Clinical Utility of the Exercise ECG in Patients With Diabetes and Chest Pain*

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Objective: **The purpose of this study was to determine the characteristics of exercise treadmill testing in diabetic patients presenting with chest pain.**

Background: **The diagnosis of coronary artery disease (CAD) in diabetic patients is confounded by different manifestations of coronary disease than are seen in the general population. Because of the association of diabetes with accelerated CAD, it is critical to assess the diagnostic utility of the standard exercise test in diabetic patients with chest pain.**

Methods: **This study was a retrospective analysis of standard exercise test results in 1,282 male patients without prior myocardial infarction who had undergone coronary angiography and were being evaluated for possible CAD at two Veterans' Administration institutions.**

Results: **In patients with diabetes, 38% had an abnormal exercise test result, and the prevalence of angiographic CAD was 69%; the sensitivity of the exercise test was 47% (95% confidence interval [CI], 41 to 58), and specificity was 81% (95% CI, 68 to 89). In patients without diabetes, 38% had an abnormal exercise test result, and the prevalence of angiographic CAD was 58%; the sensitivity of the exercise test was 52% (95% CI, 48 to 56), and specificity was 80% (95% CI, 76 to 83). The receiver operating characteristic curves were also similar in both diabetic and nondiabetic patients (0.67 and 0.68, respectively).**

Conclusion: **These data demonstrate that the standard exercise test has similar diagnostic characteristics in diabetic as in nondiabetic patients.** ***(CHEST 2001; 119:1576–1581)***

Key words: coronary artery disease; diabetes mellitus; exercise test

Abbreviations: ACIP = Asymptomatic Cardiac Ischemic Pilot; AUC = area under the curve; CAD = coronary artery disease; CI = confidence interval; MET = metabolic equivalent; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic

Cardiovascular disease overwhelmingly remains the most common cause of death in patients with diabetes mellitus.[1–3] Previous studies[4,5] have demonstrated the role of coronary artery disease (CAD) in diabetic patients and highlighted the greater severity and rate of disease progression in this group of patients. The clinical manifestations of CAD may also be different in patients with diabetes.[6,7] While the prevalence of coronary disease has declined in the United States, the decline in cardiovascular mortality in diabetic patients has not kept pace with this progress in preventive medicine.[8]

In patients with an intermediate risk of having CAD, the exercise ECG test is recommended as the first test for diagnosis because of its important yield of information and reasonable test characteristics.[9] While this is assumed to apply to diabetic patients as well, no large-scale study has closely examined the role of the exercise treadmill test in the diagnosis of CAD in diabetic patients who present with chest pain. This study attempts to demonstrate the utility of the exercise treadmill test in diabetic patients and compares the results of the tests to patients without diabetes.

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Materials and Methods

Patients

Approximately 8,000 consecutive male patients underwent exercise treadmill testing at two Veterans' Affairs Medical Centers between 1987 and 1998. Patients with previous cardiac surgery, valvular heart disease, left bundle-branch block, or Wolff-Parkinson-White syndrome on their resting ECG were excluded from the study. Prior cardiac surgery was the predominant reason for exclusion of patients who underwent exercise treadmill testing during this time period. We then selected all patients referred to evaluate chest pain possibly due to coronary disease with complete data and who undergone coronary angiography within 4 months of the exercise treadmill test. As is the case for clinical observational studies like this, there was no attempt to remove workup bias. In order to avoid falsely increasing the accuracy of the exercise treadmill test, patients with a previous myocardial infarction by history or by diagnostic Q-wave were excluded, leaving a target population of 1,282 patients.

A thorough clinical history, medications, and diabetic status were recorded prospectively at the time of exercise treadmill testing using computerized forms.[10,11] Diabetics were defined as patients who reported a history of diabetes and/or were receiving oral or parenteral medications for the treatment of diabetes.

Exercise Testing

Patients underwent treadmill testing using the US Air Force School of Aerospace Medicine (San Antonio, TX) protocol[12] or an individualized ramp treadmill protocol.[13] Before ramp testing, the patients were administered a questionnaire consisting of a list of activities presented in an increasing order according to metabolic equivalent (MET). This questionnaire estimated the patient's exercise capacity before the test and thus allowed most patients to reach maximal exercise at approximately 10 min.[14] Visual ST-segment deviation was measured at the J-junction and corrected for preexercise ST-segment depression while standing; ST-segment slope was measured over the following 60 ms and was classified as upsloping, horizontal, or downsloping. Slope was coded as 1 for horizontal, 2 for downsloping, and 0 for normal slope (upsloping or ST-segment depression of < 0.5 mm). The ST-segment response considered was the most horizontal or downsloping ST-segment depression in any lead except aVR during exercise or recovery. An abnormal response was defined as ≥ 1 mm of horizontal or downsloping ST-segment depression.

No test was classified as indeterminate,[15] medications were not withheld, and no maximal heart rate targets were applied.[16] The exercise tests were performed, analyzed, and reported per standard protocol and utilizing a computerized database (EXTRA; Mosby Publishers; Chicago, IL).[17] Decisions for cardiac catheterization were consistent with clinical practice. Analyses were performed with the investigators blinded to clinical and angiographic results.

Coronary Angiography

Coronary artery narrowing was visually estimated and expressed as percentage of lumen diameter stenosis. Patients with a 50% narrowing in one or more of the following were considered to have significant angiographic CAD: the left anterior descending, left circumflex, right coronary arteries or their major branches, or a 50% narrowing in the left main coronary artery. The 50% criterion was chosen to be consistent with the cooperative trialists' choice.[18]

Statistical Analysis

Statistical analysis was performed with a computer software program (SPSS 8.0; SPSS, Chicago, IL). Patients were classified into two groups, diabetics and nondiabetics, and compared using a two-tailed Fisher's Exact Test. Sensitivity, specificity, and area under the curves (AUCs) of receiver operating characteristic (ROC) plots were calculated for exercise testing in patients with and without diabetes. A statistically significant result was defined as a $p < 0.05$. All means were reported with $\pm$ SD. All analysis was performed blinded to the exercise treadmill and angiographic results.

Results

A total of 1,282 patients were included in this study (Table 1). Of these, 190 patients (15%) had diabetes and 1,092 patients did not have diabetes. Of the diabetics, 73 patients (38%) had a positive treadmill test result and 131 patients (69%) underwent CAD by angiography yielding, a sensitivity of 47% (95% confidence interval [CI], 41 to 58%) and a specificity of 81% (95% CI, 68 to 89%). The positive predictive value (PPV) was 85%, and the negative predictive value (NPV) was 41%. Of the nondiabetics, 418 patients (38%) had a positive exercise test results and 628 patients (58%) had angiographic CAD. For this group, the sensitivity was 52% (95% CI, 48 to 56%) and the specificity was 80% (95% CI, 76 to 83%). The PPV and NPV were 78% and 55%, respectively. Predictive accuracy was 66% in both groups.

There was no significant difference in peak systolic BP (Table 2) between diabetic and nondiabetic patients. The body mass index was significantly greater in patients with diabetes ($p = 0.001$), as were the age ($p = 0.002$) and number of diseased vessels ($p = 0.02$). Diabetic patients also had significantly lower METs ($p < 0.001$) and peak heart rate

Table 1—*Test Characteristics in Diabetic and Nondiabetic Patients**

Characteristics	Exercise-Induced ST-Segment Depression	With CAD†	Sensitivity	Specificity	PPV	NPV
With diabetes (n = 190)	73 (38)	131 (69)	47 (41–58)	81 (68–89)	85	41
Without diabetes (n = 1,092)	418 (38)	628 (58)	52 (48–56)	80 (76–83)	78	55

*Data are presented as No. (%) or as percentage (95% CI) unless otherwise indicated.
†Confirmed by angiography.

Table 2—*Comparison of Diabetic and Nondiabetic Patients**

Variables	Diabetic	Nondiabetic	p Value
Age, yr	59.4 ± 9.4	58.1 ± 10.1	0.002
Body mass index, kg/m^2	29.5 ± 4.5	27.7 ± 4.8	0.001
METs	6.8 ± 2.5	7.2 ± 3.1	0.001
Peak heart rate, beats/min	126 ± 22.9	130.9 ± 23.6	0.001
Peak systolic BP, mm Hg	170.1 ± 30.7	167.9 ± 29.1	NS
NVD	1.69 ± 0.02	1.38 ± 0.02	0.02

*Data are presented as mean ± SD. NVD = mean number of vessels with angiographic CAD per patient; NS = not significant.

(p = 0.001). In these symptomatic patients who had a positive exercise test result and evidence of CAD by angiography, silent ischemia during the treadmill test was seen in 37% of diabetic and 40% of nondiabetic patients.

ROC curves were generated in order to compare the predictive accuracy of exercise testing in both groups (Fig 1). There was no significant difference between diabetic and nondiabetic patients in the AUC (0.67 ± 0.04 and 0.68 ± 0.02, respectively).

Discussion

Previous work has suggested that exercise testing in patients suspected of harboring CAD is highly useful in confirming clinical suspicion and predicting prognosis. Patients in one high-risk subgroup, diabetic patients, have a more aggressive form of CAD and may benefit from earlier clinical detection of CAD because they may exhibit different clinical manifestations of CAD.

In patients with diabetes, the large majority of studies have focused on asymptomatic or silent ischemia. Few studies have been published looking at the utility of exercise testing in diabetics suspected of having CAD.

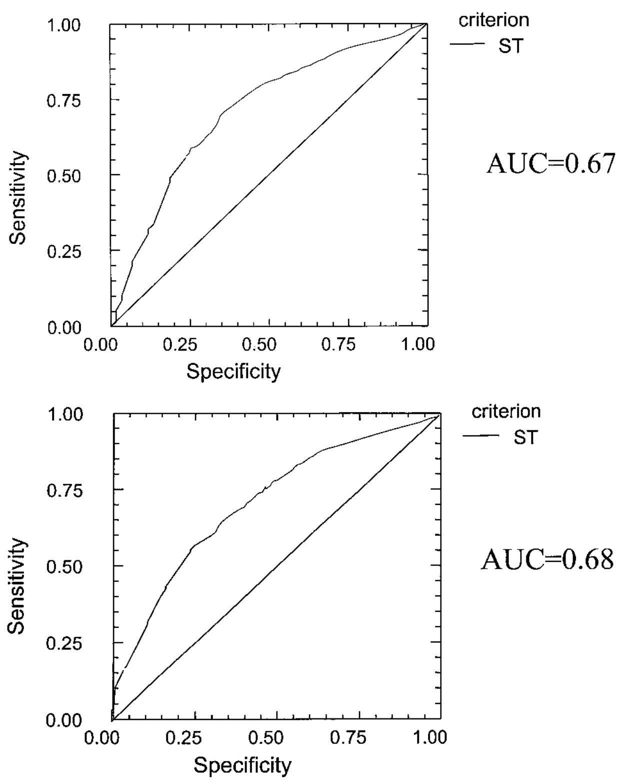

Figure 1. ROC curves in patients with (top) and without (bottom) diabetes. The AUC is similar between the two groups, suggesting comparable predictive accuracy of the exercise test.

Studies Screening Diabetic Patients for Coronary Disease

Thallium imaging and exercise ECG were performed on 136 diabetic patients without symptoms of heart disease.[19] Thirty-three patients had thallium defects, and 19 patients had abnormal ST-segment depression during exercise ECG. Results of both tests were positive in 13 patients. Coronary angiography was subsequently performed on 33 patients with either scintigraphic and/or ECG evidence of myocardial ischemia. Angiographically significant CAD was detected in 13 patients. Six patients refused cardiac catheterization. In 14 of 27 patients with perfusion defects, coronary angiography did not show any coronary artery stenoses (positive predictive accuracy, 48%). Exercise ECG showed only one false-positive ¦sesult but failed to detect coronary artery disease in three patients with abnormal scan findings. The accuracy of an abnormal exercise ECG result was better than that of nuclear perfusion scanning for detecting asymptomatic CAD in diabetic patients. Nuclear perfusion scanning had a high false-positive rate in diabetic patients.

Gerson et al[20] reported the only appropriate screening study of diabetics that we could find. To identify predictors of asymptomatic CAD, they performed noninvasive screening of 110 insulin-requiring diabetic patients with a normal resting ECG result. At entry, their mean age was 35 years and mean duration of insulin use was 19 years. Screening included history and physical examination, exercise ECG, M-mode echocardiography, and chemical laboratory testing. Approximately one fourth had abnormal ST-segment depression or an inadequate heart-rate response, but a separation of these responses is not provided. None had angina. During 8 years of follow-up, 14 patients developed clinical evidence of CAD consisting of acute myocardial infarction, sudden cardiac death, or anginal chest pain confirmed by angiography. Only three of these patients had ST-segment depression during the exercise test. Baseline variables that were univariately predictive of subsequent clinical coronary disease included age, maximal heart rate, and retinal neovascularization. According to multivariate analysis, the treadmill heart rate was the single most important predictor of subsequent development of clinical coronary disease. A treadmill ECG result that was either abnormal or inconclusive because of failure to achieve 90% of predicted maximal heart rate identified each patient in whom clinical CAD developed within 4 years after entry testing, but was only 43% sensitive at 8 years with a specificity of 77%. Thus, the entry treadmill ECG provided prognostic information not available from the history and physical examination results, but little further prognostic information was provided after the first 4 years of follow-up, suggesting the need for serial testing. More studies of similar design are needed. Unfortunately, the investigators mixed the criteria for an abnormal test result (both heart rate and ST criteria were applied) together, such that test characteristics could not be determined. It is apparent though that exercise-induced ST-segment depression had a low sensitivity (21%), with only 3 of 14 patients with end points identified.

Paillole and colleagues[21] studied 59 French diabetic men with suspected CAD who underwent ambulatory ECG monitoring, bicycle exercise testing, thallium scintigraphy, and coronary angiography. They found that the sensitivity and sensitivity of exercise testing compared favorably with the other two noninvasive tests. This would be consistent with our data, which suggest that the diagnostic utility of the exercise treadmill test is essentially equivalent in patients with and without diabetes who initially present with chest pain. The test characteristics of the exercise treadmill test were similar in both groups with good sensitivity and sensitivity, comparable to previously published data.[22] Further work is needed to confirm our findings and to determine if they are applicable outside our study population.

The prevalence of silent ischemia has been examined in many studies, and controversy exists as to whether asymptomatic ischemia is more common in diabetic patients.[23] Interestingly, our data suggest that the prevalence of silent ischemia in this population is similar between diabetic and nondiabetic patients, supporting evidence from previous studies.[24,25] For instance, in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, the investigators found that of the 558 patients studied, the 77 diabetics did not have a higher prevalence of asymptomatic ischemia as determined by ambulatory ECG monitoring and exercise testing. With respect to exercise testing, their results were very similar: 36% of diabetic patients and 39% of nondiabetic patients exhibited silent ischemia. This contrasts with results from earlier trials[26,27] that suggested a significant difference in asymptomatic ischemia between the two groups. It should be noted that different patient populations and evaluation techniques for asymptomatic ischemia may be in part responsible for the discrepancy.

The American Diabetes Association position statement on diabetes and exercise was published in 1998 and stated the place of the standard exercise test in evaluating diabetic patients about to embark on a moderate-to-high-intensity exercise program.[28] An exercise test was given a IIb indication as “may be” helpful in high-risk individuals. High risk for underlying cardiovascular disease in diabetic patients without symptoms of cardiac disease was empirically associated with one of the following criteria: age > 35 years; type 2 diabetes of > 10 years’ duration; type 1 diabetes of > 15 years’ duration; presence of any additional risk factor for CAD; presence of microvascular disease (retinopathy, nephropathy, proteinuria); peripheral vascular disease; autonomic neuropathy. In patients planning a low-level exercise program such as walking, physician judgment is to be used to decide who needs an exercise test.

The Silent Ischemia Controversy

Conflicting results have been obtained comparing diabetic to nondiabetic patients for the prevalence of silent ischemia during treadmill testing. Silent ischemia was found to be more common in diabetic patients in the following studies. Nesto et al[27] studied 50 patients with diabetes and 50 patients without diabetes selected consecutively with ischemia on exercise thallium scintigraphy, and found angina to be an unreliable index of myocardial ischemia in diabetic patients. Naka et al[29] compared patients with diabetes with nondiabetic control subjects for the prevalence of silent myocardial ischemia using treadmill testing and coronary angiography. Results of treadmill testing showed ischemic ST-segment depression in 41 of 132 diabetic patients and in 42 of 140 nondiabetic control subjects (31% vs 30%, not significant). Coronary angiography was performed in 36 of 41 diabetic patients and in 34 of 42 nondiabetic control subjects with abnormal treadmill test results who gave their consent. Among those with abnormal angiogram findings, diabetic patients had a prevalence of silent myocardial ischemia that was 2.2 times higher than that in nondiabetic control subjects.

Silent ischemia was not more common in diabetic patients undergoing exercise testing in several other studies. In a landmark Danish study,[30] the prevalence of ischemia was compared in diabetic and nondiabetic patients. A random sample of 120 users of insulin and 120 users of oral hypoglycemic agents aged 40 to 75 years living in Denmark were asked to participate. Abnormal ST-segment depression on either exercise or Holter was considered indicative of myocardial ischemia. Angina pectoris was considered present if the Rose questionnaire result was positive, or chest pain accompanied ECG evidence of ischemia. The observed prevalence of silent ischemia in diabetic patients was 13.5% and was no different in matched control subjects. An analysis was performed to determine whether diabetic patients with coronary disease enrolled in the ACIP study had more episodes of asymptomatic ischemia during exercise testing and Holter monitoring than nondiabetic patients.[25] Angiographic findings and the prevalence and magnitude of ischemia during the qualifying Holter and exercise study were compared by the presence and absence of diabetes mellitus in 558 randomized ACIP study patients. The percentages of patients without angina during the exercise test were similar in the diabetic and nondiabetic groups (36% and 39%, respectively).

The prognosis of silent ischemia during exercise testing considering diabetic status in patients referred with chest pain has been addressed in the following two studies. At the Long Beach Veterans' Affair Medical Center, we attempted to determine the prognosis of silent ischemia in 1,747 consecutive patients referred for exercise testing.[24] Secondarily, we assessed whether age or the presence of myocardial infarction or diabetes mellitus influenced the prevalence of silent myocardial ischemia during exercise testing. There were 93 insulin-dependent and 87 noninsulin-dependent diabetic patients, both with the same prevalence of silent ischemia as the nondiabetic patients (60%). The mortality rate was significantly greater among patients with abnormal ST-segment depression than in patients without ST-segment depression. The presence or absence of angina pectoris during exercise testing was not significantly related to death. The prevalence of silent ischemia was not significantly different among patients categorized according to myocardial infarction or diabetes mellitus status, but was directly related to age. We found that in patients with an ischemic ST-segment response to exercise testing, the presence or absence of angina pectoris during the test did not alter the risk of death. The prevalence of silent ischemia during exercise testing was not statistically different among patients with recent, past, or no myocardial infarction or with insulin-dependent or noninsulin-dependent diabetes mellitus. Weiner et al[31] analyzed the data on 45 such patients without anginal chest pain during exercise testing among patients with diabetes mellitus from the Coronary Artery Surgery Study registry. These patients with silent ischemia were compared with 37 diabetic patients with both ischemic ST-segment depression and chest pain (symptomatic ischemia), with 31 diabetic patients without ischemic ST-segment depression or chest pain (no ischemia), and with 429 patients without diabetes who had silent ischemia during exercise testing. All patients had documented CAD. The 6-year survival among patients with silent ischemia was worse in diabetic than in nondiabetic patients (59% vs 82%, respectively). By contrast, the 6-year survival among patients without ischemia was similar among diabetic and nondiabetic patients.

Study Limitations

It should be noted that this study was limited to a male population who had been or were complaining of chest pain. It was also a retrospective analysis and suffers from the bias inherent to such a design. There was no effort to separate out subgroups of diabetic patients, *ie*, noninsulin dependent vs insulin dependent. Finally, there was no effort to eliminate workup bias. While comparable in both groups, the test characteristics of the exercise ECG could be considered inferior to other testing modalities. However, the use of treadmill scores can increase the predictive accuracy of the test to be comparable to exercise echocardiography and nuclear perfusion.[32]

Conclusion

This study demonstrates that the exercise ECG test in diabetic patients complaining of chest pain exhibits the same diagnostic characteristics as in patients without diabetes. It also shows that the prevalence of silent ischemia is equivalent both in diabetics and in nondiabetics, adding to the controversy surrounding the prevalence of asymptomatic ischemia in diabetic patients. As part of the initial workup for chest pain, the exercise treadmill test is valuable for diabetic and nondiabetic patients.

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