

**TODD D. MILLER, MD***

Professor of Medicine, Co-Director, Nuclear Cardiology Laboratory, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN

The exercise treadmill test: Estimating cardiovascular prognosis

ABSTRACT

Abnormal hemodynamic responses to exercise treadmill testing may indicate an increased risk of coronary events and death, even if evidence of ischemia is absent. Exercise duration and the blood pressure, heart rate, and heart rhythm responses to exercise have prognostic significance.

KEY POINTS

Of the prognostic factors, exercise duration is the one most strongly associated with risk of coronary events and death, independent of age, sex, or known presence and severity of coronary artery disease.

A decrease in blood pressure with exercise can reflect severe coronary artery disease or left ventricular systolic dysfunction.

A heart rate that does not increase adequately during exercise or does not recover rapidly after exercise is associated with an increased risk of death.

Exercise training may help to improve the prognosis of patients with an abnormal hemodynamic response to exercise caused by poor general health.

TWO 55-YEAR-OLD MEN without a history of coronary artery disease both undergo an exercise treadmill test to evaluate atypical angina. Both men have normal results on electrocardiography (ECG) at rest. The results of their exercise treadmill tests are shown in **TABLE 1**. Which one of the following statements is correct?

- Patient B is more likely than patient A to develop coronary artery disease.
- Patient B has a worse cardiovascular prognosis than patient A.
- Patient A's exercise ECG results are falsely positive, whereas patient B's results are truly positive.
- On the basis of their blood pressures during exercise, patient A has a higher risk of stroke than patient B.

EXERCISE TESTING FOR DIAGNOSIS AND PROGNOSIS

When we perform a stress test such as the treadmill test, we are asking two questions: does the patient have coronary artery disease (ie, what is the patient's diagnosis) and is he or she likely to die or suffer a coronary event soon (ie, what is the patient's prognosis).^{1,2}

A stress test used diagnostically is considered to have a positive result if the patient develops signs and symptoms of ischemia during stress, ie, ST-segment depression and angina.¹ The diagnostic accuracy of exercise testing is commonly assessed separately from its prognostic accuracy. Unfortunately, diagnostic accuracy can be assessed only in the minority of patients who subsequently undergo

*Dr. Miller has disclosed that he has financial relationships with the Bristol Myers Squibb, KAI Pharmaceuticals, King Pharmaceuticals, Radiant Medical, TargeGen, and TherOx corporations.

coronary angiography—the gold standard for comparison.

In contrast, the prognostic accuracy of a stress test can be assessed in a much larger group of patients, using clinical outcomes as the comparison standard; only those who undergo early revascularization and those who are lost to follow-up are excluded from this group.

Although the stress-induced markers of ischemia used in diagnosis—ST-segment depression and angina—have prognostic value as well, other variables are more powerful predictors of outcome. In this article I will discuss those other prognostic variables and how to interpret them.

PROGNOSTIC VARIABLES

Variables measured during exercise treadmill testing that predict outcome are actually indicators of general fitness and function of the autonomic nervous system:

- Exercise duration
- Exercise hypotension
- Exercise hypertension
- Chronotropic incompetence
- Heart rate recovery
- Ventricular ectopy.

Exercise duration

In the Bruce protocol used in exercise stress testing, the test begins with the treadmill set to a low speed (1.7 miles per hour) and a 10% incline, and every 3 minutes the speed and angle of incline are increased. Other protocols are similar. The test continues for a maximum of 27 minutes (usually attainable only by well-trained individuals) or until the patient quits or develops signs or symptoms of ischemia or an arrhythmia. Average time for a middle-aged adult is 8 to 10 minutes.

Because the longer the patient goes, the harder he or she must work, exercise duration—the number of minutes the patient can continue in the protocol—is a good measure of his or her functional capacity. Another way to measure functional capacity is to measure oxygen uptake during exercise, which can be converted to metabolic equivalents (METs): 1 MET = 3.5 mL O₂/kg/min. However, most laboratories estimate functional capacity from exercise duration in a specific exercise proto-

TABLE 1

Two men, two treadmill tests

VARIABLE	PATIENT A	PATIENT B
Duration (minutes, Bruce protocol)	12	4
Chest pain during exercise	No	No
Limiting symptom	Fatigue	Dyspnea
Resting blood pressure (mm Hg)	130/80	130/80
Peak exercise blood pressure (mm Hg)	210/70	120/60
Resting heart rate (beats/minute)	70	70
Peak exercise heart rate (beats/minute)	150	150
Heart rate 1 minute recovery (beats/minute)	128	142
Exercise ST-segment depression (mm)	1.5	1.5

col (eg, the Bruce protocol) based on published nomograms.

Remarkably, the longer the patient can keep going on the treadmill, the less likely he or she is to die soon of coronary artery disease—or of *any* cause. In fact, of the prognostic variables measured during exercise treadmill testing, exercise duration is the strongest.^{1,2} Its prognostic value has been demonstrated in healthy subjects being screened for coronary artery disease (FIGURE 1)^{3–6} and in patients being evaluated for suspected or known coronary artery disease (FIGURE 2).^{7–10} The independent prognostic value of exercise duration has been demonstrated in men,^{3,4,7,8} women,^{4–7,9} and the elderly.¹¹ Although functional capacity decreases with age and generally is lower in women than men, exercise duration retains its prognostic value after adjusting for age and sex.

Exercise duration has also been shown to provide risk stratification in subsets of patients with coronary artery disease defined anatomically. The Coronary Artery Surgery Study (CASS), which analyzed 30 variables in 4,083 patients with symptomatic coronary artery disease, found that survival at 4 years was 100% in patients with three-vessel coronary disease and preserved left ventricular function who had good exercise capacity, ie, who were able to keep walking to level 5, which is 12 minutes or more.¹²

Exercise duration is such a good prognostic indicator that it is included in risk scores for exercise treadmill testing.^{13,14}

Exercise duration is the strongest prognostic variable

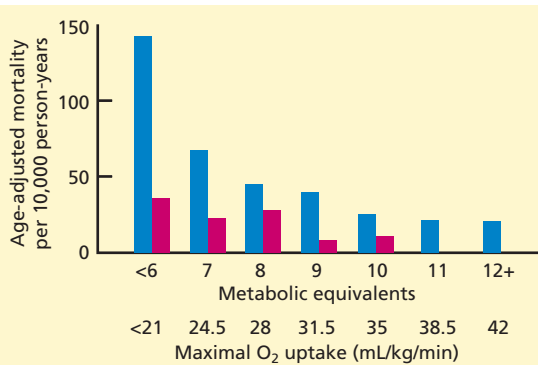


FIGURE 1. Age-adjusted, all-cause mortality rates per 10,000 person-years of follow-up by physical fitness categories in 3,120 women and 10,224 men in the Aerobics Center Longitudinal Study.

BLAIR SN, KOHL HW 3RD, PAFFENBARGER RS JR, CLARK DG, COOPER KH, GIBBONS LW. PHYSICAL FITNESS AND ALL-CAUSE MORTALITY. A PROSPECTIVE STUDY OF HEALTHY MEN AND WOMEN. JAMA 1989; 262:2395-2401. COPYRIGHT © 1989, AMERICAN MEDICAL ASSOCIATION. ALL RIGHTS RESERVED.

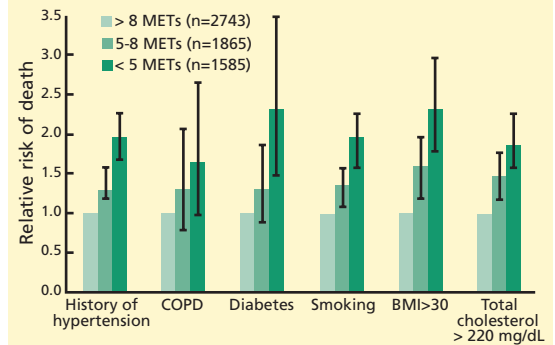


FIGURE 2. Relative risks of death from any cause among subjects with various risk factors who achieved an exercise capacity of less than 5 metabolic equivalents (METs) or 5 to 8 METs, as compared with subjects whose exercise capacity was more than 8 METs. Error bars are 95% confidence intervals for the relative risks.

BMI = body mass index; COPD = chronic obstructive pulmonary disease.

MYERS J, PRAKASH M, FROELICHER V, DO D, PARTINGTON S, ATWOOD JE. EXERCISE CAPACITY AND MORTALITY AMONG MEN REFERRED FOR EXERCISE TESTING. N ENGL J MED 2002; 346:793-801. COPYRIGHT © 2002, MASSACHUSETTS MEDICAL SOCIETY. ALL RIGHTS RESERVED.

Blood pressure during and after exercise

During exercise testing, blood pressure is usually measured by cuff sphygmomanometry. However, motion during exercise and background noise from the treadmill machine can reduce the accuracy of this measurement.

Several studies have compared blood pressures measured by cuff sphygmomanometry vs intra-arterial measurements,¹⁵ and most have found that systolic pressures are lower as measured by cuff sphygmomanometry, with smaller differences between methods at higher exercise intensity. The diastolic pressure is significantly lower as measured by cuff sphygmomanometry than by intra-arterial measurements at rest and during exercise; error increases with exercise intensity.

Hypotensive and hypertensive blood pressure responses to exercise have been defined in various ways.

Exercise hypotension is best defined as systolic blood pressure that is lower during exercise than while standing at rest before exercise.¹⁶ It reflects a failure of cardiac output to increase during exercise and is associated with severe coronary artery disease (eg, left main coronary artery or three-vessel involvement), left ventricular systolic dysfunction, or both.^{17,18}

Dubach et al,¹⁶ in a study of 2,036 patients who underwent exercise treadmill

testing to evaluate chronic coronary artery disease, found that exercise hypotension was associated with a threefold higher risk of cardiac events over 2 years.

In a large meta-analysis of exercise testing following myocardial infarction, the only independent predictors of risk were limited exercise workload and exercise hypotension.¹⁹

Exercise hypertension is defined as a rise in systolic blood pressure during exercise above a threshold, usually between 190 and 220 mm Hg.²⁰ Some studies suggest that exercise hypertension predicts future arterial hypertension in people with normal resting blood pressure.^{21,22}

Whether exercise hypertension predicts future cardiovascular events has not been extensively investigated. A Mayo Clinic study reported that exercise hypertension was significantly associated ($P = .03$) with cardiovascular events in people without symptoms or clinically evident cardiovascular disease during a mean follow-up of 7.7 years.²³ On the other hand, a study from Cleveland Clinic showed that patients being evaluated for coronary artery disease who had a hypertensive response to exercise had a lower prevalence of

Exercise hypotension is associated with severe coronary disease and left ventricular dysfunction

severe angiographic coronary disease ($P = .004$) and a lower risk of death over the next 2 years ($P = .03$) compared with the rest of the study population.²⁴

An abnormal systolic blood pressure recovery ratio, defined as an increase (rather than the expected decrease) in systolic blood pressure in the early postexercise recovery period has been shown to be a marker of underlying coronary artery disease,²⁵ but has not consistently been associated with an adverse prognosis.²⁶

Chronotropic incompetence

The heart rate normally increases with exercise and decreases as soon as exercise stops. Failure of the heart rate to increase as expected during exercise is termed chronotropic incompetence. Chronotropic incompetence predicts all-cause and cardiovascular death.^{27–30}

Different criteria for defining chronotropic incompetence were used in different studies, based on resting heart rate, exercise protocol, patient age, and medications (especially beta-blockers).

The predicted chronotropic response can be calculated by a suggested formula³¹: (peak heart rate minus resting heart rate) ÷ (220 minus age minus resting heart rate). The difference between peak heart rate and resting heart rate is known as the heart rate reserve.

Chronotropic incompetence is defined as less than 80% of the predicted value and as less than 62% for patients taking beta-blockers.^{31,32}

Heart rate recovery

When exercise stops, the heart rate returns to the pre-exercise rate over several minutes to hours, with the most marked reduction in the first few minutes. Impaired heart rate recovery (failure of the heart rate to decrease normally) predicts all-cause mortality and cardiovascular events, including sudden death, in healthy populations and in patients with coronary artery disease (FIGURE 3).^{5,30,33–36}

Several variables influence heart rate recovery, including activity (eg, complete cessation of exercise or cool-down) and position (supine, sitting, standing). Suggested thresholds for abnormal responses are³¹:

- Upright: the heart rate should slow down by at least 12 beats/minute at 1 minute

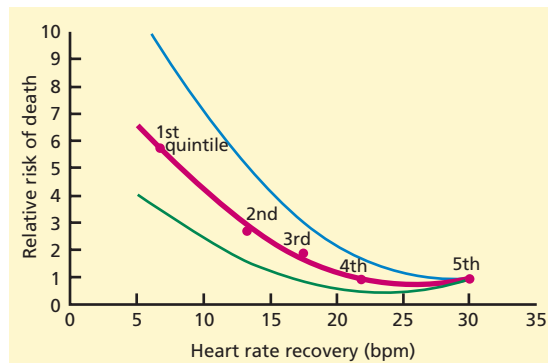


FIGURE 3. Estimates of the relative risk of death within 6 years according to heart rate recovery 1 minute after cessation of exercise. Circles represent the relative risk of death for each of the quintiles as compared with the quintile with the greatest reduction (5th). Blue and red lines represent the 95% confidence intervals.

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. COPYRIGHT © 1999, MASSACHUSETTS MEDICAL SOCIETY. ALL RIGHTS RESERVED.

- Supine: at least 18 beats/minute at 1 minute
- Sitting: at least 22 beats/minute at 2 minutes.

Heart rate variability

Heart rate variability, ie, differences in the beat-to-beat interval among successive heart cycles, can be quantified by spectral analysis, although this is not routinely available clinically. Dewey et al³⁷ measured heart rate variability during the first and last 2 minutes of exercise and during the first 2 minutes of recovery in 1,335 subjects (95% men, mean age 58 years). Markers of impaired heart rate variability measured during exercise and in recovery were independent predictors of all-cause and cardiovascular death during a mean follow-up of 5 years.

Ventricular ectopy

Uncommon types of ventricular arrhythmias can occur during exercise testing:

- Sustained ventricular tachycardia or ventricular fibrillation due to coronary artery disease or left ventricular dysfunction

Failure of the heart rate to increase as expected during exercise or decrease after stopping predicts risk of death

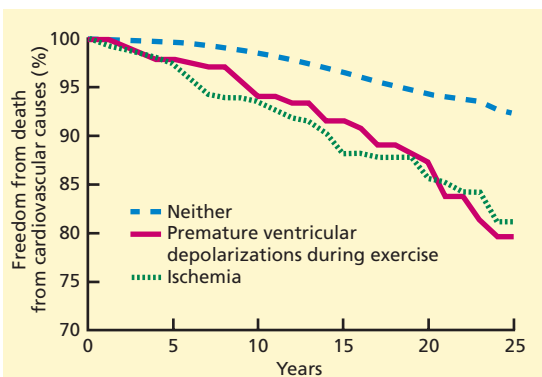


FIGURE 4. Percentage without death from cardiovascular causes among subjects with an exercise test that was positive for ischemia, subjects with frequent premature ventricular depolarizations during exercise, and subjects with neither a positive exercise test nor frequent premature ventricular depolarizations. The data were analyzed by Cox proportional hazards methods. Cox estimates were adjusted for age, tobacco use, diabetic status, body mass index, level of physical activity, systolic blood pressure, heart rate at rest, total cholesterol level, presence or absence of premature ventricular depolarizations before exercise, and presence or absence of premature ventricular depolarizations during recovery from exercise. Data were censored if subjects died of other causes.

JOUVEN X, ZUREIK M, DESNOS M, COURBON D, DUCIMETIERE P. LONG-TERM OUTCOME IN ASYMPTOMATIC MEN WITH EXERCISE-INDUCED PREMATURE VENTRICULAR DEPOLARIZATIONS. *N ENGL J MED* 2000; 343:826-833. COPYRIGHT © 2000, MASSACHUSETTS MEDICAL SOCIETY. ALL RIGHTS RESERVED.

Risk of death can be reduced by exercise training

- occurs rarely but is life-threatening.
- Ventricular tachycardia in healthy young adults without structural heart disease may arise from the right ventricular outflow tract. It is benign.³⁸
- Arrhythmogenic right ventricular dysplasia, a cardiomyopathy involving the right ventricle, can also occur in healthy young adults and has a poor prognosis. It must be distinguished from the benign form.

Short ventricular ectopies: Significance uncertain

Single ventricular premature contractions, couplets, or short episodes of nonsustained ventricular tachycardia occur during or soon

after exercise treadmill testing more commonly than the sustained ventricular arrhythmias mentioned above. The prognostic significance of these ectopies is controversial. A recent review found that ventricular ectopy during exercise testing or recovery was associated with an increased death rate in 13 out of 22 studies.³⁹ Fifteen of these studies included patient populations with symptomatic or known coronary artery disease; the other 7 studies were in healthy people without symptoms (eg, being screened for employment).

Jouven et al⁴⁰ found that among 6,101 asymptomatic male French civil servants without clinically evident cardiovascular disease who underwent exercise testing, 2.3% had frequent premature ventricular contractions (defined as > 10% of all ventricular beats) and 4.4% had ECG changes during exercise that indicated ischemia. Having frequent premature ventricular contractions was associated with a higher risk (RR = 2.67) of cardiovascular death over 23 years of follow-up, independent of ischemia (FIGURE 4).

Frolkis et al⁴¹ evaluated 29,244 patients referred to Cleveland Clinic for exercise treadmill testing and found a low prevalence of frequent ventricular ectopy (3% during exercise, 2% after exercise, and 2% both during and after exercise). The 5-year mortality rate was higher in patients with frequent ventricular ectopy during exercise vs those without (9% vs 5%, $P < .001$) and was even higher in those with frequent ventricular ectopy in recovery vs those without (11% vs 5%, $P < .001$). After adjusting for confounding variables, only frequent ventricular ectopy in recovery, but not during exercise, was associated with an increased death rate (adjusted hazard ratio 1.5; 95% CI 1.1–1.9; $P = .003$).

The associations between exercise-induced ventricular ectopy and ischemia and left ventricular function are unclear.

■ CASE STUDIES REVISITED

As for the two men described at the beginning of this article, patient B has a worse cardiovascular prognosis than patient A.

Both men have the same pretest probability of coronary artery disease (about 50%),

based on identical age, sex, and chest pain characteristics. The ST-segment response during exercise—the traditional marker of ischemia used to diagnose coronary disease—is also the same for each patient.

However, hemodynamic variables are markedly different between the two patients: patient B has several adverse prognostic indicators, including lower functional capacity, a hypotensive blood pressure response, and abnormal heart rate recovery.

The most widely used treadmill risk score, the Duke treadmill score,¹³ can be calculated as:

Exercise time (in minutes, Bruce protocol) minus 5 times the magnitude of ST-segment depression (in millimeters) minus 4 times the treadmill angina index (ie, 0 = no angina, 1 = nonlimiting angina, 2 = angina that is the reason for terminating exercise).

Applying this formula yields a Duke score of 4.5 (estimated annual cardiovascular mortality risk 0.25%) for patient A and a score of -3.5 (estimated annual cardiovascular mortality risk 2%) for patient B.

Because patient A exercised to a high workload, he is more likely to have a false-positive exercise ECG result than patient B. But whether an exercise ECG test is falsely positive or falsely negative can only be determined after coronary angiography.

Exercise hypotension, as seen in patient B, can indicate left ventricular systolic dysfunction with exercise but has not been shown to predict stroke risk.

■ MANAGEMENT CONSIDERATIONS

How to manage patients with an abnormal hemodynamic response in the absence of ischemia is uncertain. Given the excellent prognosis of patients with well-preserved exercise capacity, it is unlikely that revascularization procedures in these patients would improve outcome.

On the other hand, patients with an abnormal hemodynamic response due to poor general health or autonomic nervous system dysfunction may be able to achieve a better prognosis with interventions that improve some of the abnormal responses. Increased functional capacity through exercise training is associated with a lower mortality rate,⁴² and coronary artery bypass surgery can abolish exercise-induced hypotension.⁴³

Strategies to further evaluate and treat patients with an isolated finding of chronotropic incompetence, abnormal heart rate recovery, or frequent exercise-induced ventricular ectopy are not clear and require future study. ■

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ADDRESS: Todd D. Miller, MD, Mayo Clinic, Gonda 5, 200 First Street SW, Rochester, MN 55905; e-mail miller.todd@mayo.edu.

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