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Prognostic Value of Exercise Treadmill Testing in Asymptomatic Chronic Nonischemic Mitral Regurgitation

Phyllis G. Supino, EdD^a, Jeffrey S. Borer, MD^a, Karlheinz Schuleri, MD^b, Anuj Gupta, MD^c, Clare Hochreiter, MD^a, Paul Kligfield, MD^a, Edmund McM. Herrold, MD, PhD^a, and Jacek J. Preibisz, MD, PhD^a

Division of Cardiovascular Pathophysiology and The Howard Gilman Institute for Valvular Heart Diseases, Weill Medical College of Cornell University, New York, N.Y

Abstract

In many heart diseases, exercise treadmill testing(ETT) has useful functional correlates and/or prognostic value. However, its predictive value in mitral regurgitation(MR) is undefined. To determine whether ETT descriptors predict death or indications for mitral valve surgery among patients with MR, we prospectively followed, for 7±3 endpoint-free years, a cohort of 38 patients with chronic severe nonischemic MR who underwent modified Bruce ETT; all lacked surgical indications at study entry. Their baseline exercise descriptors also were compared with those from 46 patients with severe MR who, at entry, already had reached surgical indications. Endpoints during follow-up among the cohort included sudden death(n=1), heart failure symptoms(n=2), atrial fibrillation(n=4), LVEF<60%(n=2), LV systolic dimensions(IDs) 45 mm(n=12) and LVIDs>40mm(n=11), LVEF<60%+LVIDs 45 mm(n=3), and heart failure+LVIDs 45mm +LVEF<60%(n=1). In univariate analysis, exercise duration(p=.004), chronotropic response(p=.007), percent predicted peak heart rate(p=.01) and heart rate recovery(p<.02) predicted events; in multivariate analysis, only exercise duration was predictive(p<.02). Average annual event risk was 5-fold lower(4.62%) with exercise duration 15 minutes vs. <15 minutes(average annual risk=23.48%, p=.004). Relative risks among patients with and without exercise-inducible ST segment depression were comparable(1.3[NS]) whether defined at entry and/or during follow-up. Exercise duration, but not prevalence of exercise-inducible ST segment depression, was lower(p<.001) among patients with surgical indications at entry vs. initially endpoint-free patients. In conclusion, among asymptomatic patients with chronic severe nonischemic MR and no objective criteria for operation, progression to surgical indications generally is rapid. However, those with excellent exercise tolerance have a relatively benign course. Exercise-inducible ST segment depression has no prognostic value in this population.

We followed, for 7±3 endpoint-free years, 38 patients with chronic severe nonischemic mitral regurgitation (MR) who underwent modified Bruce exercise treadmill testing (ETT) to determine whether ETT descriptors predict death or indications for mitral valve surgery. At study entry, all lacked surgical indications. Exercise duration independently predicted subsequent events; event risks among patients with and without exercise-inducible ST segment depression were comparable. We conclude that among asymptomatic patients with chronic severe nonischemic MR

Address for Correspondence: Jeffrey S. Borer, M.D., New York-Presbyterian Hospital New York Weill Cornell Center, 525 East 68th Street, New York, N.Y. 10021, 212-746-4646=phone, 212-746-8448=fax, canadaD45@aol.com=email.

^aDepartment of Medicine, Weill Cornell Medical College, New York, NY 10021

^bDepartment of Medicine, Johns Hopkins University, Baltimore, MD

^cDepartment of Medicine, Columbia College of Physicians and Surgeons, New York, NY 11032

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and no objective criteria for operation, those with excellent exercise tolerance have a relatively benign course. Exercise-inducible ST segment depression has no prognostic value in this population.

Keywords

exercise treadmill testing; exercise capacity; mitral regurgitation; prognostication

Among asymptomatic patients with chronic, isolated, severe mitral regurgitation (MR) with normal left (LV) and right ventricular (RV) chamber performance, progression to heart failure occurs at a rate of 10%/year (1). When symptoms have developed, natural history is suboptimal even if ventricular performance is well preserved and valve surgery is performed (2). Therefore, regardless of etiology, asymptomatic patients with severe MR are closely followed to detect symptoms and/or objective ventricular dysfunction (1,3). Symptom perception varies with activity and can be difficult to elicit. Treadmill exercise tolerance testing (ETT) can unmask symptoms; ETT findings have geometric and functional correlates in aortic regurgitation (AR) (4) and prognostic value in coronary artery disease (5) and AR (6). ET correlates with RV ejection fraction, a prognosticator in MR (7). However, neither ET nor other prognostically useful ETT parameters (8) have been evaluated in MR. Also, electrocardiographic (ECG) ST segment depression during ETT is prognostically useful in coronary artery disease and is related to geometric/functional characteristics in AR, themselves related to outcome (3,9). The prognostic value of ECG ST depression has not been assessed in MR. Therefore, we prospectively evaluated 38 asymptomatic patients with chronic, isolated, pure, severe MR to test the hypotheses that ETT descriptors (a) predict subsequent clinical outcome or currently accepted objective indications for mitral valve surgery and (b) correlate with the presence of clinically silent, hemodynamically important coronary artery disease. We also examined the association between exercise duration, exercise ST depression and LV and RV geometric indices in this cohort.

Methods

Study Population

The population included patients enrolled in our ongoing prospective study of the natural histories of regurgitant valvular diseases and their predictors (protocol previously described [1,7,9]). Briefly, at study entry, among other tests, patients undergo echocardiography at rest, radionuclide cineangiography at rest and exercise, and ETT with ECG. Repeated testing is performed annually as part of routine clinical follow-up (therefore, occasional studies are not available if not ordered by the primary cardiologist); clinical evaluation is performed annually per protocol. Medications, if any, and timing of surgery, if performed, are determined by primary physicians, not by study protocol, which has been approved annually by the Committee on Human Rights in Research of Cornell University since its inception.

Between February 1981 and June 2001, 110 unoperated patients were enrolled with hemodynamically severe isolated MR confirmed at subsequent cardiac catheterization, or who had physical and echocardiographic evidence of severe MR (LV diastolic dimension >5.9 cm [men], >5.5 cm [women], and/or left atrial dimension >4.0 cm. and, since they have become available, Doppler echocardiographic findings consistent with severe MR). No patient in this series had prior evidence of previous myocardial infarction, history of angina pectoris, more than mild AR, or any mitral or aortic stenosis at entry. Twenty six patients were excluded for lack of ETT at study entry and 46 additional patients were excluded due to the presence of indications for mitral valve surgery at study entry: New York Heart Association Functional Class 3 symptoms (15 patients) or objective criteria (atrial

fibrillation [15 patients], LV systolic dimensions [IDs] ≥ 45 mm and/or LV ejection fraction $<60\%$ at rest by echocardiography [9 patients]) with or without Functional Class 2 symptoms). The remaining 38 patients were all asymptomatic (New York Heart Association Functional Class 1) and lacked objective criteria for mitral valve surgery at study entry. These patients comprise the cohort that was used to define prognostic indices from ETT.

Baseline and Follow-up Assessments

Symptom-limited (dyspnea, fatigue) upright treadmill ETT and evaluation of clinical status and cardiac function and size was conducted at study entry among all patients and approximately annually thereafter among the 38 cohort patients. ETT was performed according to the modified Bruce protocol, including an initial 3 minutes at grade 0° , 1.7 mph. Exercise duration was defined as number of minutes on ETT; also determined were heart rate recovery, chronotropic response, and percent maximum predicted peak heart rate achieved ("heart rate variables", as previously described [8,10,11]). ECG response to exercise was "positive" only when 0.1 mV (1 mm) additional horizontal or downsloping ST segment depression occurred during exercise compared with rest at 60 to 80 msec after the J point; upsloping ST segment depression and/or subthreshold ST depression were "negative." Echocardiography at rest and radionuclide cineangiography at rest and during symptom limited exercise were performed by standard methods as previously described (1,12-14). Follow-up clinical status was evaluated by a combination of personal or telephone interview and review of medical and vital records. All patients were followed until death or to currently defined predictors of significantly compromised prognosis commonly employed as bases for mitral valve surgery, i.e., new onset of heart failure symptoms (Functional Class 2) (15), LV ejection fraction_{rest} $<10\%$ higher than the lower limit of normal for the testing modality ($<60\%$ by echo [16]), new onset atrial fibrillation (17), or echocardiographic LVIDs ≥ 45 mm (18), an accepted criterion when the study was performed, and LVIDs >40 mm, a more recently suggested criterion for surgery (19) that was not employed at the time this study was undertaken. Echocardiographic effective regurgitant orifice area, recently reported to have significant prognostic impact (20), was not measured in our laboratory during this study. Follow-up among 8 patients who underwent surgery without reaching a currently accepted surgical indication was terminated at the time of operation; these patients were not considered to have reached an endpoint. Endpoint-free patients were followed 7 ± 3 (3-9) years after study entry; all but 2 patients (95%) were followed to an endpoint or ≥ 5 endpoint-free years. Presence or absence of hemodynamically important coronary artery disease ($\geq 50\%$ luminal diameter narrowing of ≥ 1 major coronary vessel) was assessed in 30/33 (91%) patients who reached a study endpoint or were operated without reaching a current surgical indication 4 ± 4 (1-16) years after study entry. The 3 patients who did not undergo coronary angiography (age at endpoint: 36 years) reached objective indications only (LV ejection fraction $<60\%$ (1 patient), LVIDs ≥ 45 mm (1 patient), LVEF $<60\%$ + LVIDs ≥ 45 mm [1 patient]) and remained unoperated during follow-up.

Statistical Analysis

Descriptive statistics are presented as mean $\pm$ standard deviation (continuous variables) or number and percent (categorical variables). Kaplan-Meier product limit estimate curves were compared by the log rank test to evaluate the univariate relation of exercise duration, heart rate response, and ST segment depression with exercise (all defined by ETT at study entry) to subsequent development of an endpoint in the cohort; these descriptors, evaluated as continuous variables, also were related to study outcomes by univariate Cox model analysis. Endpoints were defined as sudden cardiac death, heart failure symptoms, atrial fibrillation, LV ejection fraction_{rest} $<60\%$, or LVIDs ≥ 45 mm or ≥ 40 mm. ST segment depression was classified as positive or negative. Exercise times and heart rate variables were stratified by statistical terciles; the lower 2 terciles were combined for all analyses due

to statistically indistinguishable average annual risks. Multivariate Cox model analysis (entry and removal thresholds, .05 and .10, respectively), performed in series, was used to adjust each of the exercise descriptors (exercise duration, percent maximum predicted peak heart rate achieved, chronotropic response, heart rate recovery and ST segment depression) for the potentially confounding influence of baseline variations in age, gender and cardiac medications at study entry, and to compare the relative prognostic value of each of the exercise descriptors found to be statistically significant in univariate analysis. Descriptors entered into the multivariate models were partitioned according to the same cutpoints used for univariate analysis to render hazards approximately proportional across strata and to simplify interpretation. Separately, the potentially confounding influence of digoxin on the exercise ECG was controlled by restricting analysis to patients not on this drug at study entry (n=33). Patients who underwent operation (n=8) without reaching a currently accepted surgical indication were censored from analysis at the time of operation. Fisher's exact tests were used to evaluate the association of exercise-inducible ST segment depression at and after study entry to coronary artery disease; positive predictive values also were calculated. Independent samples t-tests were used to assess the relation of exercise duration (≥ 15 minutes vs. <15 minutes) and ST segment depression to indices of ventricular function and size defined at study entry. To provide a measure of internal validation for our findings, exercise duration and prevalence of exercise-inducible ST segment depression, each defined at entry in our study cohort, were compared to the distribution of these parameters among patients who were excluded from the cohort because they already had symptoms or met other (i.e., objective) criteria for surgery at study ("validation group", n=46); these comparisons were performed by Chi Square testing (with Yates Correction) or by independent samples t-test, as appropriate. The criterion for statistical significance was $p < .05$ (2-sided test). Descriptive and inferential statistical analyses were performed using SPSS v. 12.0 (Chicago, Ill). Retrospective power analysis, performed using an on-line calculating web page (21), indicated that a hazard ratio of 2.4 would be detectable with 38 study patients, and that a 2.5 hazard ratio would be detectable among the 33 patients not receiving digoxin.

Results

Characteristics of the Cohort at Study Entry (Table 1)

Patients were predominantly middle-aged males. Approximately one third received cardiac drugs chronically. At study entry, positive ST segment depression was induced by exercise in approximately a quarter of the cohort; 5 additional patients not receiving digoxin developed this descriptor only after study entry. Most (81%) patients maintained their baseline ST segment status during annual follow-up, though 2 with ST segment depression lacked this finding at subsequent testing. Exercise tolerance generally was well maintained (Tables 1,2); one-third exercised for ≥ 15 minutes, i.e., completed Bruce Stage 4 (Table 2). Exercise testing was terminated in most patients due to generalized fatigue (Table 1).

Events during Follow-up

During follow-up, 25/38 patients (68%) in the cohort reached a primary endpoint event (first event: sudden death=1, heart failure=2, atrial fibrillation=4, LV ejection fraction<60%=2, LVIDs ≥45mm=12; 4 patients had multiple endpoints simultaneously (LV ejection fraction<60% + LVIDs ≥45mm [3], heart failure + LV ejection fraction<60% + LVIDs ≥45mm [1]). Among the 24 patients whose LVIDs did not exceed 40mm at baseline, 11 developed LVIDs>40mm, 10 without reaching another endpoint and 1 in association with another endpoint: average annual risk (using LVIDs ≥45mm) among the entire population was 14.2% (15.5% using LVIDs ≥40mm); 5-year cardiac event-free survival rate was 40.0% (35.5% using LVIDs ≥40mm).

Prediction of Outcomes (Tables 2 and 3)

Exercise duration, percent predicted heart rate achieved, chronotropic response, and heart rate recovery each were inversely associated with the rate of progression to cardiac endpoints when analyzed as terciles ($p < .02$, hazard ratios: 2.9, all variables [Table 2]). Parallel results were obtained with either LVIDs criterion. All but heart rate recovery (NS) also predicted endpoints when analyzed as continuous variables ($p < .03$ [exercise duration], $p < .02$ [maximum predicted peak heart rate achieved], $p = .02$ [chronotropic response]). By multivariate analysis (Table 3), exercise duration was predominantly and independently predictive of outcome when evaluated pairwise vs. each of the heart rate variables ($p = .008$ – $< .02$). It also remained independently predictive when all variables were incorporated in the model ($p < .02$ [exercise duration], NS vs. other heart rate variables [Table 3]). Moreover, no statistical interactions existed between exercise duration and any of the heart rate variables, suggesting that heart rate response did not modify or otherwise influence predictions by exercise duration. When the clinical course of patients who exercised ≥ 15 minutes (the lower bound of the upper tercile of the exercise time distribution) was compared with the experience of those who exercised < 15 minutes, the former group progressed to cardiac endpoints at one-fifth the rate of those with shorter exercise times ($p = .004$, Figure 1, Table 3). This relation of event risk to exercise duration remained statistically significant ($p = .008$) when analysis was adjusted for baseline variations in age, gender, etiology, LV mass or chronic use of any cardiac drug. It also remained statistically significant when analysis was restricted to patients not on digoxin at study entry ($n = 33$, $p = .01$) or to those with mitral valve prolapse only ($n = 32$, $p = .01$). No significant differences in baseline exercise times were found between patients reaching echocardiographic endpoints alone vs. those who died suddenly or developed heart failure symptoms or atrial fibrillation (12 ± 3 vs. 11 ± 2 minutes, $n = 17$, 7). Exercise times also were similar among endpoint-free patients vs. those censored when surgery occurred without currently-accepted indications (14 ± 2 vs. 15 ± 2 minutes, $n = 5$, 8, NS all comparisons).

In contrast, event rates with and without exercise inducible ST segment depression were statistically indistinguishable among the subgroup of 33 cohort members not on digoxin at study entry (hazard ratio=1.2, NS, Figure 2, Table 3) and also among all 38 patients on or off digoxin at entry (hazard ratio=1.5, NS, Table 3); similar patterns again were obtained with either LVIDs criterion. Data were analyzed, post hoc, to determine whether ST segment depression first occurring after study entry added to the predictive value of this parameter, as it does for coronary artery disease (22); risk of endpoints was identical (hazard ratio=1.0, NS, Table 3) among patients with and without ST segment depression when the 5 patients who developed ST depression after study entry were added to those with ST depression at study entry and also was similar when these 5 patients were compared with those who did not manifest ST depression either at study entry or during follow-up (hazard ratio=0.9, NS, Table 3). ST depression with exercise had no predictive value for subsequent events even when analyses were adjusted for baseline variations in age, gender, etiology and chronic use of any cardiac medication or when the magnitude of the ST change was evaluated post hoc (NS, all comparisons) as a continuous variable, and no significant interaction was found between ST segment depression with exercise and exercise duration.

Prediction of Coronary Artery Disease

Eight of 38 patients (21%) in the cohort had clinically silent, hemodynamically important coronary artery disease discovered at pre-operative catheterization after study entry (1-vessel disease, 6 patients; 2-vessel disease, 2 patients). There was no association between exercise duration at study entry, or ST depression at entry or during follow-up, and presence of coronary disease (NS, all comparisons) with or without digoxin use.

Geometric and Functional Correlates of Exercise Duration and Exercise ST Depression in MR

Among cohort members, exercise duration at study entry was associated with magnitude of change in LV and RV ejection fractions from rest to exercise ($p<.03$, $p=.03$, respectively, Table 4) but not with LV size or LV or RV ejection fractions at rest. None of the ejection fraction or size descriptors carried independent predictive value for outcome when ETT duration already was entered into the multivariate model. Exercise-inducible ST segment depression was not associated with ventricular geometric or functional indices (Table 4).

Exercise Duration and Exercise ST segment Depression at Entry in “Validation Group” vs. Study Cohort

Patients who, at study entry, already met criteria for surgery exercised for only 7 ± 3 minutes; almost all (96%) had exercise durations <15 minutes ($p<.001$, $p=.001$, respectively, vs. cohort). Prevalence of exercise-inducible ST segment depression was 28% (NS vs. cohort) in absence of digoxin.

Discussion

Our data indicate that among asymptomatic patients with chronic severe nonischemic MR and who initially lack objective operative criteria, progression to current indications for mitral valve surgery generally is relatively rapid, suggesting the need for frequent assessment, as previously reported by us and other groups (1,19,23). However, the subgroup of patients with excellent exercise tolerance on initial evaluation can expect a relatively benign course, particularly in comparison with those manifesting poorer exercise tolerance. The prognostic importance of exercise tolerance is buttressed by our observation of significantly lower exercise times among our internal validation group. These findings are consistent with our earlier observation (7), correlating exercise tolerance with LV ejection fraction and, more prominently, with RV ejection fraction in MR. Indeed, since exercise intolerance in MR generally is related to pulmonary vascular congestion and RV ejection fraction is responsive to impedance to RV outflow, our finding is consistent with accepted pathophysiology. Our data parallel investigations that have documented the prognostic value of exercise duration in AR (6) and coronary artery disease (5) and its correlation with symptoms in patients with mixed MR and AR (24). They also suggest that exercise tolerance from ETT can be useful in detecting unreported symptoms from MR, as is true, and prognostically useful, among patients with aortic stenosis (25). Since patients may minimize activity without recognizing the cause, observation of exertional dyspnea by the clinician during ETT (found in almost a quarter of our patients during index testing) may be useful in defining subsequent management. The results also indicate the predictive value of ETT heart rate variables in MR, as reported for other patient populations (8,10). However, multivariate models suggest that heart rate variables have no independent prognostic importance once exercise duration is considered.

In contrast to exercise duration or heart rate response, exercise-induced ST segment depression during ETT, whether identified at or after initial testing, does not appear to predict clinical or functional deterioration in patients with MR and its prevalence is statistically indistinguishable among patients initially without vs. those with surgical indications. Thus, inferences drawn from this parameter should not be employed as a basis for the timing of mitral valve surgery. Our findings are consistent with the results of Massie et al (26), Greenspan et al (27), and Malcolm et al (28), who demonstrated the lack of predictive value of ST depression for coronary artery disease in patients with mitral valve prolapse (the most frequent etiology for MR among our patients). However, in these earlier studies, MR commonly was minimal or mild (among patients in whom MR was

documented) and analyses uniformly were cross-sectional without follow-up. Thus, our data extend these earlier observations to patients with severe MR and also indicate that ST depression does not predict subsequent development of symptomatic coronary disease during >7 years follow-up, albeit in patients with low pre-test likelihood of coronary disease (as patients with clinically evident coronary disease were excluded from entering our study).

Results in these patients with MR differ from those reported previously in cohorts with AR (4) in which ST segment depression during exercise was associated with prognostically important indices of LV function and size. The reasons for this difference are not clear. However, myocardial loading is highly dissimilar between these diseases and might well result in differences in ETT/ECG findings as they do for prognostic ventricular function indices derived from echocardiography (3) and radionuclide cineangiography (9).

Of necessity, as in any long-term follow-up study, our measurements for confirming disease severity used the technology available at the time of study entry though new measures, as they became available, provided results consistent with earlier entry findings. Recent precise, quantitative measures of MR severity (echocardiographic effective orifice areas, regurgitant fractions) were not available in the 1980s when most patients entered the study. Thus, patients with relatively poor exercise tolerance might have had more severe MR than those with better exercise tolerance. However, baseline estimates of left atrial or ventricular dilatation, obtained in all patients, did not vary as a function of exercise tolerance, suggesting that unmeasured differences in MR severity were unlikely to have confounded the present findings. Also, performance of respiratory gas analysis could have added a precise confirmatory measure, though the strong relation of outcome to exercise tolerance alone suggests the value of this approach.

Population size limited the precision of our subgroup-specific event risk estimates and hazard ratios. Accordingly, these should be considered tentative. The population also was relatively small for firm conclusions about the lack of relation between exercise-inducible ST segment depression and outcome or descriptors of LV/RV function. It is possible that a substantially larger number of study subjects (e.g., >800 similar patients not on digoxin at study entry, by retrospective sample size calculation) might have produced statistically significant results. Nonetheless, the near superimposition of the Kaplan-Meier curves during the first 8 years after index testing and the very low hazard ratio associated with this variable throughout the entire period of observation suggests that, if any relation exists, it is too weak to be of clinical importance.

Only a relatively small number of patients manifested newly developing ST segment depression after study entry, limiting our ability to assess the association between this descriptor and subsequent events, a relation previously reported among patients with coronary artery disease (22). However, events did not cluster among these patients; indeed, there was not even a non-significant tendency for such clustering. This finding, coupled with the identical hazards observed when ST depression was considered either at entry or at any time during follow-up, suggests that our findings are unlikely to stem primarily from lack of statistical power.

Finally, though all study patients were included who met the entry criteria, the cohort included relatively few elderly patients. It is possible that a different segregation point for exercise duration might provide better risk stratification among older patients; we are unable to test this hypothesis. However, from published age-related exercise capacities (29), it is possible to infer a 10% decline per decade over age 40 years. Even with minimum exercise times of 16 minutes (age <40), 15 minutes (age 40-49), 14 minutes (age 50-59), and 13 minutes (age 60-69), clear separation into low and high risk groups is possible.

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References

- Rosen SE, Borer JS, Hochreiter C, Supino P, Roman MJ, Devereux RB, Kligfield P, Bucek J. Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. *Am J Cardiol*. 1994; 74:374–380. [PubMed: 8059701]
- Tribouilloy CM, Enriquez-Sarano M, Schaff HV, Orszulak TA, Bailey KR, Tajik AJ, Frye RL. Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation. Rationale for optimizing surgical indications. *Circulation*. 1999; 99:400–405. [PubMed: 9918527]
- Bonow RO, Carabello B, de Leon AC, Edmunds LH Jr, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Gibbons RJ, Russell RO, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/ American Heart Association task force on practice guidelines (committee on management of patients with valvular heart disease). *J Am Coll Cardiol*. 1998; 32:1486–1582. [PubMed: 9809971]
- Chen J, Okin PM, Roman MJ, Hochreiter C, Devereux RB, Borer JS, Kligfield P. Combined rest and exercise electrocardiographic repolarization findings in relation to structural and functional abnormalities in asymptomatic aortic regurgitation. *Am Heart J*. 1996; 132:343–347. [PubMed: 8701896]
- Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med*. 1991; 325:849–853. [PubMed: 1875969]
- Bonow RO, Borer JS, Rosing DR, Henry WL, Pearlman AS, McIntosh CL, Morrow AG, Epstein SE. Preoperative exercise capacity in symptomatic patients with aortic regurgitation as a predictor of postoperative left ventricular function and long-term prognosis. *Circulation*. 1980; 62:1280–1290. [PubMed: 6777072]
- Hochreiter C, Niles N, Devereux RB, Kligfield P, Borer JS. Mitral regurgitation: relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients. *Circulation*. 1986; 73:900–912. [PubMed: 3698235]
- Lauer MS, Francis GS, Okin PS, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA*. 1999; 281:524–529. [PubMed: 10022108]
- Borer JS, Hochreiter C, Herrold EM, Supino P, Aschermann M, Wencker D, Devereux RB, Roman MJ, Szulc M, Kligfield P, Isom OW. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. *Circulation*. 1998; 97:525–534. [PubMed: 9494022]

10. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med*. 1999; 341:1351–1357.
11. Robergs RA, Landwehr R. The surprising history of the “HRmax=220-age” equation. *JEPonline*. 2002; 5:1–10.
12. Ganau A, Devereux RB, Atlas SA, Packer M, Roman MJ, Vargiu P, Cody RJ, Laragh JH. Plasma atrial natriuretic factor in essential hypertension: relation to cardiac size, function and systemic hemodynamics. *J Am Coll Cardiol*. 1989; 14:715–724. [PubMed: 2527901]
13. Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med*. 1977; 296:839–844. [PubMed: 846493]
14. Goldberg HL, Herrold E, Hochreiter C, Moses JW, Fisher J, Tamari I, Borer JS. Videodensitometric determination of right ventricular and left ventricular ejection fraction. *Am J Noninvasive Cardiol*. 1987; 1:18–23.
15. Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, Frye RL. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med*. 1996; 335:1417–1423. [PubMed: 8875918]
16. Enriquez-Sarano M, Tajik AJ, Schaff AV, Orszulak TA, Bailey KR, Frye RL. Echocardiographic prediction of survival after surgical correction of organic mitral regurgitation. *Circulation*. 1994; 90:830–837. [PubMed: 8044955]
17. Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL, Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation. Determinants and long-term outcome. *J Am Coll Cardiol*. 2002; 40:84–92. [PubMed: 12103260]
18. Zile MR, Gaasch WH, Carroll JD, Levine HJ. Chronic mitral regurgitation: predictive value of preoperative echocardiographic indexes of left ventricular function and wall stress. *J Am Coll Cardiol*. 1984; 3:235–242. [PubMed: 6693615]
19. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O’Gara PT, O’Rourke RA, Otto CM, Shah PM. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease). *Circulation*. 2006; 114:450–527. *J Am Coll Cardiol*. 2006; 48:598–675.
20. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005; 352:875–883. [PubMed: 15745978]
21. Pezzullo JC. 2005 Retrospective Power Calculations [Interactive Computer software]. Retrieved March 29, 2006 from <http://statpages.org/postpower.html>
22. Doyle JT, Kinch SH. The prognosis of an abnormal electrocardiographic stress test. *Circulation*. 1970; 41:545–553. [PubMed: 5415991]
23. Enriquez-Sarano M, Basrajian AJ, Rossi A, Bailey KR, Seward JB, Tajik AJ. Progression of mitral regurgitation. A prospective Doppler echocardiographic study. *J Am Coll Cardiol*. 1999; 34:1137–1144. [PubMed: 10520803]
24. Kim HJ, Park SW, Cho BR, Hong SH, Park PW, Hong KP. The role of cardiopulmonary exercise test in mitral and aortic regurgitation: it can predict post-operative results. *Korean J Intern Med*. 2003; 18:35–39. [PubMed: 12760266]
25. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart*. 2001; 86:381–386. [PubMed: 11559673]
26. Massie B, Botvinick EH, Shames D, Taradash M, Werner J, Schiller N. Myocardial perfusion scintigraphy in patients with mitral valve prolapse. Its advantage over stress electrocardiography in diagnosing associated coronary artery disease and its implications for the etiology of chest pain. *Circulation*. 1978; 57:19–26. [PubMed: 618388]
27. Greenspan M, Iskandrian AS, Mintz GS, Croll MN, Segal BL, Kimbiris D, Bemis CE. Exercise myocardial scintigraphy with ²⁰¹Thallium. Use in patients with mitral valve prolapse without associated coronary disease. *Chest*. 1980; 77:47–52. [PubMed: 7351146]

28. Malcolm AD, Boughner DR, Kostuk WJ, Ahuja SP. Clinical features and investigative findings in presence of mitral valve prolapse. Study of 85 consecutive patients. *British Heart Journal*. 1976; 38:244–256. [PubMed: 1259839]
29. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for healthcare professionals from the American Heart Association. *Circulation*. 1995; 91(2):580–615. [PubMed: 7805272]

Figure 1.

Relation of exercise duration at study entry to cardiac event free survival (primary endpoints) among the 38 patient subgroup (Group I patients). Events include sudden death, heart failure symptoms, atrial fibrillation, LVEF<60% at rest and/or LV dimensions at systole ≥45mm (initial event[s] during follow-up). The dotted line denotes patients who exercised ≥15 minutes, including stage 0, or the highest tercile of the distribution of exercise times). The solid line denotes patients who exercised <15 minutes, including stage 0 (or the lower 2 terciles of the distribution of exercise times). The p value is unadjusted.

Figure 2.

Relation of electrocardiographic ST segment depression (horizontal or downsloping) at study entry to cardiac event free survival (primary endpoints) among the 33/38 patients not receiving digoxin (Group I patients). Events are as in Figure 1. The dotted line denotes patients without exercise inducible ST segment depression. The solid line denotes patients with exercise-inducible ST segment depression. The p value is unadjusted.

Table 1

Clinical, Etiologic and Exercise Characteristics at Study Entry (n=46)

Variable			
Age (years, avg)	50±12	Exercise duration (minutes, avg)	13± 3 (7-18)
Men	26 (68%)	Bruce stage completed (avg)	3± 1 (1-4)
Etiology		Systolic blood pressure at peak exercise (mmHg, avg)	164±22 (120-215)
<i>Mitral Valve Prolapse</i>	32 (84%)	Diastolic blood pressure at peak exercise (mmHg, avg)	75±11 (50-100)
<i>Rheumatic</i>	3 (8%)	Heart rate at peak exercise (beats per minute, avg)	158±20 (96-194)
<i>Infective Endocarditis</i>	1 (3%)	Exercise inducible ST depression: all patients	10 (26%)
<i>Ruptured Chordae</i>	2 (5%)	patients off digoxin	7 (21%)
Treatment		Reason for stopping test	
<i>Digoxin</i>	4 (11%)	<i>General/leg fatigue</i>	19 (50%)
<i>Angiotensin Converting Enzyme Inhibitor</i>	1 (3%)	<i>Dyspnea</i>	5 (13%)
<i>Angiotensin Receptor Blocker</i>		<i>General/leg fatigue + dyspnea</i>	4 (11%)
<i>Beta Blocker</i>	2 (5%)	<i>Arrhythmia</i>	4 (11%)
<i>Beta Blocker + Digoxin</i>	1 (3%)	<i>Fall in systolic blood pressure</i>	1 (3%)
<i>Angiotensin Receptor Blocker + Beta Blocker</i>	1 (3%)	<i>Other/unknown</i>	5 (13%)

Table 2

Cardiac Event Risk* Among Subgroups

	N (%)	Avg Annual Risk† (%)	P‡	Hazard Ratio§(95% CI)
Exercise Duration: ≥ 15 minutes	13 (34)	4.6	.004	1.0[//]
< 15 minutes	25 (66)	23.5		4.3 (1.5-12.6)
Maximum Predicted Peak Heart Rate Achieved¶: ≥ 99%	13 (34)	5.8	.007	1.0[//]
< 99%	25 (66)	22.3		3.6 (1.3-9.5)
Chronotropic Index#: ≥ .98	13 (34)	5.4	.01	1.0[//]
< .98	25 (66)	24.1		3.4 (1.3-9.1)
Heart Rate Recovery**: ≥ 29 beats per minute	11 (33)	5.8	<.02	1.0[//]
< 29 beats per minute	22 (67)	20.7		3.3 (1.1-10.0)
0 ST segment depression with exercise at entry††	26 (79)	11.7	NS	1.0[//]
+ ST segment depression with exercise at entry††	7 (21)	15.4		1.2 (0.4-3.3)
0 ST segment depression with exercise at or after entry‡‡	19 (63)	11.5	NS	1.0[//]
+ ST segment depression with exercise at or after entry‡‡	11 (37)	12.0		1.0 (0.4-2.5)
+ ST segment depression with exercise after entry only‡‡	4 (13)	8.7		0.9 (0.5-1.7)

* Events=sudden death, heart failure symptoms, atrial fibrillation, left ventricular ejection fraction<60% at rest and/or dimension at systole >45mm

† from Kaplan-Meier estimates

‡ from log rank test

§ from Cox model

[//] referent

¶ (heart rate at peak exercise)/(220-age) × 100

(heart rate at peak exercise-rest)/(220-age)-heart rate at rest (evaluable in 33 patients)

** heart rate at peak exercise-rest @ 1' post exercise

†† among 33 patients off digoxin (entry)

‡‡ among 30 patients off digoxin (entry, follow-up evaluations)

Table 3Independent Value of Exercise Duration vs. Heart Rate Variables for Prediction of Cardiac Event Risk^{*}

Multivariate Model	Covariates	Hazard Ratio (95% Confidence Interval) [†]	P [‡]
1	Exercise Duration	4.3 (1.5-12.6)	.008
	% Predicted Peak Heart Rate Achieved	—	NS
2	Exercise Duration	4.3 (1.5-12.6)	.008
	Chronotropic Index	—	NS
3	Exercise Duration	3.9 (1.3-11.7)	<.02
	Heart Rate Recovery	—	NS
4	Exercise Duration	3.9 (1.3-11.7)	<.02
	% Predicted Peak Heart Rate Achieved	—	NS
	Chronotropic Index	—	NS
	Heart Rate Recovery	—	NS

* Events as in Table 2

[†] hazard ratio adjusted for other covariates in model; not computed for variables that are not significant in multivariate model

[‡] p value from final step of Cox regression model

Table IV
Geometric and Functional Correlates of Exercise Duration and Exercise-Inducible ST Depression at Study Entry

Variables *	Exercise Duration (minutes)		Exercise Induced ST Depression †	
	<15 (n=25)	15 (n=13)	Yes (n=7)	No (n=26)
Right ventricular ejection fraction: at rest (%)	42±4 (35-50)	41±4 (36-51)	44±4(38-49)	42±5 (35-51)
Right ventricular ejection fraction: at peak exercise(%)	42±7(30-53)	46±8 (36-67)	44±7 (35-52)	43±8 (30-67)
Right ventricular ejection fraction: change rest→peak exercise (%)	0±6 (-9-11)	4±5(-2-11)‡	0±5 (-7-+7)	1±6 (-9-+16)
Left ventricular ejection fraction: at rest (%)	75±8 (60-85)	74±7(62-82)	73±7 (60-81)	74±8 (60-85)
Left ventricular ejection fraction: change rest→peak exercise (%)	2±5 (0-24)	7±6 (-5-14)‡	3±4(-4-6)	4±6(5-24)
Left ventricular dimension at systole (mm)	38±5(25-44)	39±4(32-44)	38±3 (34-43)	39±5 (25-46)
Left ventricular dimension at diastole (mm)	64±8 (50-83)	64±5 (54-73)	63±6 (55-72)	64±8 (50-83)
Left atrial dimension (mm)	47±7 (31-60)	44±6 (37-55)	45±9 (33-58)	46±7 (31-60)
Fractional shortening (%)	39±5 (31-52)	40±4(34-48)	39±6 (32-48)	39±5 (31-52)
Left ventricular mass (g/m ²)§	144±37 (92-241)	132±20 (102-169)	135±20 (97-154)	145±35 (92-241)

* data expressed as mean±standard deviation

† among 33 patients not receiving digoxin

‡ p<.05 vs. exercise duration <15 minutes (other comparisons not significant)

§ indexed to body surface area