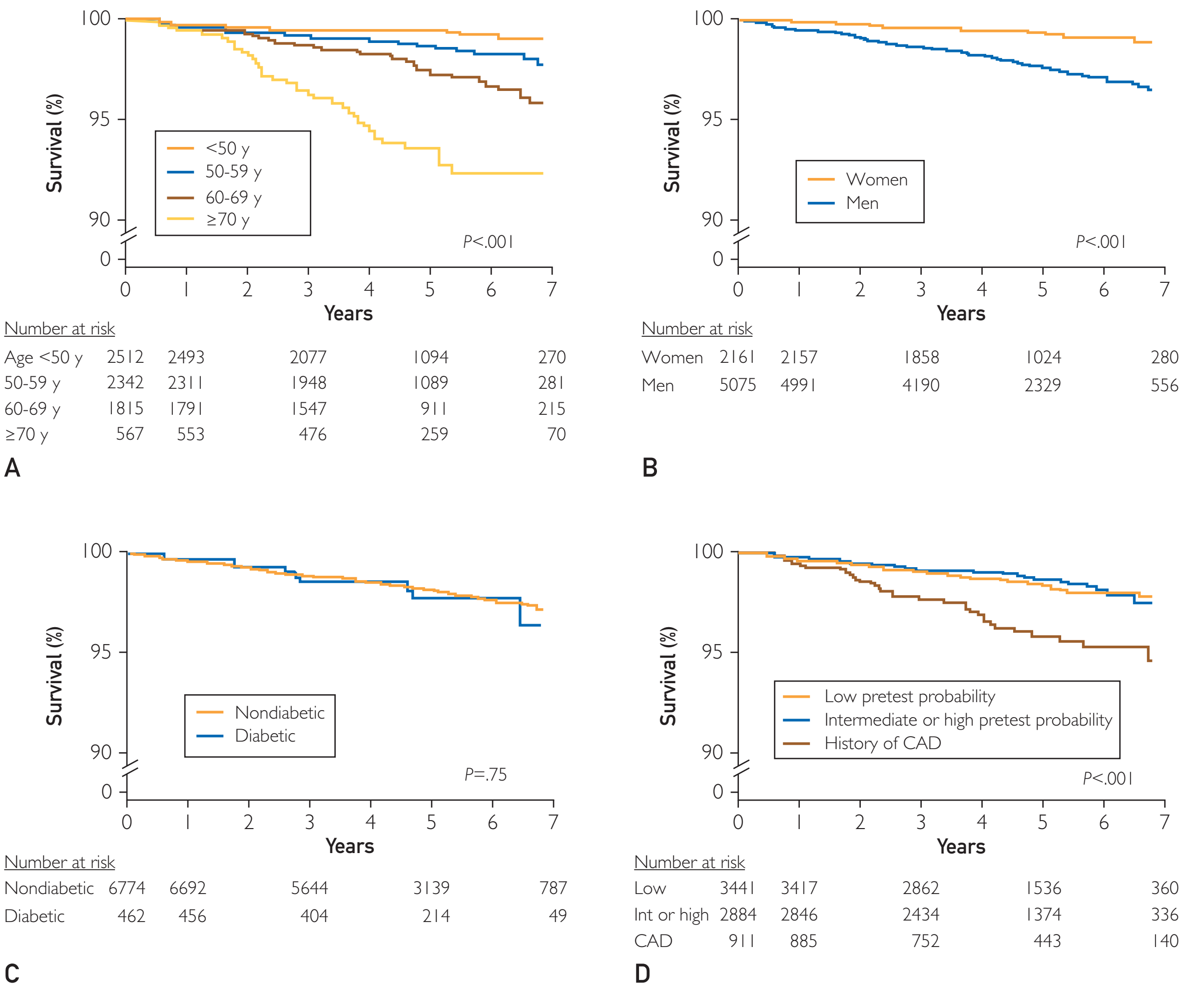

FIGURE 1. Survival after exercise echocardiography of patients with excellent exercise capacity (censored for revascularization within 30 days of exercise echocardiography), stratified according to (A) age, (B) sex, (C) diabetic status, and (D) pretest probability of CAD. CAD = coronary artery disease; Int = intermediate.

exercise echocardiography, we found that 18% of the patients had abnormal echocardiographic results and 12% had exercise echocardiographic results that were positive for ischemia. Four percent of the patients had extensive myocardial ischemia. Overall, the prognosis of this study population was excellent. This observation was true even for patients who are often considered to be at higher risk, such as those with diabetes, a history of CAD, an intermediate or high pretest probability of CAD; those who did not achieve an MAPHR of 85% or more or who had a positive exercise ECG result; and those who had extensive echocardiographic ischemia. Although certain exercise ECG and echocardiographic characteristics had some discriminating value with regard to outcome, this effect was modest and did not result in the identification of sizable patient subgroups at substantial risk of death in the short term or medium term. Neither exercise ECG nor echocardiographic variables added incremental value with respect to the risk of mortality in these patients who were able to achieve a high workload. Furthermore, only 3.2% of the patients underwent coronary angiography within 30 days after exercise echocardiography and only one-fourth of those patients actually had coronary revascularization, illustrating

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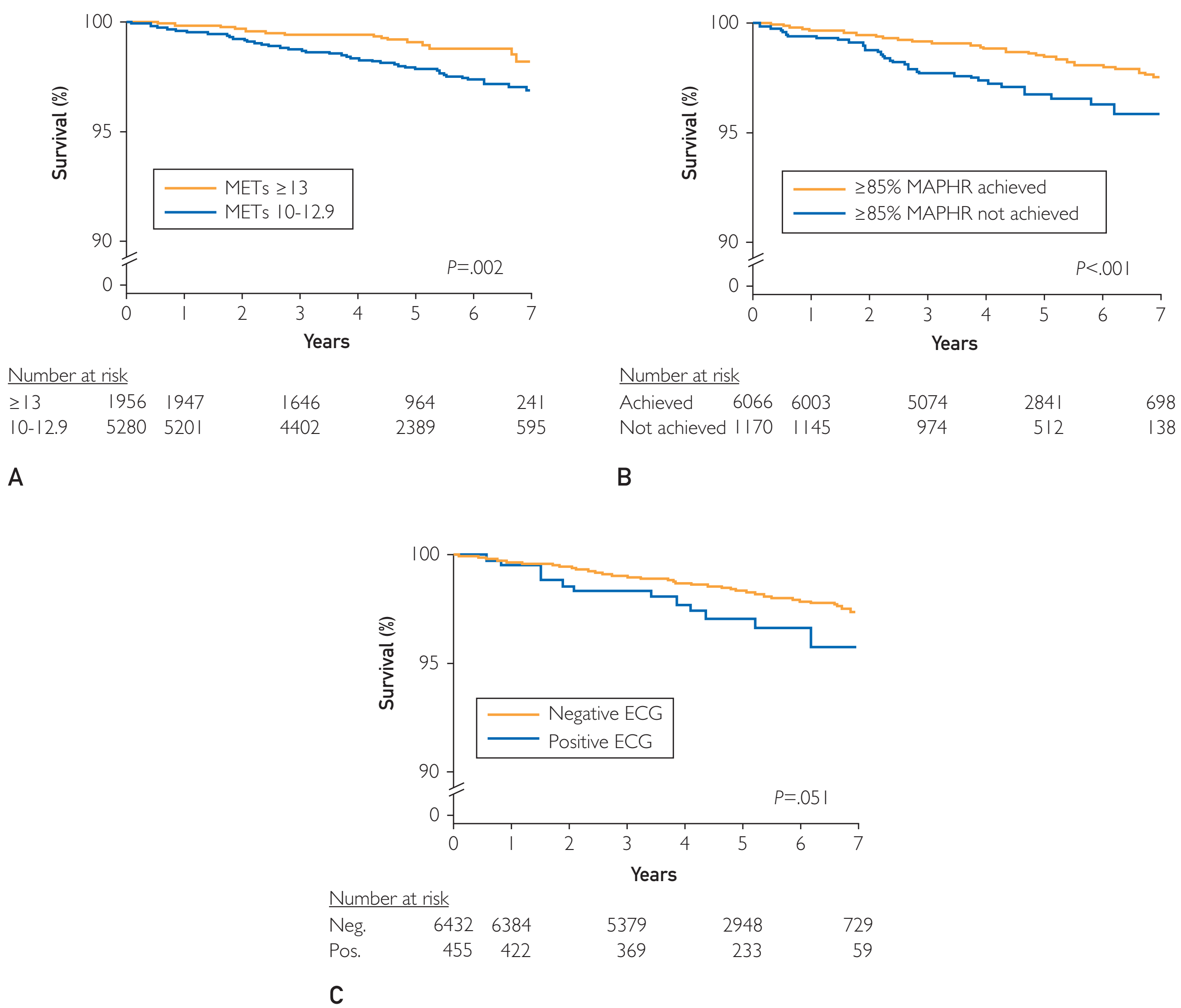

FIGURE 2. Survival after exercise echocardiography of patients with excellent exercise capacity (censored for revascularization within 30 days of exercise echocardiography), stratified according to exercise ECG variables: (A) workload achieved, (B) 85% or more of MAPHR achieved, and (C) exercise ECG result. ECG = electrocardiogram; MAPHR = maximal age-predicted heart rate; MET = metabolic equivalent; Neg. = negative; Pos. = positive.

the limited role stress imaging had in detecting revascularizable CAD in patients with excellent exercise capacity. This study reaffirms that patients who achieve a workload of 10 or more METs at the time of exercise testing have an excellent prognosis, and it adds to the growing body of evidence showing that noninvasive cardiac imaging in such patients is of limited value.

More than 2 decades ago, by using data from the Coronary Artery Surgery Study Registry, Weiner et al[8] established that an exercise capacity of 10 or more METs was associated with a favorable prognosis even if patients had multivessel CAD and subsequently reported that these patients derived less benefit from coronary revascularization than did patients who had lower exercise capacity.[30,31] Others have similarly found that a higher exercise workload and a low-risk Duke Treadmill Score are associated with low risk and less benefit from revascularization.[32-34] Additionally, investigators at the Cooper Institute included cardiorespiratory fitness, measured as METs achieved during

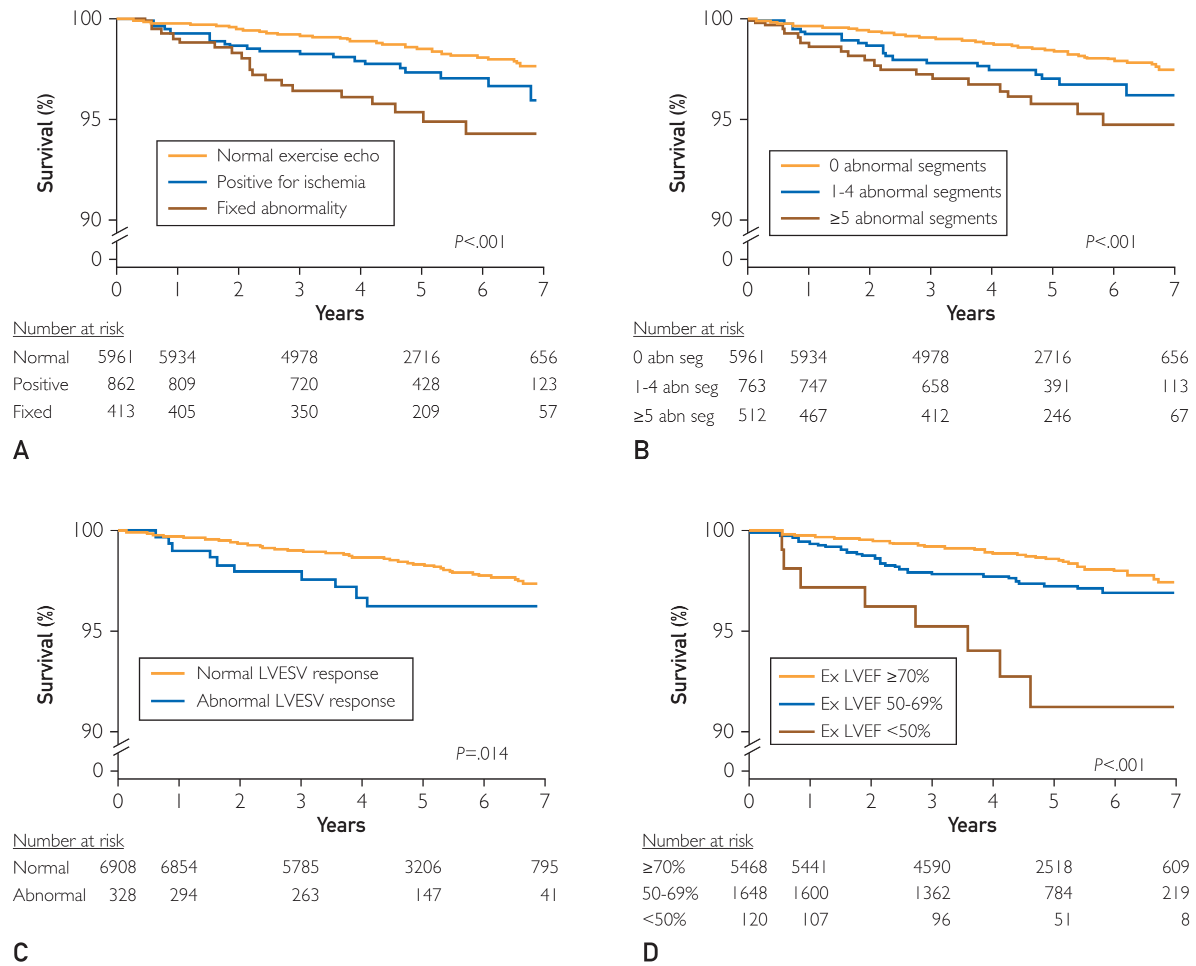

FIGURE 3. Survival after exercise echocardiography (echo) of patients with excellent exercise capacity (censored for revascularization within 30 days of exercise echo), stratified according to exercise echo variables (data given as annualized mortality rates per person-year of follow-up with 95% CI in parentheses): (A) exercise echo result: normal, 0.30% (0.24%-0.37%); positive, 0.53% (0.33%-0.80%); fixed, 0.93% (0.56%-1.46%); (B) extent of exercise RWMAs: 0 segments (seg), 0.30% (0.24%-0.37%); 1 to 4 seg, 0.55% (0.34%-0.84%); 5 or more seg, 0.85% (0.52%-1.31%); (C) LVESV response: normal, 0.35% (0.29%-0.42%); abnormal, 0.75% (0.37%-1.33%); and (D) LVEF immediately after exercise: 70% or more, 0.30% (0.23%-0.37%); 50% to 69%, 0.51% (0.36%-0.69%); less than 50%, 1.72% (0.79%-3.28%). The annualized cardiovascular mortality rates per person-year of follow-up (95% CI) for the above subgroups were as follows: (A) exercise echo result: normal, 0.05% (0.03%-0.08%); positive, 0.22% (0.10%-0.41%); fixed, 0.25% (0.05%-0.74%); (B) extent of exercise RWMAs: 0 seg, 0.05% (0.03%-0.08%); 1 to 4 seg, 0.18% (0.07%-0.38%); 5 or more seg, 0.30% (0.12%-0.61%); (C) LVESV response: normal, 0.07% (0.05%-0.11%); abnormal, 0.27% (0.07%-0.69%); and (D) LVEF immediately after exercise: 70% or more, 0.06% (0.04%-0.10%); 50% to 69%, 0.10% (0.04%-0.20%); less than 50%, 0.77% (0.21%-1.96%). abn = abnormal; Ex LVEF = left ventricular ejection fraction immediately after exercise; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RWMA = regional wall motion abnormality.

treadmill exercise testing, in a validated clinical scoring system for predicting all-cause mortality risk in men.[35]

The findings of our study mirror those of studies that have examined the utility of other cardiovascular imaging modalities. For example, in recently published studies, investigators have shown that the presence of important ischemia, measured semiquantitatively using MPI in patients achieving a workload of 10 or more METs, is an uncommon finding.[9,10] *Important ischemia* was defined as the involvement of 10% or more of the LV and ranged from 0.4% to 13% in frequency. The prognosis of patients in these studies was good, and abnormalities measured using MPI were not predictive of cardiovascular events or outcome.[10,11] In contrast to our findings, Peteiro et al[19] reported that for men who achieved a workload of 10 or more METs and women who achieved a workload of 8 or more METs, exercise echocardiography added incremental prognostic information to clinical and exercise ECG variables when the end points of nonfatal MI and cardiac death were considered. In that study, 29% of the patients had a history of MI, 4% had an LVEF of less than 40% at rest, and 11% had an LVEF of less than 45% immediately after exercise. In our study, only 6% of the patients had a history of MI, 0.5% had an LVEF of less than 40% at rest, and 1.7% had an LVEF of less than 50% immediately after exercise.

There has been substantial growth in the use of cardiac imaging procedures for the evaluation of CAD in the past 10 years. This has contributed to marked increases in health care expenditures.[36,37] The findings of our study have potentially important implications with regard to the use of stress imaging for the evaluation of patients who are capable of exercising to a high level and could lead to more effective use of health care resources. Physicians who use nonimaging treadmill exercise ECG tests to assess patients can reassure them that their prognosis is favorable if they achieve a high workload, even if they do not achieve an MAPHR of 85% or more or if they have a positive exercise ECG result. A small subset of patients who may be at higher risk can be identified using transthoracic echocardiography, which can be performed if there is a history of MI or pathologic Q waves on the ECG. Patients who are able to perform physical activities, such as carrying a 25 lb weight upstairs, jogging slowly for 5 or more minutes, cycling with moderate effort (~12 mph outdoors or ~100 W when stationary), or playing recreational sports such as full-court basketball or singles tennis, are likely to achieve a workload of 10 or more METs at the time of symptom-limited exercise testing.[38] Such patients can initially undergo confirmatory treadmill exercise testing without imaging.

Ours is a single-center study and retrospective in design; therefore, referral bias cannot be excluded. Although we ascertained all-cause and cardiovascular mortality rates, we did not collect data on nonfatal cardiovascular end points such as MI or late coronary revascularization. It is likely that patients who have abnormal exercise echocardiographic results despite an excellent exercise capacity are still at some risk of having these clinical end points. The number of variables that could be included in the multivariate analysis for the primary end point of all-cause mortality was limited by the relatively small number of events occurring during the follow-up period. Although efforts were made to include the most clinically relevant variables, it is possible that others that could not be entered might have affected the results.

CONCLUSION

Patients who are able to achieve a high workload (≥10 METs) at the time of exercise testing do not often have extensive abnormalities on echocardiography. Although exercise echocardiographic results provide some prognostic information, it is not of incremental value for these patients, who generally have an excellent short-term and medium-term prognosis.

APPENDIX: Patient categorization according to pretest probability of CAD

Patients in the low pretest probability subgroup were those without a history of CAD or diabetes and who had no symptoms or nonanginal chest pain (women younger than 60 years and men younger than 40 years) or atypical angina (women younger than 50 years). Women younger than 50 years who had dyspnea but no chest pain were also included in this subgroup. In a previous study, we classified patients with dyspnea in a way similar to patients with atypical angina for assessing the pretest probability of disease.[22] The intermediate or high pretest probability subgroup was composed of the remainder of the patients without a history of CAD and included patients who had diabetes. This subgroup included patients who had typical angina, nonanginal chest pain (women aged 60 years or older and men aged 40 years or older), atypical angina (women aged 50 years or older and all men), or dyspnea but no chest pain (women aged 50 years or older and all men).

Abbreviations and Acronyms: **CAD** = coronary artery disease; **ECG** = electrocardiographic; **HR** = hazard ratio; **IDI** = integrated discrimination improvement; **LV** = left ventricular; **LVEF** = left ventricular ejection fraction; **LVESV** = left ventricular end-systolic volume; **MAPHR** = maximal age-predicted heart rate; **MET** = metabolic equivalent; **MI** = myocardial infarction; **MPI** = myocardial perfusion imaging; **OR** = odds ratio; **RWMAs** = regional wall motion abnormalities

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