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Stress Testing in Patients With Diabetes Mellitus Diagnostic and Prognostic Value

Anne R. Albers, MD, PhD; Marc Z. Krichavsky, MD; Gary J. Balady, MD

Exercise ECG and stress imaging tests are used for diagnostic and prognostic purposes and to monitor the effects of therapeutic interventions.^{1,2} Such testing is most often applied to individuals with known or suspected coronary artery disease (CAD), and its value has been well studied.¹ CAD is more severe, more prevalent, and occurs at a younger age in patients with diabetes mellitus (DM). Diabetic patients without known CAD have similar rates of subsequent myocardial infarction (MI) compared with nondiabetic patients with a previous MI.³ Accordingly, DM is considered a risk equivalent to established CAD, and national guidelines for treatment of cardiac risk factors recommend similar goals for diabetic patients and those with known CAD.^{4–8} Diabetic patients have significantly higher rates of silent ischemia than the general population, and it has been postulated that this contributes to more advanced CAD on initial presentation and worse outcomes in diabetic patients.⁹ Because of this altered natural history, investigators have evaluated stress testing and its diagnostic and prognostic value among patients with DM. In particular, the utility of stress testing among asymptomatic diabetic patients remains an area of active study.

The following article seeks to review the diagnostic and prognostic value of exercise ECG and stress imaging tests in symptomatic and asymptomatic patients with DM. Additionally, it aims to identify gaps in the current literature and summarize what recommendations can be made from the available data. PubMed and Medline 1966 through June 2005 databases were searched to identify all studies that addressed stress testing primarily among patients with DM using the following keywords: diabetes mellitus, stress testing, coronary arteriosclerosis, myocardial infarction or ischemia, exercise test, predictive value of tests, or electrocardiography. References within each article were evaluated for inclusion as well. Studies that comprised >50 patients were included for review. Studies in which stress testing was used primarily to assess perioperative cardiovascular risk were excluded.

Diabetes and Cardiovascular Disease

It is estimated that there are 18.2 million people with the diagnosis of DM in the United States.¹⁰ In 2001, the preva-

lence of DM was 7.9% in the United States, but it has increased 61% since 1990.¹¹ A total of 1.3 million new cases of DM and 798 000 new cases of type 2 DM (T2DM) occur each year.¹⁰ Impaired glucose tolerance (fasting glucose >100 mg/dL and <126 mg/dL) is estimated to be present in 35% of the elderly US population, and its prevalence is on the rise in overweight adolescents.^{7,12} DM is the fifth-leading cause of death in the United States and is associated with a 2- to 8-fold higher prevalence of, incidence of, and mortality from cardiovascular disease.⁷ Remarkably, 65% to 75% of patients with DM die of cardiovascular disease.^{13,14} By age 55 years, 35% of patients with type 1 DM (T1DM) have died of CAD.¹³ Direct and indirect healthcare costs of DM totaled \$132 billion in 2002 and are expected to rise to \$192 billion dollars by the year 2020.^{10,11,15}

The association between DM and CAD is becoming increasingly better understood. Endothelial dysfunction is heightened in DM and may represent a common pathophysiologic pathway for CVD. Vascular endothelium plays a key role in regulating vascular tone, leukocyte attraction, vascular smooth muscle growth, nutrient delivery and waste removal, inflammation, coagulation, and thrombosis.¹⁶ Nitric oxide (NO) has been shown to be a key regulatory factor of endothelial function, and hyperglycemia in DM is thought to decrease NO bioavailability. Increased endothelial cell matrix metalloproteinase is produced, which decreases vascular smooth muscle cell collagen in the fibrous caps of atheromas and increases the risk of plaque rupture and thrombosis. Plasminogen activator inhibitor type 1 (PAI-1) levels are elevated in DM, which inhibits fibrinolysis. These alterations in vasoconstriction, inflammation, and thrombosis collectively create a dysfunctional endothelium and contribute to the microvascular and macrovascular sequelae seen in DM.¹⁷

Silent Ischemia and Diabetes

There are as many as 12.5 million diabetic patients with asymptomatic CAD.¹⁸ The reported prevalence varies widely in the literature (4% to 75%),^{19,20} which likely reflects variation in the cohort studied and in the definition of silent ischemia itself (eg, the absence of angina with an abnormal ECG, stress test, or angiogram). Diabetic patients mostly

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TABLE 1. Summary of Studies Using Stress Testing in the Diagnosis of Suspected CAD in Patients With Diabetes

Type of Test	Study	DM Subjects, n	Reference Standard	Sensitivity, %	Specificity, %	PPV, %	NPV, %
ECG	Lee et al ³⁰	190	Angiography	47	81	85	41
DSE	Hennessy et al ³¹	52	Angiography	82	54	84	50
Nuclear	Kang et al ³²	138	Angiography	86	56	N/A	N/A

PPV indicates positive predictive value; NPV, negative predictive value; ECG, exercise ECG stress test; DSE, dobutamine stress echocardiography; and N/A, not available.

have been shown to have a higher incidence of silent ischemia than nondiabetic patients.^{19–21} One study, however, by Falcone et al²² found equivalent rates of ischemia during exercise ECG testing in the absence of angina (58% versus 64%, $P=NS$). However, only patients with documented CAD by angiography were included, and those with neuropathy and retinopathy were excluded. It has been hypothesized that afferent sympathetic fibers play a key role in the sensation of angina and that these fibers may be disrupted in those with autonomic dysfunction.²¹ A study of T1DM patients found an association between glycemic control and silent CAD.²³ The pathophysiology of silent ischemia remains controversial, and other factors may also play a role, including differences in plasma opioid receptors, ischemic damage to nerve endings, and psychological factors.²² Regardless of the cause, silent ischemia may delay or mask the diagnosis of CAD, contributing to more advanced disease when it is finally discovered.

Diagnostic Utility of Stress Testing and the Issue of Verification Bias

Because of the well-established association between DM and CAD, clinicians commonly request stress tests in diabetic patients to diagnose CAD; however, the use of stress testing for diagnostic purposes has inherent limitations, as do many of the studies evaluating the diagnostic accuracy of various stress testing modalities. One flaw is that the “gold standard,” coronary angiography, has well-recognized limitations and may underestimate disease.²⁴ Additionally, most studies evaluating the sensitivity and specificity of various stress testing modalities suffer from “verification bias,” also called “workup bias,” “posttest referral bias,” or “selection bias.” This occurs when the decision to perform the “gold standard” test is influenced by the outcome of the diagnostic test itself. Most trials investigating noninvasive stress tests are organized so that primarily patients with abnormal stress tests proceed to invasive angiography. This creates a higher-risk subgroup within the study population who undergo angiography, most likely with a higher prevalence of CAD. Accordingly, the sensitivity of the stress test is overestimated, and the specificity is underestimated.²⁵ In a study designed to eliminate verification bias, more than 800 patients with suspected coronary disease underwent exercise ECG testing, followed by angiography regardless of the outcome.²⁶ This study found a sensitivity of 45% and specificity of 85%, which differs significantly from the traditionally accepted 70% sensitivity and specificity for exercise ECG testing.²⁷ Similar findings have been found for stress echocardiography and stress nuclear imaging.^{28,29}

Exercise ECG Testing

Diagnostic Value

Graded exercise tests are widely used clinically to assess the ability of an individual to safely tolerate increased physical activity while ECG, hemodynamic, and symptomatic responses are monitored for the development of myocardial ischemia, electrical instability, or other exertion-related abnormalities. The exercise ECG remains an inexpensive test that has been well validated in the general population, and it can be used as the first diagnostic test for patients with an intermediate risk of having CAD. Given the differences in presentation of CAD within the diabetic population and particularly the higher incidence of silent myocardial ischemia, various groups have attempted to evaluate whether the exercise ECG has similar accuracy in a diabetic population.

Lee et al³⁰ (Table 1) retrospectively evaluated 190 diabetic patients among 1282 male veterans presenting with chest pain who underwent an exercise ECG test and coronary angiography within a 4-month period. With standard ECG criteria used to define a positive test,¹ 38% of diabetic patients had an abnormal exercise test, whereas 69% had CAD as defined by angiography. The sensitivity of the exercise test among diabetic patients was 47%, and the specificity was 81%, with a positive predictive value of 85% and negative predictive value of 41%. This did not differ significantly from the 1092 patients without DM (sensitivity 52%, specificity 80%, positive predictive value 78%, and negative predictive value 55%). Although the study was limited by a relatively small percentage of diabetic patients (15%) and was subject to verification bias, it suggests that exercise ECG testing offers similar diagnostic value for patients with and without DM who present with chest pain.

Exercise ECG testing has also been used to assess asymptomatic diabetic patients for CAD. Blandine et al⁹ (Table 2) prospectively screened 203 diabetic patients without anginal symptoms who had normal resting ECGs with exercise ECG tests (stress nuclear imaging was used if exercise ECG testing was contraindicated or inconclusive). Sixteen percent of the group had an abnormal stress test, whereas 9% had silent CAD as defined by angiography. The vast majority of patients (84%) with silent angiographic CAD had T2DM. Koistinen et al³³ studied 136 asymptomatic diabetic patients who underwent exercise ECG testing and thallium imaging, with subsequent cardiac catheterization if noninvasive testing was positive. Exercise ECG testing was abnormal in 14% of these asymptomatic patients, with a positive predictive value of 94%. This result is higher than previous studies and may reflect the relatively older, male, and poorly controlled

TABLE 2. Summary of Studies Using Stress Testing in the Diagnosis of CAD in Asymptomatic Patients With Diabetes

Type of Test	Study	DM Subjects, n	Reference Standard	Sensitivity, %	Specificity, %	PPV, %	NPV, %
ECG	Blandine et al ¹⁹	98	Angiography	N/A	N/A	90	N/A
ECG	Koistinen et al ³³	136	Angiography	N/A	N/A	94	N/A
ECG	Bacci et al ³⁴	206	Angiography	N/A	N/A	79	N/A
ECG	Penfornis et al ³⁵	56	Angiography	N/A	N/A	60	N/A
DSE	Penfornis et al ³⁵	56	Angiography	N/A	N/A	69	N/A
Nuclear	Blandine et al ¹⁹	103	Angiography	N/A	N/A	63	N/A
Nuclear	Wackers et al ¹⁹	1123	None	N/A	N/A	N/A	N/A
Nuclear	Rajagopalan et al ²⁰	1427	Angiography	92	68	89	60
Nuclear	Penfornis et al ³⁵	56	Angiography	N/A	N/A	75	N/A

Abbreviations as in Table 1.

diabetic cohort (mean HgA_{1c} 11.3%) with a higher incidence of CAD. Bacci et al³⁴ evaluated 206 consecutive higher-risk, asymptomatic, T2DM patients with peripheral arterial disease (PAD) and at least 2 cardiovascular risk factors (CRFs); 19% had an abnormal test. Coronary angiography was performed in 71 patients (27 with a positive test and 44 randomly selected patients with a negative test). Of these, 29% had significant CAD. The positive predictive accuracy of the exercise ECG was 79%. Although relatively small in size and often subject to verification bias, these studies collectively support the notion that among higher-risk cohorts of asymptomatic patients with DM, up to nearly one third may have unrecognized CAD, and that exercise ECG testing may provide useful diagnostic information to identify these patients.

Prognostic Value

Although the literature suggests that exercise ECG tests may identify CAD in diabetic patients, national guidelines recommend that all diabetic patients should be treated as if they have CAD with regard to blood pressure management, lipid goals, aspirin use, and other secondary preventive measures. Therefore, a key issue facing clinicians is to risk-stratify the long-term likelihood of morbidity and mortality due to CAD and to identify those patients who might benefit from more aggressive treatment strategies to mitigate these risks.

In a study of 68 asymptomatic male veterans with DM, Rubler et al³⁶ (Table 3) found that exercise ECG testing had a 50% sensitivity and 83% specificity for predicting subsequent cardiac events (cardiac death, MI, or angina) over an average of 41 months of follow-up. The Milan Study on Atherosclerosis and Diabetes (MiSAD)³⁷ prospectively screened 735 asymptomatic diabetic patients for CAD and followed this group for cardiac events for 5 years. All patients underwent exercise ECG, with a positive test prompting stress nuclear testing and additional therapy as guided by participating cardiologists. Selection criteria favored a relatively low-risk cohort, excluding those with nephropathy (creatinine >1.5 mg/dL), retinopathy, cerebrovascular disease, or peripheral vascular disease, with a mean hemoglobin A_{1c} of 7.3. Among the 638 subjects (87%) with a normal exercise ECG test, the incidence of cardiac events (death, MI,

or angina) was 0.97/100 person-years (CI 0.66 to 1.38) compared with 3.85/100 person-years (CI 1.84 to 7.07) in those with abnormal stress testing ($P<0.0001$). Although these data are limited by verification bias, they suggest that asymptomatic patients with uncomplicated DM who have a negative exercise ECG test have a lower cardiac event rate and relatively favorable prognosis. The prognostic implications of a negative exercise ECG test in asymptomatic diabetic patients with higher-risk profiles, including PAD and multiple CRFs, has not been addressed in the literature to the best of our knowledge.

Non-ST-Segment Variables

Significant diagnostic and prognostic information beyond the ST-segment response and presence of angina can be obtained from the carefully performed exercise ECG test. Exercise capacity is well established as a predictor of cardiovascular mortality, and tools like the Duke Treadmill Exercise Score are commonly used to provide prognostic information.⁵⁴ More recently, investigators have identified additional parameters that provide prognostic information in both general clinical and diabetic populations. These include heart rate recovery (HRR) after exercise and chronotropic response (percentage of heart rate reserve used). Autonomic dysfunction and alterations in sympathetic and parasympathetic tone have been hypothesized to play a role in these physiological parameters. Diabetic patients have a higher incidence of autonomic dysfunction.⁵⁵ Prolonged HRR after exercise predicts mortality in the general population.⁵⁶ An abnormal HRR is variably defined in the literature. In one large study from the Cleveland Clinic,⁵⁷ it is defined as failure to decrease heart rate by at least 12 bpm 1 minute after peak exercise. Recent studies have applied HRR analysis to patients with DM. Seshadri et al³⁸ found that increasing blood sugar levels correlated with decreased HRR and that the diagnosis of DM was an independent predictor of an abnormal HRR response to exercise. Cheng et al³⁹ followed up 2333 diabetic men for 15 years after exercise ECG testing, in which the HRR was measured 5 minutes after maximal exercise. The cohort was divided into quartiles based on HRR. Both cardiovascular and all-cause mortality were highest in the patients with impaired HRR ($P<0.001$ for trend).

TABLE 3. Summary of Studies Using Stress Testing to Assess Prognosis in Patients With Diabetes

Type of Test	Study	DM Subjects, n	Summary
ECG	Rubler et al ³⁶	68	Exercise ECG among asymptomatic DM predicted CE over 41 months with sensitivity 50%, specificity 83%, PPV 30%, NPV 88%
ECG	Faglia et al ³⁷	735	Negative exercise ECG in relatively low-risk asymptomatic diabetes cohort provided favorable prognosis: 0.97 CE/100 person-years vs 3.85/100 person-years, $P<0.0001$
ECG	Seshadri et al ³⁸	51	DM was an independent predictor of an abnormal HRR (adjusted OR 2.1, $P=0.04$)
ECG	Cheng et al ³⁹	2333	DM with impaired HRR 5 minutes after exercise had highest rates of CV and overall mortality (P for trend <0.001)
ECG	Wei et al ⁴⁰	1263	Strong association among DM males between poor fitness and mortality (RR 2.1)
Echocardiography			
Exercise, DSE	Marwick et al ⁴¹	937	Abnormal test independent predictor of mortality (HR 1.8). Inability to exercise most powerful predictor of mortality (HR 3.9)
Exercise	McCully et al ⁴²	206	DM (RR 1.9), prior MI (RR 2.4), and exercise-induced LV dysfunction (RR 1.6) were multivariate predictors of cardiac death or MI in cohort with good exercise capacity
Exercise	Elhendy et al ⁴³	563	Increased risk of cardiac death or MI at 5 years (23% vs 7%, $P<0.0001$) with abnormal test. Negative test associated with no events at 2 years, 8% at 5 years.
DSE	Kamalesh et al ⁴⁴	144	Increased incidence of CE despite negative stress echocardiography in DM cohort (6% vs 2.9%/year). Event rate increased significantly in DM after 18 months.
DSE	Sozzi et al ⁴⁵	396	WMSI on DSE predicted CE (χ^2 37 vs 18, $P<0.05$) and mortality (χ^2 52 vs 43, $P<0.05$)
DSE, dipyridamole	Bigi et al ⁴⁶	259	Abnormal test associated with lower event-free survival (OR 2.9, $P<0.001$). WMSI only independent predictor of CE.
Nuclear	Rajagopalan et al ²⁰	1427	Annual mortality rate among asymptomatic diabetic patients varies significantly based on low- (3.6%), medium- (5.0%), or high-risk (5.9%) test ($P<0.001$)
Nuclear	Giri et al ⁴⁷	929	Diabetic patients had significantly more cardiac events than nondiabetics (8.6% vs 4.5%, $P<0.0001$)
Nuclear	Kang et al ⁴⁸	1080	Increasing annual rate of cardiac death or MI with normal (1–2%), mildly abnormal (3–4%), and moderately to severely abnormal ($>7%$) test ($\chi^2=36$, $P<0.0001$)
Nuclear	Schinkel et al ⁴⁹	207	Abnormal test conferred greater risk of cardiac death (HR 7.2, $P<0.0001$) in a high-risk diabetic cohort unable to exercise. No deaths in 2.5 years after a normal test.
Nuclear	Hachamovitch et al ⁵⁰	1818	Presence of DM, known CAD, age, gender, and inability to exercise provided incremental prognostic information beyond the stress test result.
Nuclear	Vanzetto et al ⁵¹	158	Ability to exercise associated with low risk of future CE, and nuclear imaging provides limited additional value. Inability to exercise associated with higher risk (OR 6.8, $P=0.001$), particularly with abnormal scan (OR 7.9, $P<0.005$).
Nuclear	De Lorenzo et al ⁵²	180	Increasing annual rates of cardiac death or MI among high-risk asymptomatic DM with no (3%), 1 (10%), and multiple ($>31%$) perfusion defects ($P=0.0001$)
Nuclear	Berman et al ⁵³	1222	Among diabetics, T1DM had higher annual mortality than T2DM (9% vs 5%, $P<0.05$); females had greater annual mortality than males ($P<0.0001$).

CE indicates cardiac events; PPV, positive predictive value; NPV, negative predictive value; CV, cardiovascular; DSE, dobutamine stress echocardiography; RR, relative risk; HR, hazard ratio; and WMSI, wall motion score index.

A patient's cardiorespiratory fitness level, obtained by maximal exercise testing, predicts mortality in patients with DM.⁴⁰ A total of 1263 men with T2DM underwent a medical evaluation including exercise ECG testing and were prospectively followed up for 12 years. Study patients were categorized as low, moderately, or highly fit on the basis of maximal metabolic units (METs) achieved, normalized for age and gender. There was a strong association between low fitness and increased mortality in diabetic patients, with an adjusted relative risk for death of 2.1 (CI 1.5 to 2.9). Each 1-MET increase in exercise capacity was associated with a 25% (CI 17% to 32%) decrease in mortality in the multivariate analysis ($P<0.001$). Rubler et al³⁶ further showed that duration of exercise on exercise ECG testing was the single predictor of cardiac events (death, MI, or angina) in a cohort

of 68 diabetic patients followed up for a mean of 41 months ($P<0.005$).

Summary

Exercise ECG testing remains a well-established, inexpensive test available to assist clinicians in the diagnosis and prognosis of CAD in diabetic patients. It appears to have similar diagnostic sensitivity ($\approx 50%$) and specificity ($\approx 80%$) for diabetic patients presenting with angina as for nondiabetic patients. It can identify a subgroup of asymptomatic diabetic patients who have significant CAD as defined by angiography, and in lower-risk diabetic cohorts, it may offer short-term prognostic reassurance to those asymptomatic patients with negative tests. However, considerable prognostic power of the exercise ECG test lies beyond the ST-segment response

and the presence of angina during exercise. Parameters including exercise capacity and HRR offer significant information, particularly in diabetic patients, who may not experience angina during exercise and who may have increased autonomic dysfunction. Chronotropic response during exercise testing has not been studied in diabetic patients. Further studies are needed to assess the value of these non-ST-segment variables and the value of the Duke Prognostic Score among patients with DM.

Stress Echocardiography

Diagnostic Value

Stress testing with imaging is well recognized to provide greater diagnostic accuracy than exercise ECG testing in the general clinical population.^{58,59} Stress echocardiography has a mean sensitivity of 86% and a specificity of 81% in the general population.⁵⁸ There are limited data that specifically address the utility of stress echocardiography in patients with DM. Hennessy et al³¹ (Table 1) evaluated 52 patients with DM referred for cardiac assessment using dobutamine stress echocardiography (DSE). Significant CAD was defined as >50% stenosis on coronary angiography. Sensitivity, specificity, and positive and negative predictive values of DSE for CAD detection were 82%, 54%, 84%, and 50%, respectively. Although the study was limited by the small size of the cohort, it demonstrated similar diagnostic accuracy for DSE in a diabetic population. Penformis et al³⁵ (Table 2) compared the efficacy of DSE to exercise ECG testing and SPECT (single-photon emission computed tomography) nuclear perfusion imaging in 56 asymptomatic diabetic patients with 3 additional CRFs but normal resting ECGs. Participants underwent all forms of noninvasive stress testing, but coronary angiography was only performed if at least 1 test was abnormal (47%), which precluded the measurement of diagnostic sensitivity and specificity. Positive predictive value was 69% for DSE, 60% for exercise ECG, and 75% for thallium SPECT.

Prognostic Value

Several studies have evaluated the prognostic value of stress echocardiography among diabetic patients. Marwick et al⁴¹ (Table 3) reported on the use of stress echocardiography to predict mortality in 937 diabetic patients with known or suspected CAD over 4 years of follow-up. Exercise echocardiography was performed in 333 patients (36%), whereas 604 (64%) underwent DSE. An abnormal test was an independent incremental predictor of mortality (hazard ratio 1.77). However, the strongest predictor of mortality was referral for pharmacological stress testing, which conferred a 4-fold higher risk compared with those who underwent exercise echocardiography. This likely reflected more severe comorbidities in those unable to exercise. However, imaging results do appear to offer incremental information in addition to exercise capacity. McCully et al⁴² reported the outcome of 206 diabetic and 1874 overall patients with good exercise capacity (≥ 5 METs in females, ≥ 7 METs in males) but abnormal exercise echocardiograms. After a mean follow-up of 3 years, the annual rate of cardiac death or nonfatal MI was 2%. DM, history of MI, and exercise-induced left ventricular

(LV) dysfunction were multivariate predictors of adverse outcome.

Elhendy et al⁴³ studied the outcomes of 563 diabetic patients with known (30%) or suspected CAD undergoing exercise echocardiography over a median follow-up of 3 years. Patients with an abnormal stress echocardiography result had a higher event rate (cardiac death and MI) than those with a normal test at 1 year (2% versus 0%), 3 years (12% versus 2%), and 5 years (23% versus 8%). Resting LV ejection fraction and the number of ischemic segments during exercise provided independent incremental prognostic information above clinical and exercise data. Evidence of multivessel distribution of echocardiographic abnormalities conferred the worst prognosis. The event rate was poorly predicted by a prior history of angina or by stress-induced angina during the test, which reinforces the notion that the absence of symptoms does not necessarily imply low cardiac risk among diabetic patients. Notably, there were no cardiac events among patients with a normal test through 2 years of follow-up. By 5 years, the event rate had increased to 8%. Kamalesh et al^{44,60} reviewed multiple stress echocardiography and stress nuclear studies in diabetic cohorts and found similarly concerning late event rates (beyond 2 years) among diabetic patients with normal stress imaging results. This phenomenon is not seen in the nondiabetic population and is hypothesized to reflect the challenge of detecting diffuse small-vessel disease in diabetic patients, as well as an increased propensity for future events due to rapid progression of atherosclerosis, increased inflammation, thrombosis, and risk of plaque rupture. This has led some to suggest that a repeat stress test may be indicated after 2 years to reassess cardiac risk in diabetic patients, although to date, this strategy has not been studied prospectively in the literature.^{43,60}

Sozzi et al⁴⁵ studied the incremental value of DSE for risk stratification in diabetic patients who were unable to exercise. A total of 396 patients with known limited exercise capacity underwent DSE for evaluation of known or suspected CAD and were followed up for cardiac events (cardiac death and nonfatal MI) and all-cause mortality for a median of 3 years. Clinical predictors of cardiac events were a history of congestive heart failure, previous MI, hypercholesterolemia, and resting LV ejection fraction. Quantification of ischemia using a wall-motion score index on DSE (with higher numbers reflecting increasingly abnormal wall motion at peak exercise) offered significant additional prognostic value for cardiac events (χ^2 37 versus 18, $P < 0.05$) and all-cause mortality (χ^2 52 versus 43, $P < 0.05$). Bigi et al⁴⁶ also assessed the value of pharmacological stress echocardiography for risk stratification of diabetic patients with known or suspected CAD. A total of 259 patients with DM underwent dobutamine (42%) or dipyridamole (58%) stress echocardiography and were followed up for a mean of 2 years for cardiac death and nonfatal MI. Wall-motion score index was the sole independent predictor of events on multivariate analysis. A positive stress echocardiogram was associated with a 3-fold lower event-free survival.

Summary

Stress echocardiographic imaging provides improved sensitivity and specificity compared with exercise ECG testing.

Increasing data are available to support both its diagnostic accuracy and, in particular, its prognostic ability to risk-stratify diabetic patients for future cardiac events. The presence of resting LV systolic dysfunction and stress-induced wall-motion abnormalities provides incremental prognostic information to clinical and exercise parameters in multiple studies involving both exercise and pharmacological stress echocardiography. Patients referred for pharmacological stress echocardiography demonstrate a higher risk for cardiovascular events than those referred for exercise testing, which likely reflects more severe underlying cardiovascular disease and comorbidities. Diabetic patients with normal stress echocardiograms appear to have a greater risk for subsequent cardiovascular events than nondiabetic patients, particularly beyond 2 years. The hypothesis that diabetic patients require more frequent follow-up testing merits further investigation.

Stress Nuclear Testing

Diagnostic Value

Stress nuclear testing has a sensitivity of 88% and specificity of 74% (uncorrected for verification bias) for the detection of angiographic CAD in the general clinical population and has been found to have similar diagnostic value among diabetic cohorts.⁵⁹ Among stress imaging modalities, stress nuclear testing is the most extensively studied in diabetic populations. Kang et al³² (Table 1) retrospectively evaluated 138 diabetic (12% T1DM) and 188 nondiabetic patients with suspected CAD who underwent exercise or pharmacological SPECT imaging and coronary catheterization within 6 months. The sensitivity and specificity of SPECT were 86% and 56% in diabetic patients versus 86% and 46% in nondiabetic patients ($P=NS$), which suggests that stress nuclear testing has similar diagnostic accuracy in diabetic patients and nondiabetic patients with suspected CAD.

The DIAD Study was designed by Wackers et al¹⁹ (Table 2) to prospectively study the prevalence and severity of CAD in asymptomatic diabetic patients and to assess the ability of current American Diabetes Association (ADA) guidelines⁶¹ to identify those with silent ischemia. A total of 1123 patients with T2DM and no prior history of CAD by symptoms, ECG, stress testing, or angiography were enrolled. Fifty percent (561) of these patients underwent a screening adenosine nuclear stress test with low-level exercise when possible (50%), in addition to regular follow up. Twenty-two percent had an abnormal study, and 6% were “markedly abnormal,” with moderate or large stress defects. On the basis of current ADA guidelines (resting ECG suggestive of ischemia or infarction, PAD, age >35 years and starting an exercise program, 2 or more CRFs in addition to DM), 60% of the patients enrolled met the criteria for a “screening” stress test. Twenty-two percent of patients in this cohort had abnormal tests, identical to the remainder of the cohort. There was also no difference in the incidence of “markedly abnormal” tests between the 2 subgroups. Notably, 41% of all abnormal tests would have been missed by only screening patients on the basis of current ADA guidelines, which led the authors to suggest that all diabetic patients may merit screening stress nuclear imaging.

Rajagopalan et al²⁰ retrospectively studied 1427 asymptomatic diabetic patients who were referred to the Mayo Clinic for stress nuclear testing (50% for preoperative evaluation, 39% for screening purposes, 3% for vague non–chest-related symptoms, 5% miscellaneous). Of these, 59% had an abnormal test and 18% had “high-risk” results based on summed stress scores. This surprisingly high rate of abnormal tests was hypothesized by the authors to reflect a relatively higher-risk group of asymptomatic patients, half of whom were undergoing preoperative assessment that was clinically prompted by their referring physician. A total of 212 (15%) of the patients underwent coronary catheterization within 6 months of the stress test. Of those with “high-risk” SPECT results, 61% had “high-risk” angiographic CAD (left main, 3-vessel, or proximal left anterior descending disease). The presence of Q waves on resting ECG was the strongest predictor of an abnormal stress test, followed by PAD, HgA_{1c}, sex, age, LDL cholesterol, and inability to exercise. Twenty-six percent of patients with abnormal resting ECGs (Q waves or ST/T-wave abnormalities) and 28% with PAD had “high-risk” SPECT scans. Although data were obtained retrospectively and were subject to verification bias, this study provides additional support for screening stress tests in asymptomatic diabetic patients with abnormal ECGs, PAD, and other CRFs.

Prognostic Value

Patients With Known or Suspected CAD

Several studies (Table 2) have addressed the prognostic value of stress nuclear imaging among diabetic patients with known or suspected CAD.^{47–51} Each demonstrates that abnormal stress nuclear scans confer an increased risk of cardiovascular events. This is well shown in 2 large studies. The multicenter study by Giri et al⁴⁷ retrospectively analyzed 929 diabetic patients among a larger cohort of 4755 patients who underwent adenosine or exercise nuclear testing for suspected CAD. Subjects were followed up for a mean of 2.5 years for cardiac death, MI, and revascularization. Diabetic patients had significantly more cardiac events than nondiabetics (8.6% versus 4.5%, $P<0.0001$). An abnormal stress nuclear test conferred an increased risk of cardiac events in both populations, with a greater number of ischemic or fixed segments predicting a worse prognosis in a stepwise fashion. The large prospective study by Kang et al⁴⁸ evaluated the prognostic efficacy of adenosine and exercise nuclear testing in 1080 diabetic patients and 5130 nondiabetic patients referred for unspecified indications. Diabetic patients had more perfusion defects and higher event rates (cardiac death, nonfatal MI, or revascularization) over a mean of 24 months of follow-up. Stratification of diabetic patients according to normal, mildly abnormal, and moderately to severely abnormal SPECT results predicted cardiac death ($\chi^2=36$, $P<0.0001$). These studies and others^{43,49,50,60} demonstrate a low event rate within 2 years of a normal test. However, after 2 years, diabetic patients begin to have higher cardiac event rates, despite a normal test. These data suggest that it may be useful to retest diabetic patients with normal perfusion scans more frequently in follow-up.

Asymptomatic Patients

Stress nuclear testing appears to be useful in risk stratification among higher-risk asymptomatic diabetic patients.^{20,51,52} In the largest series reported, Rajagopalan and colleagues²⁰ assessed the prognostic implications of stress nuclear testing in their cohort of 1427 asymptomatic diabetic patients. When patients were stratified by their stress nuclear test results into low-, medium-, and high-risk groups, the authors found a significant difference among annual mortality rates (3.6%, 5.0%, and 5.9% respectively; $P < 0.001$ for trend). Vanzetto et al⁵¹ studied 158 patients with T2DM and ≥ 2 of the following risk factors: age ≥ 65 years, active smoking, blood pressure $\geq 160/95$ mm Hg, hypercholesterolemia, history of CAD, PAD, abnormal resting ECG, and microalbuminuria. Most patients (78%) were asymptomatic. Thirteen percent of patients who underwent exercise nuclear stress had abnormal exercise ECG components of the stress test, and 56% had abnormal SPECT imaging. Those with abnormal SPECT imaging had an increased rate of major events (death or MI, OR 2.9, $P = 0.04$). Similarly, De Lorenzo et al⁵² reported that among 180 asymptomatic diabetic patients who underwent exercise or dipyridamole nuclear stress testing, 26% had abnormal SPECT imaging. Death or MI occurred in 3% of those with no perfusion defects, 10% of those with perfusion defect in a single territory, and 31% of those with perfusion defects that involved more than 1 territory ($P = 0.0001$).

Inability to Exercise

Studies of symptomatic⁵⁰ and asymptomatic⁵¹ diabetic patients demonstrate that the inability to exercise is associated with up to a 7-fold higher mortality rate compared with those who could perform an exercise test. Among those patients unable to exercise in the study by Vanzetto et al,⁵¹ perfusion defects in ≥ 2 segments conferred an annual mortality rate of 22%, 7.8 times higher than that of similar patients with perfusion defects in < 2 segments.

Gender

Berman et al⁵³ evaluated the relationship between DM and gender in 1222 diabetic patients with known or suspected CAD undergoing an adenosine stress nuclear test for prognostic purposes. Receiver operator curves showed that adenosine stress nuclear testing offered prognostic information equally well in males and females (0.78 versus 0.83, $P = \text{NS}$). However, among diabetic patients, females had a worse outcome than males for any severity of perfusion defects. Subgroup analysis found that T1DM patients with abnormal tests had an even worse outcome than T2DM patients (9% versus 5% annual cardiac mortality). Additional investigation of gender and its interaction with diabetes and stress testing is needed.

Summary

Stress nuclear testing has the most extensive literature supporting its use in diabetic populations for both diagnostic and prognostic purposes. There is emerging evidence to support the use of screening stress testing in selected asymptomatic diabetic patients, particularly those with abnormal ECGs, multiple CRFs, PAD, and diabetic comorbidities. However, data demonstrating an improvement in outcome after screen-

ing and subsequent directed cardiovascular treatment have not yet been reported in the literature. Normal stress nuclear tests, even among higher-risk cohorts, are helpful in defining a relatively low-risk patient, although only in the short term. Diabetic patients, particularly those with significant comorbidities or advanced disease, may merit more frequent reevaluation. Limited data suggest that female and T1DM subgroups have even worse prognoses than other diabetic cohorts for any given severity of nuclear perfusion defect.

Current Guidelines on Stress Testing in Diabetic Patients

Current American College of Cardiology/American Heart Association guidelines on exercise testing¹ do not specifically address the diagnostic and prognostic utility of exercise ECG testing among diabetic patients, and in particular, asymptomatic diabetic patients. The American Heart Association Prevention VI Conference^{6,7} emphasized that there are no outcome data to support stress testing in asymptomatic diabetic patients. The ADA^{8,61} advocates for stress testing in diabetic patients with (1) typical or atypical cardiac symptoms, (2) resting ECG suggestive of ischemia or infarction, (3) peripheral or carotid occlusive arterial disease, (4) sedentary lifestyle, age ≥ 35 years with plans to begin a vigorous exercise program, and (5) 2 or more of the following risk factors in addition to DM: total cholesterol ≥ 240 mg/dL, LDL ≥ 160 mg/dL, HDL ≤ 35 mg/dL, blood pressure $\geq 140/90$ mm Hg, smoking, family history of premature CAD, and microalbuminuria or macroalbuminuria. The committee acknowledged (at the time of publication, in 1998) that these guidelines were based on expert consensus clinical judgment, because there were no available data to provide supporting evidence.

Several guidelines have provided specific recommendations about the use of exercise ECG testing among diabetic patients before they engage in an exercise training program. The American College of Cardiology/American Heart Association^{1,62,63} and the ADA recommend that an exercise ECG test be performed among patients with DM and the following conditions before they engage in a moderate to vigorous exercise training program: (1) known or suspected CAD, (2) T1DM for > 15 years, (3) T2DM for > 10 years or age ≥ 35 years, (4) additional atherosclerotic risk factors, or (5) evidence of microvascular disease, PAD, or autonomic neuropathy. The US Preventive Services Task Force⁶⁴ concluded that there was insufficient evidence to recommend for or against screening for CAD in asymptomatic patients, including before they begin an exercise program.

Conclusions

DM is becoming increasingly widespread, and CAD is more severe, more prevalent, and occurs at a younger age in patients with DM. Silent myocardial ischemia is more common among diabetic patients, and it has been hypothesized that this may alter not only the natural history of CAD but also the utility of stress testing. There is an increasing body of literature to support the use of stress testing, particularly stress imaging testing, in diabetic patients for both diagnostic and prognostic purposes. Many questions remain unanswered, and the issue of verification bias continues to be a

confounding problem that must be considered when one interprets the literature. Although exercise ECG testing remains a well-established, inexpensive test, it has limited diagnostic power, and much of its prognostic power lies beyond the ST segment. Parameters including cardiorespiratory fitness and the HRR appear to offer important information, particularly in diabetic patients with autonomic dysfunction. There is presently inadequate evidence to recommend routine screening of asymptomatic diabetic patients with an exercise ECG test.

Stress imaging provides improved sensitivity compared with exercise ECG testing, and it is often the first test of choice when baseline ECG abnormalities are present. It provides additional information, including localization, quantification, and reversibility of perfusion defects, as well as evaluation of LV systolic function. Among diabetic patients with known or suspected CAD, there is ample evidence to support the use of stress imaging studies, particularly stress nuclear testing, for their diagnostic and prognostic power. Evidence of MI or inducible ischemia appears to predict an increased risk of future cardiovascular events. Studies consistently demonstrate that diabetic patients who are unable to perform an exercise test or who have a poor exercise capacity have a worse prognosis. More studies are needed to specifically evaluate the diagnostic and prognostic value of stress testing in clearly defined clinical populations of diabetic patients (type and duration of DM, sex, glycemic control, and associated diabetic complications). Multiple authors suggest that among diabetic patients, a truly low-risk cohort is difficult to define on the basis of a normal stress test and that more frequent testing may be necessary in this population. Additional studies are needed to better define the "warranty" of a normal scan and to identify additional clinical parameters that characterize a truly low-risk population. One approach might be to evaluate a large cohort of patients with DM who are able to perform an exercise imaging study. Data would be stratified according to the results of the exercise ECG portion, using ST-segment and non-ST-segment variables, and the imaging portion of the test. Accordingly, patient outcomes over several years would be assessed for each of 3 subgroups as follows: those with both normal ECG and imaging test results; either portion abnormal; and both portions abnormal. Accordingly, the incremental value of imaging could be assessed among patients with normal and abnormal exercise ECG tests, and perhaps low-, intermediate-, and high-risk subgroups could be identified. In addition, further research on the value of stress testing among patients with the metabolic syndrome is needed, especially in the face of the worldwide obesity epidemic.

Although the use of stress testing in asymptomatic diabetic populations remains unsettled, Bayesian analysis would suggest that stress testing among asymptomatic diabetic patients who are likely to have a higher prevalence of CAD (long-standing disease, multiple CRFs, resting ECG abnormalities, and PAD) should provide useful diagnostic information. Recent emerging data support the utility of stress imaging testing in identifying diabetic patients with preclinical CAD, particularly among patients with high-risk features and comorbidities as outlined above. However, once these patients

have been identified, there are no data to demonstrate that treatment interventions improve their subsequent outcomes. Accordingly, further studies are needed to address this issue.

One possible example is a clinical trial in which asymptomatic T2DM patients with DM for ≥ 10 years are randomized to an exercise ECG test versus no exercise ECG test. All subjects are provided with aggressive secondary preventive measures as recommended by the American College of Cardiology/American Heart Association. Subjects with a high-risk exercise ECG undergo further workup that includes stress imaging tests and coronary angiography, with revascularization and medical therapy provided on the basis of these test results. The 2 cohorts are evaluated for the primary endpoints of all-cause mortality and nonfatal MI. Clearly, the cost of screening all high-risk asymptomatic diabetic patients would be significant. Although 1 study⁶⁵ concluded that screening for CAD in asymptomatic diabetic patients with ≥ 2 additional CRFs was cost-effective and acceptable from a societal perspective, additional analyses of both the utility and cost of various treatment strategies are warranted.

Disclosures

None.

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