

IS THERE COINCIDENCE BETWEEN IMPAIRED GLUCOSE TOLERANCE AND SILENT MYOCARDIAL ISCHEMIA?

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Key words: impaired glucose tolerance, silent myocardial ischemia, adults

SUMMARY

The aim of the study was to estimate the rate of coincidence of silent myocardial ischemia episodes with impaired glucose tolerance in patients treated at Outpatient Cardiology Clinic. The study included 93 patients divided into two groups according to the glucose tolerance test results. Study group included 48 subjects with impaired glucose tolerance, while the remaining 45 patients served as a control group. Besides oral glucose tolerance test, anthropometric and clinical characteristics and biochemical analyses were recorded in all study subjects. The patients underwent clinical examination, blood pressure measurement and twelve-lead electrocardiogram (ECG) at rest. Silent myocardial ischemia episodes were recorded during exercise test and Holter 24-h ECG. The mean glucose concentration in venous blood showed significant between-group difference ($p < 0.001$). Holter ECG recording indicated ten (20.8%) study group patients and three (6.6%) control

group patients to have developed episodes of silent myocardial ischemia. The number and duration of silent myocardial ischemia episodes were significantly greater in the study group. Silent myocardial ischemia episodes occurred significantly more often among patients with impaired glucose tolerance in comparison with those with normal glucose tolerance.

INTRODUCTION

The phenomenon of silent myocardial ischemia (SMI) deserves special observation among the miscellaneous variants of the ischemic heart disease because its mechanism and range of occurrence are not yet fully known. Silent ischemia is transient myocardial ischemia revealed by objective diagnostic tests and taking course with neither coronary (retrosternal) pain nor its equivalents like dyspnea, short breath, pressure or discomfort in the chest. Typical changes on electrocardiogram (ECG) during exercise test or on Holter ECG recording, abnormality of myocardial perfusion caught on isotope radiography tests or disturbance of kinetics of the particular walls visible during ultrasound cardiography are considered to be the objective expressions of the ischemia (1,2).

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To make the diagnosis and to estimate the risk of sudden coronary incidents easier, in the early 1980s Cohn proposed a classification of the states of silent ischemia as follows (3): type I – completely asymptomatic patients (about 4%-5% of the whole asymptomatic population); type II – asymptomatic patients after myocardial infarction in the past (painless ischemia in about 30% of patients); and type III – patients with coronary pains and episodes of silent ischemia (most of the patients with ischemic heart disease).

Patients belonging to type I are those that had been diagnosed accidentally during routine control tests as having incidents of silent ischemia. They had never suffered from typical retrosternal symptoms or myocardial infarction. In this group, the risk of occurrence of symptomatic myocardial ischemia and sudden myocardial death is 3- to 5-fold that in healthy population. Considering the lack of typical cardiologic history, this group should be initially qualified on the grounds of the risk factors that can make the identification easier. The gold standard of Framingham tests (4) is obligatory in this case. It includes increased levels of total cholesterol and its LDL fraction, decreased level of HDL fraction, increased blood pressure, cigarette smoking, diabetes, patient age (considered mainly in the category of exposure to risk factors) as the basic risk factors for myocardial ischemic disease. Little by little, abdominal obesity, lack of physical activity, positive family history, and ethnic and psychosocial factors have been added to this list. Ever more attention has been paid to the role of carbohydrate metabolism abnormality in the etiopathogenesis of SMI (5-8).

About 20% of persons with ischemic myocardial disease show metabolic disturbances like fasting hyperglycemia and reactive (postprandial) or constant (diabetes) hyperglycemia. It has been ascertained that individuals with fasting plasma glucose levels closer to the upper limit of the arbitrarily normal glycemia range have a higher morbidity rate of myocardial ischemic disease in comparison with those with lower glycemia values.

Whitehall Study was one of the first studies demonstrating dependence between the increased risk of coronary disease and mortality and elevated glycemia level (9). Similar results reported from another prospective study, Funagata Diabetes Study, pointed to the effect of impaired glucose tolerance (IGT) on the risk and increased morbidity of myocardial ischemic disease (10).

Then DECODE study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) carried out in 25,000 subjects showed that fasting glycemia of 7 mmol/L did not increase the risk of acute coronary events and death due to coronary reasons in comparison with hyperglycemia of 11.1 mmol/L found in the second hour of the glucose tolerance test in a statistically significant manner (11). Therefore, the question whether disturbances of myocardial perfusion occur in people with IGT in spite of negative clinical history seems to be interesting enough.

The aim of the study was to try to answer the following question: are the incidents of SMI more common in people with IGT than in those free from IGT?

PATIENTS AND METHODS

The study population included 93 patients treated at Outpatient Cardiology Clinic in Silesia between 2001 and 2003. The subjects were recruited during prophylactic examination and included according to the following criteria: 1) fasting glycemia <126 mg/dL (without any abnormalities of carbohydrate metabolism diagnosed before); 2) normal ECG recording at rest; 3) no symptoms and negative history of ischemic heart disease; 4) no other heart disease (cardiomyopathy, valvuloplasty, etc.); and 5) no positive family history of diabetes, ischemic heart disease, obesity or hyperlipidemia. Patients were divided into two groups according to glucose tolerance test results: group 1 (study group) with IGT consisting of 48 subjects, 28 male and 20 female, mean age 52.7 ± 9.0 ; and group 2 (control group) without IGT

Table 1. Anthropometric and clinical characteristics of study group and control group patients

	Study group (n=48)	Control group (n=45)	P-value
Age (yrs)	52.7±9.04	50.8±10.3	NS
Sex (male/female)	28/20	26/19	NS
Body mass (kg)	78.2±11.6	73.1±16.7	NS
Body mass index (kg/m ²)	27.5±4.1	26.0±4.88	NS
Fasting glycemia (mg/dL)	119.2±5.4	91.1±6.8	P<0.001
HbA _{1c}	5.4±0.32	4.91±0.21	NS
Hemoglobin (mmol/L)	8.42±0.13	8.26±0.34	NS
Platelets (x10 ³ /μL)	225±65.3	211±45.8	NS
Systolic blood pressure (mm Hg)	129±10	127±11	NS
Diastolic blood pressure (mm Hg)	78±9	74±10	NS
Heart rate	77.2±7.7	75.7±9.4	NS

consisting of 45 subjects, 26 male and 19 female, mean age 50.8±10.3. Characteristics of both groups are shown in Table 1.

An individual patient card was prepared to collect all necessary data and to enter biochemical and cardiologic results.

Day 1

Thorough history was taken from each subject before qualification for the test. Each patient underwent clinical examination, blood pressure measurement (after minimum 10 min of initial examination) with mercury sphygmomanometer and twelve-lead ECG at rest. Anthropometric measurements included body mass index (BMI) expressed as quotient of body mass and second power of height.

Day 2

Fasting venous blood samples were obtained for laboratory tests of erythrocyte sedimentation rate (ESR), smear morphology, electrolytes, transaminases, glucose, glycosylated hemoglobin, total cholesterol and its fractions, triglycerides, uric acid, creatinine and general urine test.

Next day – assigned term of examination

Fasting glucose load test with 75 g of glucose (diluted in 250-300 mL of water) was done. Venous blood glucose level was measured in fasting state and after 120 min.

Next days

Exercise test on moving track and Holter ECG recording (24-h) were performed at the outpatient

clinic according to appointments. When all test results were collected, the patient was considered to have completed the study. Resting 12-lead ECG was recorded using Ascard 33 Aspel on graph paper, tape speed 50 mm. The record was evaluated according to the Minnesota code.

Exercise test with 50 W load increase every 3 min on Trackmaster moving track was performed using an M-14W monitor and Ascard 3 Aspel electrocardiograph for registration. Diagnostic evaluation was based on Bruce's protocol. Blood pressure was monitored every three minutes during the test. The test was considered diagnostic if the patient attained a rate of acceleration corresponding to 85% of maximal heart rate standard for sex and age (Sheffield modification). The quantity of strain made on moving track was evaluated in MET (metabolic equivalent). MET corresponds to oxygen consumption at rest that is equal to 3.5 mL/kg body weight/min. The increase in blood pressure and pulse rate from baseline values was estimated.

Holter ECG was done by 24-hour recording using an MR63 three-channel tape-recorder. Reading was done with the help of a computer unit working in Suprima system (Oxford) with medical verification of the results.

The maximal, minimal and average heart rate, and type and frequency of heart rate disorders were qualified and the parameters of SMI episodes evaluated. Horizontal or slanting down ST segment depression exceeding or equal to 1 mm at a distance of

70 ms from point J lasting for at least 1 min and occurring without retrosternal pain or its equivalents was considered as SMI episode.

Results were statistically processed using the Statistica software.

RESULTS

Group 1 patients (study group) were comparable with group 2 (control group) patients according to anthropometric, clinical and biochemical features (Tables 1 and 2). Glucose, total cholesterol, LDL-cholesterol and triglyceride concentrations in venous blood were higher in group 1 patients in comparison with group 2 patients (mean 119.2 ± 5.4 vs. 91.1 ± 6.8 mg/dL; $P < 0.001$ and 6.09 ± 1.38 vs. 5.9 ± 0.91 mmol/L; 3.78 ± 1.23 vs. 3.56 ± 1.12 mmol/L; 1.91 ± 0.91 vs. 1.59 ± 0.78 mmol/L) (Tables 1 and 2). The values of mean resting systolic and diastolic blood pressure and heart rate were comparable in the groups (Table 1). Positive exercise test was found in 13 (27.1%) group 1 patients and four (8.8%) control group patients

($P < 0.05$). In both groups, interruption of exercise test was caused by attaining pulse rate limit or impaired ability of finishing exercise test (Table 3). There were no significant between-group differences in the range of mean, minimal and maximal heart rate, ventricular and supraventricular ectopic beats found on Holter ECG recordings. In both groups, ventricular ectopic beats were in class I and II according to Lown and Wolf (Table 4). All Holter ECG recorded episodes of ST segment depression were silent (Table 5). SMI episodes occurred in 10 (20.8%) study group patients and three (6.6%) control group patients ($P < 0.05$)

Table 3. Results of exercise test on moving track (Trackmaster) with 50 W load increase every 3 min in study group and control group patients

	Study group (n=48)	Control group (n= 45)
Negative test	26 (54.1%)	36 (75%)
Positive test	13 (27.1%)	4 (8.8%)
Reduced ability of completing exercise test	9 (18.7%)	5 (11.1%)

Table 2. Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and uric acid levels in study group and control group patients

	Study group (n=48)	Control group (n=45)	P-value
Total cholesterol (mmol/L)	6.09 ± 1.38	5.9 ± 0.91	NS
HDL-cholesterol (mmol/L)	1.29 ± 0.79	1.41 ± 0.77	NS
LDL-cholesterol (mmol/L)	3.78 ± 1.23	3.56 ± 1.12	NS
Triglycerides (mmol/L)	1.91 ± 0.91	1.59 ± 0.78	NS
Uric acid (μ mol/L)	245 ± 83	229 ± 54	NS

Table 4. 24-hour ECG monitoring (Holter method) in study group and control group patients (mean \pm SD)

Parameter	Study group	Control group	P-value
Average heart rate	77.2 ± 6.52	73.9 ± 7.72	NS
Minimal heart rate	50.6 ± 6.3	53.1 ± 7.3	NS
Maximal heart rate	125 ± 16.7	119 ± 20.4	NS
Ventricular extrasystole	24.4 ± 77	19.5 ± 81	NS
Supraventricular extrasystole	145.6 ± 432	121 ± 301	NS

Table 5. Silent myocardial ischemia (SMI) severity in study group and control group patients

Parameter	Study group	Control group	P-value
Max ST segment depression	1.76 ± 0.39	1.59 ± 0.26	NS
SMI persisting time (min/24 h)	39 ± 24	3 ± 2	0.001
Number of SMI episodes	18 ± 9	4 ± 2	0.001
Number of SMI episodes: 1 min (n/24 h)	10 ± 6	2 ± 1	0.001
Number of SMI episodes: 2-4 min (n/24 h)	6 ± 2	2 ± 1	0.001
Number of SMI episodes: >5 min (n/24 h)	2 ± 2	0	0.004
Duration of longest SMI episode (min)	10 ± 4	2 ± 1	0.002
Number of patients with SMI registered on Holter ECG	10 (20.8%)	3 (6.6%)	0.05

(Table 5). The number of SMI episodes irrespective of duration was significantly greater in the study group of patients.

DISCUSSION

Silent myocardial ischemia is a phenomenon observed and examined quite often in the last 25 years. Group 1 patients according to Cohn classification appear to pose a diagnostic problem, considering that in this patient population the diagnosis of silent ischemia is a matter of coincidence rather than planned procedure expected to explain the pathogenesis of retrosternal pain. It is obvious that it occurs more often in patients with diabetes, although its conditioning is not known yet. Some literature reports suggest that a higher risk of cardiovascular complications may develop years before the diagnosis of diabetes (12,13).

Diabetic patients are particularly liable to suffer from cardiac complications in comparison with the general population. Diabetic metabolic disorders and a higher frequency of hypertension are the reasons for the high risk of atherosclerosis including coronary atheromatosis (14). SMI episodes recorded in patients with metabolic disturbances such as IGT may have important prognostic implications. Kuch and Mamcarz report on the frequency of SMI events in diabetic patients on Holter test to be about 30% versus 10% in control group (non-diabetic patients) (2). Similar results were obtained by other authors (15,16), however, only few investigators analyzed the occurrence of SMI in subjects with IGT. Many previous data have shown the risk of coronary heart disease to be twofold in patients with IGT (10,17).

Our study revealed that subjects with IGT displayed significantly higher susceptibility to SMI than the control group on both exercise test (27.1% vs. 8.8%) and Holter ECG recording (20.8 vs. 6.6%). The results of exercise test obtained in our study exceeded those

reported by Kuusisto *et al.* comparing similar groups of subjects (7). In this group, total SMI duration was longer (39±24 vs. 3±2 min/24 h) and total number of SMI events *per day* greater (18±9 vs. 4±2; $P<0.001$). At the same time, the higher percentage of patients with SMI in the study group, the longer duration and the greater number of episodes of ST segment depression might suggest intensification of ischemia in these subjects.

There is a lack of information on the real prevalence of SMI and its prognostic value in patients with IGT from available sources (17).

Our study pointed to this important problem and to the need of additional research. We do not know whether there is a specified level of SMI intensity (number of episodes, total duration time, profoundness of ST segment depression) that could be diagnostic and prognostic in patients with no coronary heart disease symptoms but with its risk factors. At the same time, the possibility to identify this particular group of patients at a regional outpatient cardiology clinic appears to be very relevant indeed.

CONCLUSIONS

- SMI episodes appeared significantly more frequently in patients with IGT than in the control group.
- Asymptomatic patients with irregular glucose tolerance test ought to consult a cardiologist to estimate the level of their cardiovascular risk.
- Positive results of exercise test on moving track were significantly more frequently recorded in patients with IGT.
- The possible tendency of higher occurrence of the silent ischemia phenomenon in patients with IGT suggests the necessity of introducing the rules of primary prevention in all subjects from this group in order to decrease their cardiovascular risk.

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