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CLINICAL STUDY

Screening for silent myocardial ischaemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test

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Abstract

Objective: Coronary artery disease (CAD), a major cause of mortality in patients with type 2 diabetes (T2D), is often diagnosed late because of silent myocardial ischaemia (SMI). Exercise electrocardiogram testing (ECG) stress is the most utilized screening test for SMI. Its applicability and accuracy, which have never been reported in asymptomatic high-risk T2D patients, have been investigated in this study.
Design: A cross-sectional study with coronary angiography as the gold standard for detecting CAD was used.
Methods: Two hundred and six consecutive T2D patients, without symptoms and resting ECG signs of ischaemia but with peripheral vascular disease (PVD) and/or $\geq$ two atherogenic factors, were studied. Ischaemia at ECG stress was indicated by horizontal or downsloping ST segment depression ≥ 1 mm at 0.08 s after the J point. CAD was defined by stenosis $\geq 70\%$.
Results: Only 141/206 (68%) patients had a diagnostic test: 27 (19%) tested positive and 114 (81%) tested negative. Coronary angiography in 71 patients (the 27 who tested positive and 44 randomly selected patients who tested negative) indicated a CAD prevalence of 29% and the ECG stress accuracy was 79%. 'False negative' patients (18%) had a higher prevalence ($P < 0.01$) of long duration of diabetes and PVD.
Conclusions: This is the first study which provides insights into the applicability and accuracy of ECG stress in screening SMI in high-risk patients with T2D. Due to the high prevalence of CAD, alternative screening tests in patients unable to perform the test and in those with a high chance of being 'false negative' should be looked for and validated.

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Introduction

Coronary artery disease (CAD) is the major cause of mortality in diabetic patients, so its early detection is important to improve medical intervention and outcome (1–3). Screening is particularly needed for those patients who, apart from diabetes, show additional atherogenic risk factors (4–8). These high-risk diabetic patients should also be screened for CAD with a provocative test when no symptoms and signs are present (9, 10). In fact, irrespective of the presence or absence of angina, ST segment depression during exercise is a predictor of an increased risk of death (11, 12). In addition, among patients with silent myocardial ischaemia (SMI), the mortality rate is higher in diabetic than in non-diabetic individuals (12). Finally, among diabetic patients, those unable to perform the exercise are at higher risk of mortality (13). The exercise stress test is the most widely utilized low-cost, non-invasive screening test for SMI (12, 14, 15–19); however, its applicability and diagnostic accuracy as compared with the gold standard coronary angiography have never been reported in asymptomatic diabetic patients. Our study was aimed at investigating both the applicability and the accuracy of the exercise stress test for screening SMI in patients with type 2 diabetes (T2D) with additional atherogenic risk factors. Notably, because coronary angiography was also performed in randomized samples of patients with a negative stress test, we are here able to report for the first time both sensitivity and specificity (i.e. accuracy) of the exercise stress test for screening SMI in asymptomatic high-risk patients with T2D.

Subjects and methods

Two hundred and six consecutive T2D patients (age of diabetes onset ≥ 40 years, no episodes of ketosis),

attending our clinic from April 1997 to October 1999, were studied. Inclusion criteria were the presence of additional atherogenic risk factors for CAD as indicated by: peripheral vascular disease (at ultrasound Doppler if lumen stenosis was ≥40%) and/or two or more of the following risk factors: family history of myocardial ischaemia at <65 years of age; cigarette smoking; urinary albumin excretion rate >20 μg/min; arterial hypertension (>140/90 mmHg) or antihypertensive treatment; low density lipoprotein (LDL) cholesterol >3.36 mmol/l and/or high density lipoprotein (HDL) cholesterol <0.9 mmol/l in male and <1.16 mmol/l in female patients and/or triglycerides >2.26 mmol/l or antidyslipidaemic treatment.

Exclusion criteria were the presence of clinical symptoms: typical angina or chest pain; resting electrocardiographic (ECG) signs of myocardial ischaemia; severe and poor prognosis systemic diseases; age >70 years; claudicatio observed at <400 m and left bundle branch block on resting ECG.

All patients ($n = 206$) fulfilling both inclusion and exclusion criteria were recruited and underwent the exercise stress test. A maximal symptom-limited exercise protocol was used with a treadmill (Quinton Q 5000, Quinton Instruments, Botnell, WA, USA; Formula OTE Biomedica, Firenze, Italy) according to the Bruce protocol. Twelve ECG leads were recorded every minute and blood pressure was measured at rest and at the end of each step during exercise. Ventilatory oxygen consumption, expressed in multiples of resting requirements (METS), was estimated by exercise duration. The test was stopped when one of the following end-points was reached: target heart rate, 85% of the predicted heart rate (220 beats/min minus age in years); severe fatigue; systolic blood pressure reduction; hypertensive response (systolic blood pressure increase >250 mmHg and/or diastolic blood pressure >115 mmHg) (2). The exercise test was defined as maximal if the patient reached 85% of the predicted heart rate for the age or submaximal if the patient did not reach that target. Submaximal tests without ECG signs and/or symptoms of ischaemia were considered not diagnostic.

Finally, the exercise stress test was considered not diagnostic if exercise induced ventricular arrhythmia or intraventricular conduction abnormalities. Cardiovascular drugs including β-blockers and Ca-channel blockers were stopped 48 h before the test. Ischaemia at exercise test was indicated by: horizontal or downsloping ST segment depression of 1 mm or more calculated at 0.08 s after the J point, which is the junction between QRS complex and ST segment, and/or typical angina pectoris. Coronary angiography was carried out within 60 days of the exercise stress test.

In all positive ($n = 27$) and in 44 randomly selected patients from the 114 having a negative exercise stress test, coronary angiography was performed and evaluated by two independent observers on the percentage of major epicardial coronary arteries (left anterior descending, left circumflex and right coronary arteries) stenosis. Coronary angiography was regarded as positive if the lumen stenosis was ≥70%.

Blood pressure (phase I/V) was estimated as the mean of three measurements with a standard mercury sphygmomanometer. Glycated haemoglobin (HbA1c) was determined by high-pressure liquid chromatography after removal of the labile fraction (HPLC Diamat Analyzer; Bio-Rad, Richmond, CA, USA). Urinary albumin concentration evaluated as a median of three timed nocturnal collections was determined by the nephelometric method (Behring Nephelometer Analyzer; Behring, Marburg, Germany). Detection of retinopathy included fundoscopy followed if necessary by fluorescein angiography. Neuropathy was determined as somatic peripheral nerve dysfunction by electromiography.

This study began before the institution of Ethical Committees in our country; therefore, according to the Helsinki Declaration of 1975 and 1983, all patients were informed about the aim, procedures and possible benefits of the study and gave their informed consent for coronary angiography. Two patients randomly recruited from the exercise stress test negative group refused coronary angiography.

Results are expressed either as means±S.D. or as median with range in parentheses or as percentages. Means of two groups were compared by the Student's *t*-test or the Mann–Whitney U test, as appropriate. Rate of proportion was compared by χ^2 test. P values <0.05 were considered to indicate significance.

Results

Fifty-nine out of 206 patients (29%) were unable to complete the exercise stress test: 45 because of fatigue,

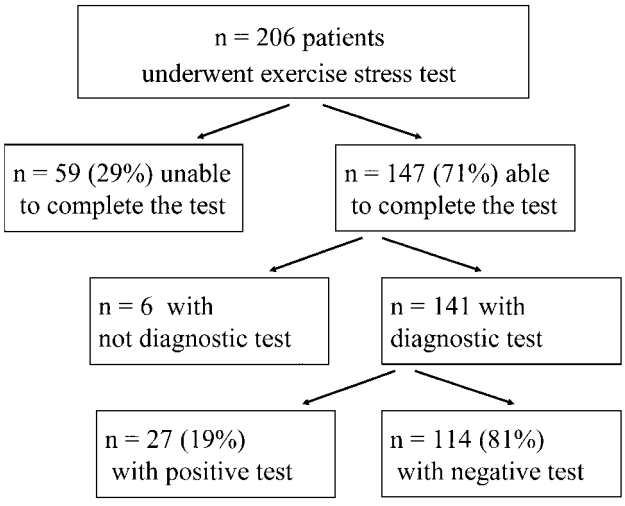

Figure 1 Patient flow diagram.

six because of dizziness, six because of claudicatio (although as for selection criterion no claudicatio <400 m was observed on the day before the test) and two because of hypertensive response (Fig. 1). Six of the 147 completed tests were considered not diagnostic because of the appearance of conduction abnormalities (Fig. 1). None of the clinical and metabolic variables tested were different between these 65 $(59+6)$ patients and the remaining 141 patients who were able to complete an exercise stress test that was considered diagnostic (data not shown).

These latter patients were subdivided into those having a positive exercise stress test ($n=27$, 19%) and those having a negative exercise stress test ($n=114$, 81%) respectively. Only one patient had symptomatic ischaemia during exercise: ST segment depression and angina (i.e. inducible ischaemia). Clinical and metabolic variables of the two groups are shown and compared in Table 1. A significant difference in gender distribution and presence of peripheral vascular disease was observed between the two groups.

Coronary angiography was performed in all positive exercise stress test patients ($n=27$) and in 44/114 (38%) patients with a negative test, randomly selected by means of random number tables. At coronary angiography, one patient had widespread itching for 10 min after medium contrast infusion and one patient had a tiny subcutaneous haematoma on the right femoral artery area which spontaneously disappeared within 48 h. In the positive exercise stress test group, coronary stenosis $\geq 70\%$ was observed in 20 (74%) patients (nine patients with three vessel, eight with two vessel and three with one vessel disease); of the remaining seven patients, one presented a lumen reduction $\geq 50-70\%$ and six had either lumen reduction $<50\%$ or no lumen reduction.

In the 44 patients randomly selected from the negative exercise stress test group, coronary stenosis $\geq 70\%$ was observed in eight (18%) patients (three with two vessel and five with one vessel disease); of the remaining 36 patients, six had coronary lumen reduction $\geq 50-70\%$ and 30 had either lumen reduction $<50\%$ or no lumen reduction. Among the 71 patients who underwent coronary angiography, those having a three vessel disease ($n=9$) were all positive at the exercise stress test. Clinical features of patients with or without positive coronary angiography are shown in Table 2. A significant difference in age, duration of diabetes, peripheral vascular disease, neuropathy, retinopathy, use of insulin and (almost significant) in gender distribution was observed between the two groups.

Table 1 Clinical and metabolic data of positive and negative patients at exercise stress test. Metabolic data are means±S.D. except for lipoprotein a which is the median with the range in parentheses. Additional data are shown as number (n) of subjects with the percentage in parentheses.

Exercise stress test	Positive	Negative	*P* value
Number	27	114	
Male/female	21/6	43/71	0.0002
Age (years)	59±8	57±7	
Age of onset of diabetes (years)	49±7	48±8	
Duration of diabetes (years)	11±7	9±7	
Body mass index (kg/m^2)	30±4	31±7	
HbA1c (%)	8.3±2	8.9±2	
Cholesterol (mmol/l)	5.7±0.9	5.8±1.0	
LDL cholesterol (mmol/l)	3.6±0.7	3.7±0.9	
HDL cholesterol (mmol/l)	1.2±0.4	1.2±0.3	
Triglyceride (mmol/l)	1.8±0.8	2.2±1.2	
Lipoprotein a (mg/dl)	21.3 (10–106)	22.8 (8–114)	
Uric acid (mg/dl)	4.9±1	4.7±2	
Fibrinogen (mg/dl)	344±88	360±73	
Family history of CAD (n (%))	11 (40)	34 (30)	
Hypertension (n (%))	13 (48)	75 (66)	
Smokers (n (%))	8 (30)	22 (19)	
Carotid ateromasy (n (%))	17 (63)	23 (20)	<0.0001
Leg ateromasy (n (%))	15 (55)	17 (15)	<0.0001
Nephropathy (n (%))	3 (11)	25 (22)	
Neuropathy (n (%))	11 (41)	26 (23)	
Retinopathy (n (%))	13 (48)	36 (31)	
Treatments			
Diet (n (%))	4 (15)	14 (12)	
OHA (n (%))	11 (41)	62 (54)	
Insulin/insulin + OHA (n (%))	12 (44)	38 (34)	
Antihypertensive agents (n (%))	10 (37)	66 (58)	
ACE inhibitors (n (%))	5 (18)	42 (37)	

OHA, oral hypoglycaemic agents; ACE, angiotension-converting enzyme.

Table 2 Clinical and metabolic data of positive and negative patients at coronary angiography. Metabolic data are means±S.D. except for lipoprotein a which is the median with the range in parentheses. Additional data are shown as number (*n*) of subjects with the percentage in parentheses.

Coronary stenosis	Yes	No	*P* value
Number	28	43	
Male/female	18/10	18/25	0.06
Age (years)	61±5	55±7	0.001
Age of onset of diabetes (years)	50±6	46±7	0.02
Duration of diabetes (years)	12±6	8±6	0.01
Body mass index (kg/m^2)	30±4	31±4	
HbA1c (%)	8.5±2	8.8±2	
Cholesterol (mmol/l)	5.8±1.0	5.8±0.8	
LDL cholesterol (mmol/l)	3.8±0.8	3.6±0.7	
HDL cholesterol (mmol/l)	1.3±0.4	1.2±0.3	
Triglyceride (mmol/l)	1.6±0.6	2.0±1.0	
Lipoprotein a (mg/dl)	28 (10–138)	25 (8–114)	
Uric acid (mg/dl)	4.8±1	4.9±1	
Fibrinogen (mg/dl)	359±86	368±74	
Family history of CAD (*n* (%))	11 (31)	13 (30)	
Hypertension (*n* (%))	15 (53)	29 (67)	
Smokers (*n* (%))	4 (14)	12 (28)	
Carotid ateromasy (*n* (%))	19 (68)	13 (30)	0.0018
Leg ateromasy (*n* (%))	17 (61)	6 (14)	<0.0001
Nephropathy (*n* (%))	3 (11)	9 (21)	
Neuropathy (*n* (%))	14 (50)	7 (16)	0.002
Retinopathy (*n* (%))	18 (64)	7 (16)	<0.0001
Treatments			
Diet (*n* (%))	2 (7)	6 (14)	
OHA (*n* (%))	11 (39)	28 (65)	0.03
Insulin/insulin + OHA (*n* (%))	15 (53)	9 (21)	0.004
Antihypertensive agents (*n* (%))	13 (46)	20 (46)	
ACE inhibitors (*n* (%))	9 (32)	17 (39)	

Sensitivity, specificity, positive and negative predictive values, accuracy and positive likelihood ratio of the exercise stress test, as indicated by comparison vs coronary angiography, are shown in Table 3.

In detail, seven out of 27 (26%) patients with positive exercise stress tests were, in fact, 'false positive' and eight out of 44 (18%) patients with negative exercise stress tests were, in fact, 'false negative'. Five out of the seven 'false positive' patients showed, at coronary angiography, myocardial thinning vessels with extensive atherogenic lesions. 'False positive' patients had ST segment depression ≥1.2 mm defined 'positive' according to the diagnostic criteria and showed no significant differences as compared with 'true positive' patients in the other features of the exercise stress, including length of exercise (6.7±4 vs 6.0±3 min), maximal heart rate (146±13 vs 136±11 beats/min), double product (heart rate × systolic blood pressure) at peak exercise ($26.2\pm53\times10^3$ vs $24.5\pm50\times10^3$) and METS (9.2±3 vs 9.3±3). As compared with 'true negative', 'false negative' patients showed a higher prevalence of both peripheral vascular disease ($7/8 = 87\%$ vs $12/36 = 33\%$, $P = 0.005$) and long duration of diabetes (≥10 years) ($7/8 = 87\%$ vs $16/36 = 44\%$, $P = 0.03$). 'False negative' patients had an upsloping ST segment depression of <0.8 mm and showed no differences as compared with 'true negative' patients in any features of the exercise stress data including time of exercise (5.03±1.6 vs 5.8±2.5 min), maximal heart rate (149±25 vs 145±13 beats/min), double product at peak exercise ($29.2\pm75\times10^3$ vs $26.4\pm36\times10^3$) and METS (7.04±2.4 vs 7.7±2.8). The accuracy of the exercise stress test was not different between male (75%) and female (83%) patients. However, in the subgroup of female patients without vascular disease ($n = 17$), the exercise stress test showed the highest possible performance, reaching 100% sensitivity and specificity.

The prevalence of coronary stenosis in our cohort of all 141 patients able to perform a diagnostic ECG stress, as calculated by extrapolating data of coronary angiography to the entire population, was 29%.

Table 3 Diagnostic performance of exercise stress test.

Parameter	All	Male	Female
Sensitivity	71%	83%	50%
Specificity	84%	67%	96%
Positive predictive value	74%	71%	83%
Negative predictive value	82%	80%	83%
Accuracy	79%	75%	83%
Positive likelihood ratio	4.43	2.5	12.5

Discussion

Epidemiological data clearly show the independent major contribution to CAD of diabetes *per se*, but also show the additional risk increase of other atherogenic factors (3–8). In addition, some (9, 10, 14, 15, 20) but not all (21) clinical studies support the hypothesis that SMI is more frequent in diabetic patients as compared with non-diabetic individuals. A higher risk of death is significantly associated with ST segment depression during the test, irrespective of the presence or absence of angina (11, 12). Finally, among patients with SMI, mortality rate is higher in diabetic than in non-diabetic subjects and, in the former group, survival rates are improved by revascularization in respect to pharmacological treatment (12). Taken together, these data suggest a strong indication that those patients with T2D having additional risk factors for CAD should be screened for SMI.

The exercise stress test is a provocative test which in diabetic patients may have a higher positive predictive value for SMI than other non-invasive tests, including ECG, 24-hr ambulatory ECG monitoring and thallium tomographic imaging (14, 18). However, up to date, no information on the applicability and diagnostic accuracy of this test has been available in asymptomatic patients with T2D. The lack of information on accuracy is due to the fact that in previous studies (14, 15, 19) coronary angiography was not performed in patients negative at the screening test. To the best of our knowledge, this is the first report which, thanks to the careful study design, is able to show the diagnostic accuracy and limitations of the exercise stress test for the screening of SMI in T2D patients with additional risk factors for CAD.

As far as the applicability of the test is concerned, it is worth noting that a considerable proportion of patients (29%) showed a poor exercise capacity, failing to achieve 85% of the maximal heart rate response to stress. This is a clinically relevant problem. Alternative tests for these patients are mandatory, not only because they have, by selection criteria, a high pretest probability of CAD (which, in fact, we have found in this population), but also because the inability to exercise is an important further predictor for CAD-related mortality (13).

Among 'false positive' patients, five out of seven showed myocardial thinning vessels with extensive atherogenic lesions. In these patients, small vessel disease and endothelial dysfunction abnormalities, secondary to diabetes, may be the cause of myocardial hypoxia and might confer a bad prognosis for future cardiac events (22–25). Among 44 patients with negative exercise stress test, eight were 'false negative' (18%) indicating that asymptomatic coronary stenosis $\geq 70\%$ may not be revealed by the criteria we used to define a positive exercise stress test (i.e. planar or downsloping ST depression ≥ 1 mm persisting ≥ 0.08 s after the J point). 'False negative' patients were characterized by a higher proportion of both peripheral vascular disease and long duration of diabetes. In these patients, coronary stenosis could simply not be haemodynamically significant; however, in order to avoid a possible misdiagnosis it seems reasonable to suggest that, when screening for SMI among patients with these latter clinical features, those with a negative exercise stress test (20% in our population) are eligible for additional tests. The data reported on the prevalence of SMI in diabetic patients are conflicting (14, 15, 19, 26). This may depend on differences in the diagnostic test and/or the patient selection criteria. According to a positive exercise stress test, in our population SMI has a prevalence of 19%, whereas, by combining exercise stress data on the 141 patients able to perform a diagnostic test and data from coronary angiography obtained in a subgroup of 71 patients, which were extrapolated to the entire cohort, the prevalence of asymptomatic coronary stenosis in our population is 29%. This latter prevalence is higher than those previously reported in other studies using the same criteria to define a positive coronary angiography (i.e. stenosis $\geq 70\%$) (14, 15, 19), probably because of the more restrictive selection criteria we used for patient recruitment and also because, at variance with other studies (14, 15, 19), coronary angiography was also performed in a randomly selected subset of patients who were negative at the ECG stress test; some of them (18%), in fact, turned out to have coronary stenosis. According to a positive exercise stress test, in the T2D patients at risk for CAD studied, SMI is associated with the male gender and peripheral vascular disease but not with peripheral neuropathy, a finding previously reported (20, 21). In the subgroup of patients who underwent coronary angiography, coronary stenosis is associated with peripheral vascular disease and more severe clinical conditions as indicated by a longer duration of diabetes, the use of insulin (instead of diet alone or in combination with oral hypoglycaemic agents) and the presence of retinopathy and/or neuropathy. These results are in agreement with some but not all previous reports (15, 19, 27–29). The lack of association between CAD and elevated urinary albumin excretion rate in our study could be due to the use of antihypertensive agents, with the majority of our patients being on ACE inhibitors.

In conclusion, this is the first report showing the applicability and accuracy of ECG stress for screening for SMI in asymptomatic T2D patients with additional risk factors for CAD. The results obtained in terms of accuracy clearly indicate that the ECG stress test may be proposed as the first test for screening for SMI in this population.

However, approximately 30% of these patients were not able to perform the test and the majority of 'false negative' cases had both peripheral vascular disease and long duration of diabetes. As previously

discussed, in the first subgroup of patients an alternative pharmacological stress test is mandatory, while in the second subgroup an additional provocative test may be suggested to provide a higher degree of reassurance.

Further studies are needed to investigate which other non-invasive test may be chosen and to validate it in order to eventually propose a rationale and applicable flow-chart for screening for SMI in high-risk diabetic patients.

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