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Silent Myocardial Ischemia: Role of Subclinical Neuropathy in Patients With and Without Diabetes

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Objectives. **Silent myocardial ischemia is common in patients with diabetes. This study was designed to assess the role of subclinical autonomic impairment in diabetic patients with silent ischemia.**

Background. **Studies have suggested that silent ischemia is more common in diabetic patients with microvascular complications, but this has not been a consistent finding.**

Methods. **Twenty-two diabetic and 30 nondiabetic patients with proved coronary artery disease and a history of angina and ischemia on treadmill stress testing underwent clinical tests of autonomic function and measurement of 24-h heart rate variability. Diabetic patients with a history of microvascular complications were excluded.**

Results. **Although all 52 patients manifested ischemia during treadmill testing, only 36 patients experienced angina (angina group), whereas 16 did not (silent ischemia group). Diabetic and nondiabetic patients were similar in age (59 ± 1 vs. 61 ± 2 years, p = 0.56) and extent of coronary artery disease. However, clinical tests showed reduced parasympathetic function in the diabetic patients (Valsalva ratio 1.38 ± 0.07 vs. 1.60 ± 0.06, p = 0.007). Patients in the silent ischemia group were more often diabetic (33% vs. 63%, p = 0.05) and had prolonged time to ischemia on treadmill testing (200 ± 20 vs. 271 ± 20 s, p = 0.03). In addition, autonomic function was impaired in the silent group (supine/standing heart rate ratio 1.15 ± 0.02 vs. 1.05 ± 0.02, p = 0.002). Subgroup analysis showed that abnormalities of autonomic function were confined to the diabetic patients in the silent group.**

Conclusions. **Despite the absence of overt microvascular complications, diabetic patients with silent exertional ischemia have evidence of significant autonomic impairment compared with findings in symptomatic patients. This difference is not seen in nondiabetic patients and indicates that subclinical neuropathy is an important cause of silent ischemia in patients with diabetes.**

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Diabetic patients are particularly prone to silent myocardial infarction (1,2), which has been attributed to autonomic neuropathy affecting the sensory innervation of the heart (3,4). Whether silent ischemia is also more prevalent in diabetic patients is uncertain. Some investigators have reported an increased prevalence (5,6), but Callaham et al. (7) found that silent ischemia was no more common in diabetic patients undergoing treadmill stress testing. The role of autonomic neuropathy is also controversial. Thus, although some investigators have reported a relation between silent ischemia and neuropathy in patients with diabetes (8), others have been unable to confirm this (9).

We (10) have previously shown that diabetic patients who experience angina during treadmill stress testing take almost twice as long to develop symptoms after the onset of ST segment depression as do nondiabetic control subjects. In the present study, attention was directed toward patients with silent exertional ischemia during treadmill testing who were compared with symptomatic control subjects. The purpose of the study was to clarify the role of autonomic neuropathy in the pathophysiology of silent ischemia using clinical tests of autonomic function and measures of heart rate variability, which are particularly sensitive to subclinical neuropathic changes in diabetic patients (11–13).

Methods

Ethical approval. The study was approved by the Newham Health District Ethical Committee, and written informed consent was given by all patients.

Patients. Patients were recruited consecutively from those undergoing exercise treadmill testing for the assessment of angina. Any patient who developed ≥0.1 mV of planar or downsloping ST segment depression on exercise treadmill testing was eligible. Patients with diabetes were excluded if there was a history of impotence or postural hypotension or evidence of other microvascular complications (retinopathy or microalbuminuria). Patients with symptoms or clinical signs of peripheral neuropathy or any other neurologic disease or a history of alcohol abuse were also excluded. Normal renal and liver function and hemoglobin

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Table 1. Clinical Characteristics, Exercise Variables and Autonomic Function in Nondiabetic and Diabetic Patients

	Nondiabetic Patients (n = 30)	Diabetic Patients (n = 22)	p Value
Age (yr)	61 ± 2	59 ± 1	0.56
Male patients	23	18	0.92
Single-/multivessel disease	8/22	8/14	0.66
Left ventricular ejection fraction (%)	57 ± 1	56 ± 2	0.74
Time to ischemia (s)	207 ± 20	244 ± 23	0.24
Exercise duration (s)	383 ± 33	355 ± 22	0.97
Autonomic function			
Clinical tests			
Valsalva ratio	1.60 ± 0.06	1.38 ± 0.07	0.007
Supine/standing heart rate ratio	1.15 ± 0.02	1.08 ± 0.02	0.02
Heart rate variation, deep breathing (beats/min)	17.4 ± 1.5	12.1 ± 1.5	0.02
Decrease in systolic pressure, supine/standing (mm Hg)	8 ± 2	8 ± 2	0.98
Increase in diastolic pressure, handgrip (mm Hg)	25 ± 1	21 ± 2	0.15
Heart rate variability			
High frequency (0.15–0.40 Hz) peak (ms)	10.0 ± 1.0	13.0 ± 0.8	0.45
Low frequency (0.04–0.15 Hz) peak (ms)	23.9 ± 2.1	21.8 ± 1.7	0.85
SDANN (ms)	130 ± 7	106 ± 5	0.06
rMSSD (ms)	26.4 ± 3.5	24.8 ± 1.8	0.56
pNN50 (%)	7.0 ± 2.0	5.4 ± 1.0	0.63

Values presented are mean value ± SEM or number. pNN50 = proportion of adjacent RR intervals >50 ms different; rMSSD = root mean square difference of successive RR intervals; SDANN = standard deviation of 5-min mean RR intervals.

levels were confirmed in all cases. The study group comprised 52 patients who fulfilled these criteria. There were 41 men and 11 women, with a mean age of 60 ± 1 years (range 37 to 77).

Study design. Antianginal medication was withdrawn 5 days before the study, but short-acting nitrates were disallowed only on the day of the study. No medication was taken on the morning of the study. Patients underwent an exercise treadmill test, autonomic function tests and assessment of heart rate variability.

Exercise treadmill test. A symptom-limited treadmill test was performed according to the Bruce protocol. A 12-channel electrocardiogram (ECG) was monitored continuously, and blood pressure was recorded at baseline, at the end of each exercise stage, at the onset of ischemia (defined as 0.1 mV of planar or downsloping ST segment depression) and at peak exercise. Exercise was stopped when the patient indicated that the limit of exercise tolerance was reached, or sooner if any of the following occurred: a decrease in systolic blood pressure >10 mm Hg, significant ventricular arrhythmias or >0.5-mV ST segment depression. On the basis of the test, patients were classified into the angina group (those who developed angina during treadmill testing) or the silent ischemia group (those who did not develop angina).

Autonomic function tests. Five standard tests were performed (14) that are known to be repeatable (15): Valsalva ratio, supine/standing heart rate ratio, heart rate variation during deep breathing, systolic blood pressure response to standing from the supine position and increase in diastolic blood pressure with sustained handgrip.

Heart rate variability. Patients underwent 24-h ambulatory ECG (Holter) monitoring for measurement of heart rate variability, which has previously been shown to be repeatable (16,17). Holter monitoring was similarly performed while the patient was taking no antianginal therapy. Recordings were made using a Marquette Series 8000 recorder, and spectral and nonspectral measures of heart rate variability were made using Marquette software.

Coronary angiography and ventriculography. All patients underwent routine coronary angiography to confirm the presence of coronary artery disease, which was quantified by counting the number of main vessels with >75% diameter stenosis. Left ventricular function was calculated from standard contrast ventriculography using the area method.

Statistical analysis. All averaged results are expressed as mean value ± SEM. The angina and silent ischemia groups and the diabetic and nondiabetic patients were compared using the unpaired *t* test for normally distributed variables and by the Mann-Whitney *U* test for other variables (left ventricular ejection fraction, blood pressure measure during treadmill testing, exercise time on treadmill, all measures of heart rate variability, Valsalva ratio and supine/standing blood pressure). The distribution of multivessel coronary artery disease and diabetic patients were compared using the chi-square test. Two-sided p values were considered significant at the 5% level.

Table 2. Clinical Characteristics and Exercis. Variables in the Angina and Silent Ischemia Groups

	Angina Group (n = 36)	Silent Ischemia Group (n = 16)	p Value
Age (yr)	60 ± 2	60 ± 2	0.90
Diabetic patients	12 (33)	10 (63)	0.05
Single-/multivessel disease	10/26	6/10	0.71
Left ventricular ejection fraction (%)	57 ± 1	56 ± 2	0.59
Time to ischemia (s)	200 ± 20	271 ± 20	0.03
Exercise duration (s)	329 ± 22	466 ± 38	0.003
Sum of ST segment depression (mV)	0.80 ± 0.08	0.90 ± 0.23	0.69

Values presented are mean value ± SEM or number (%).

Results

Diabetic versus nondiabetic patients (Table 1). Of the 52 patients included in the study, 22 (42%) were diabetic. There were no differences between the diabetic and nondiabetic patients with regard to age, left ventricular function and severity of coronary artery disease. However, clinical tests showed reduced parasympathetic function in the diabetic patients, and measures of heart rate variability tended to be lower.

Stress testing (Table 2). Although all patients developed ischemia, only 36 (69%) experienced angina (angina group). In the remainder, exertional ischemia was silent (silent ischemia group). The silent ischemia group contained relatively more diabetic patients than did the angina group (33% vs. 63%, p = 0.05), but there were no differences between groups with regard to age, left ventricular function and severity of coronary disease. However, time to ischemia and exercise duration were all significantly greater in the angina group.

Autonomic function testing (Tables 3 and 4). The silent ischemia group showed significant parasympathetic impairment compared with findings in the angina group, as reflected by reductions in the Valsalva and supine/standing heart rate ratios. Parasympathetic impairment in the silent ischemia group was associated with a consistent trend toward reduced heart rate variability. Subgroup analysis (Table 4) showed that these differences in autonomic function between groups were confined to the diabetic patients.

Discussion

Mechanisms of silent myocardial ischemia. There are two main theories to account for silent ischemia. The first is the mass effect, which proposes that a critical amount of myocardium is rendered ischemic before symptoms develop so that patients with less extensive coronary disease are less likely to experience pain. The second is abnormalities in the perception of ischemia, perhaps caused by impairment of nerve conduction in pain pathways (18).

Role of severity of ischemia. In this study of exertional myocardial ischemia, we examined diabetic and nondiabetic patients, all of whom had stable angina. To study a homogeneous group of diabetic patients, we were careful to exclude those with microvascular complications. We found an excess of diabetic patients among the group that experienced no angina during treadmill stress testing. However, the severity of coronary artery disease was no less severe in diabetic than in nondiabetic patients or in the silent ischemia compared with the angina group. Indeed, in the diabetic patients, ST segment depression tended to occur earlier during treadmill stress testing, suggesting that ischemia in this group may be more severe than in nondiabetic patients. It is unlikely therefore that any propensity to silent ischemia in the patients with diabetes was due to a smaller mass of ischemic myocardium.

Role of impaired perception. If silent ischemia in diabetes cannot be explained by the theory of ischemic mass, perceptual abnormalities provide a likely alternative. Patients with diabetes frequently have impaired nerve conduction due to

Table 3. Autonomic Function in the Angina and Silent Groups

Autonomic Function	Angina Group (n = 36)	Silent Ischemia Group (n = 16)	p Value
Clinical tests			
Valsalva ratio	1.56 ± 0.05	1.40 ± 0.09	0.08
Supine/standing heart rate ratio	1.15 ± 0.02	1.05 ± 0.02	0.002
Heart rate variation, deep breathing (beats/min)	15.9 ± 1.2	13.6 ± 2.4	0.30
Decrease in systolic pressure, supine/standing (mm Hg)	8.6 ± 1.3	7.6 ± 2.6	0.70
Increase in diastolic pressure, handgrip (mm Hg)	24.7 ± 1.3	21.9 ± 1.8	0.32
Heart rate variability			
High frequency (0.15–0.40 Hz) peak (ms)	10.4 ± 0.8	9.4 ± 1.2	0.43
Low frequency (0.04–0.15 Hz) peak (ms)	24.3 ± 1.8	19.9 ± 1.7	0.23
SDANN (ms)	123 ± 6	111 ± 8	0.23
rMSSD (ms)	27.2 ± 2.7	22.2 ± 2.6	0.12
pNN50 (%)	7.0 ± 1.5	4.8 ± 1.9	0.10

Values presented are mean value ± SEM. Abbreviations as in Table 1.

Table 4. Autonomic Function in the Angina and Silent Groups of Diabetic and Nondiabetic Patients

	Diabetic Patients			Nondiabetic Patients		
	Angina Group (n = 12)	Silent Ischemia Group (n = 10)	p Value	Angina Group (n = 24)	Silent Ischemia Group (n = 6)	p Value
Age (yr)	59 ± 2	60 ± 2	0.62	61 ± 2	60 ± 5	0.76
Autonomic function						
Clinical tests						
Valsalva ratio	1.47 ± 0.08	1.28 ± 0.11	0.11	1.60 ± 0.07	1.61 ± 0.12	0.90
Supine/standing heart rate ratio	1.14 ± 0.03	1.01 ± 0.02	0.003	1.16 ± 0.02	1.13 ± 0.02	0.28
Heart rate variation, deep breathing (beats/min)	13.8 ± 2.0	10.1 ± 2.3	0.23	16.9 ± 1.5	19.5 ± 4.3	0.48
Decrease in systolic pressure, supine/standing (mm Hg)	6.9 ± 1.8	10.2 ± 3.4	0.38	9.5 ± 1.7	3.3 ± 3.5	0.13
Increase in diastolic pressure; handgrip (mm Hg)	22.5 ± 2.9	19.1 ± 3.4	0.50	25.2 ± 1.5	23.9 ± 1.6	0.71
Heart rate variability						
High frequency (0.15–0.40 Hz) peak (ms)	11.5 ± 1.2	8.4 ± 0.8	0.06	9.8 ± 1.0	11.4 ± 3.3	0.65
Low frequency (0.04–0.15 Hz) peak (ms)	24.6 ± 2.5	18.4 ± 1.9	0.11	24.1 ± 2.5	22.8 ± 3.4	1.00
SDANN (ms)	110 ± 4	102 ± 10	0.15	130 ± 8	130 ± 14	0.77
rMSSD (ms)	28.7 ± 2.6	20.1 ± 1.9	0.01	26.4 ± 4.0	26.5 ± 6.8	0.95
pNN50 (%)	7.48 ± 1.36	3.01 ± 0.97	0.01	6.65 ± 2.19	8.24 ± 5.21	1.00

Values presented are mean value ± SEM. Abbreviations as in Table 1.

microvascular disease, and postmortem studies have associated silent myocardial infarction with neuropathic changes in intracardiac sympathetic and parasympathetic afferent fibers (4). However, clinical evidence for an association between silent myocardial ischemia and neuropathy has been conflicting. Langer et al. (8) studied 58 patients with diabetes and no clinical evidence of cardiac disease and found that myocardial perfusion defects on thallium scintigraphy were more common in those with impaired autonomic function. In contrast, Nesto et al. (5), although confirming a high prevalence of silent exertional ischemia in diabetic patients with abnormal thallium scintigrams, could find no difference in microvascular complications between the silent ischemia and symptomatic subgroups.

Diabetic versus nondiabetic patients. In the present study, evaluation of autonomic function utilized not only bedside techniques but also measures of heart rate variability, which are particularly sensitive to early neuropathy in diabetes (12). We found significant abnormalities of autonomic function in the patients with silent ischemia, as reflected by reductions in the Valsalva and supine/standing heart rate ratios. In addition, there was a consistent trend toward reduced heart rate variability on Holter monitoring. However, the data in Table 4 clearly show that the autonomic abnormality in the patients with silent ischemia was confined to the diabetic subgroup. In the latter, the parasympathetic defect on standard bedside testing was associated with significant reductions in parasympathetic indexes of heart rate variability (low frequency spectral peak, root mean square of difference of successive RR intervals and the proportion of adjacent RR intervals >50 ms different) compared with findings in the symptomatic patients. In contrast, in the nondiabetic subgroup, autonomic function was generally better preserved and showed no tendency toward impairment in those who experienced no symptoms.

Conclusions. This study showed that despite the absence of overt microvascular complications, diabetic patients with silent exertional ischemia have evidence of significant autonomic impairment compared with findings in symptomatic patients. This difference is not seen in nondiabetic patients and indicates that subclinical neuropathy is an important cause of silent ischemia in patients with diabetes.

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