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SILENT MYOCARDIAL ISCHEMIA IN ASYMPTOMATIC PATIENTS WITH MULTIPLE CORONARY RISK FACTORS

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Summary. *Myocardial ischemia which occurs in the absence of chest pain or its equivalents (silent myocardial ischemia) is common in patients with coronary artery disease. Silent myocardial ischemia may also be found in asymptomatic patients, particularly those with underlying risk factors. It is important for physicians to identify the existence of silent myocardial ischemia because it is predictive of increased cardiac risk.*
Objective: To evaluate the frequency and characteristics of silent myocardial ischemia in asymptomatic patients with multiple coronary risk factors ("high coronary risk" patients).
Methods: *Study group consisted of 360 male pts (age from 35 to 70 years) with multiple coronary risk factors free of previously diagnosed coronary artery disease. In study pts the most frequent risk factors for coronary artery disease were arterial hypertension (74%) and cigarette smoking (60%). In all pts maximal, or ST segment depression of ≥ 0.2 mV or symptom-limited exercise test was performed. In those with ST-segmant depression on exercise electrocardiogram, stress echocardiography was additionally performed in order to confirm myocardial ischemia.*
Results: *Out of 360 patients 290 (81%) patients had neither ST-segment depression nor anginal pain during exercise stress testing, 52 (14%) patients had ischemic type of ST-segment depression on exercise electrocardiogram without chest pain and 18 (5%) patients had ischemic ST-segment depression and the first occurrence of chest pain (symptomatic myocardial ischemia). All patients with symptomatic myocardial ischemia had an echocardiographic marker for ischemia but out of 52 patients with asymtpomatic ST-segment depression 43 patients had echo markers for ischemia (silent miocardial ischemia), while in 9 patients stress echocardiography was without regional wall motion abnormality (false positive exercise electrocardiogram). Thus both types of myocardial ischemia were recorded in 61 (17%) "high coronary risk" patients (12% silent and 5% symptomatic myocardial ischemia). There were no significant difference in regard to magnitude and duration of ST-segment depression and exercise tolerance between patients with symptomatic and silent myocardial ischemia, but wall motion score index was bigger in patients with symptomatic than in those with silent myocardial ischemia (P<0.01).*
Conclusion: *This study showed that in 12% of asymptomatic "high coronary risk" patients silent myocardial ischemia during exercise test was found. There were no differences between two types of myocardial ischemia in the exercise electrocardiogram but symptomatic ischemia had a higher degree of wall motion abnormality on stress echo than silent myocardial ischemia.*

Key words: *Silent myocardial ischemia, echocardiography stress test, coronary risk factors*

Introduction

Traditionally, angina has been relied upon as the hallmark presentation of patients who come to clinical attention with coronary artery disease. However, numerous studies in the past few years clearly demonstrated that silent myocardial ischemia is the common manifestation of coronary artery disease (1-4).

Silent myocardial ischemia occurs when there is objective evidence of myocardial ischemia in the absence of anginal pain or equivalents of anginal pain (dyspnea, fatigue or syncopa). It has been demonstrated that chest discomfort is the last event in the chain of ischemic changes. Generally speaking, abnormalities of left ventricular function and ischemic electrocardiographic changes precede such pain.

Up to 50% of patients having a coronary artery disease may have evidence of silent myocardial ischemia (2). Importantly, even in patients with a history of angina, it is estimated that up to 75% of ischemic episodes are silent during daily activities. It is clear that the presence of ischemia per se, regardless of whether or not it is accompanied by pain, that determines the clinical outcome in patients with coronary artery disease (2-4).

Exercise electrocardiogram is the preferred screening technique for diagnosis of silent myocardial ischemia. Although moderately sensitive in detecting coronary artery disease, exercise testing has an unacceptably

high false positive rate. Thus, silent myocardial ischemia suspected on the basis of exercise screening must be subsequently confirmed with radionuclide imaging techniques (perfusion scintigraphy or exercise ventriculography) or stress echocardiography. We previoulsly proposed a guidelines for detecting of silent myocardial ischemia in asymptomatic "high coronary risk" patients (Figure 1) (5,6).

Aim of the study

The purpose of this study was to evaluate the frequency and characteristics of silent myocardial ischemia in asymptomatic patients with "high coronary risk".

Methods

Patients selection. We studied 360 asymptomatic male patients (age from 35 to 70 years) with multiple coronary risk factors (more than 20% absolute risk for coronary heart disease over ten years) according to Framingham criteria (7) or an absolute risk of fatal cardiovascular disease more than 5%, according to the SCORE (Systemic Coronary Risk Evaluation) chart (8) free of previous diagnosed coronary artery disease. Patients with congestive heart failure and conduction disturbances were excluded from the study. In study patients most frequent risk factors for coronary artery disease were arterial hypertension (74%) and cigarette smoking (60%), Table 1.

Table 1. Patients population

Mean age (years)	52.8 ± 8.4
Male sex	360 (100%)
Arterial hypertension	266 (74%)
Cigarette smoking	216 (60%)
Diabetes	80 (22%)
Hypercholesterolemia	135 (38%)
Three or more risk factors	244 (68%)

Exercise testing. All patients underwent exercise testing, which performed on an electricaly braked bicycle ergometer in the upright position. Exercise was started at 25 watts and was increased by 25 watts every four minutes. Continuous ECG monitoring was displayed on an oscilloscope throughout of the test. Test was terminated if one of the following criteria were met: attainment of age predicted maximal heart rate; occurence of ≥ 0.2 mV horisontal or downsloping ST-segment depression without anginal pain or occurence of anginal pain which increased with further exercise.

In patients with ST-segment depression ≥0.1mV stress echocardiography was additionally performed in order to confirm myocardial ischemia (Figure 1). For analysis of segmental kinetic - left ventricle was divided in 11 segments. Segmental kinetic was assessed semiquantitatively and graded as – normokinesis, hypokinesis, akinesis and dyskinesis (from 1 to 4 for every segment) before and after test. Index of wall motion score was calculated when summa of all segments was divided with their number (9). Criterion for myocardial ischemia was appearance of transient segmental wall motion abnormality.

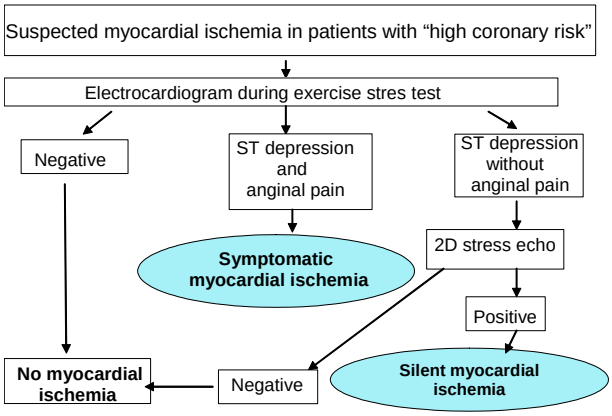

Fig. 1. Guidlines for detecting silent myocardial ischemia in asymptomatic "high coronary risk" patients

Results

Frequency of silent myocardial ischemia

During exercise stress test in the most of patients (81%) no ST-segment depression nor anginal pain were found. In 52 (14%) patients only ST-segment depression was recorded (asymptomatic ST-segment depression) and in the smollest group of patients (5%) both ST-segment depression and anginal pain (first occurence of pain) were detected (Figure 2).

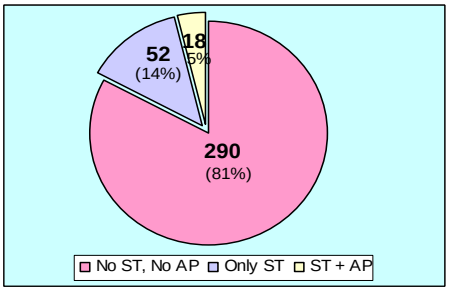

Fig. 2. Exercise findings in asymptomatic "high coronary risk" patients
ST- ST depression; AP – anginal pain

In all patients with both ST-segment depression and anginal pain myocardial ischemia was confirmed on stress echocardiography (symptomatic myocardial ischemia). Out of 52 patients with ST-segment depression on exercise electrocardiogram but without anginal pain in 43 patients on stress echocardiography signs for myocardial ischemia were found (silent myocardial ischemia) while in 9 patients stress echocardiography was without regional wall motion abnormality (false positive exercise electrocardiogram). Thus both types of

myocardial ischemia were recorded in 61 (17%) "high coronary risk" patients (12% silent and 5% symptomatic myocardial ischemia) and in 299 (83%) patients myocardial ischemia was not found (Figure 3).

Out of 43 patients with silent myocardial ischemia 15 have diabetes (35%) and out of 18 patients with symptomatic myocardial ischemia only 3 have diabetes (17%).

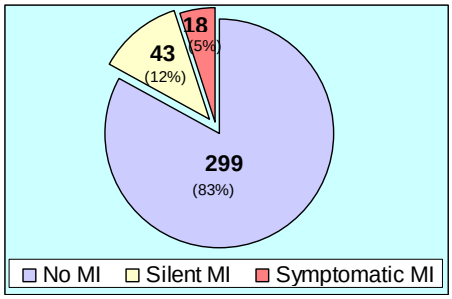

Fig. 3. Frequency of both types of myocardial ischemia in "high coronary risk" patients on stress tests
MI – myocardial ischemia

Some characteristics of silent myocardial ischemia

Magnitude of ST segment depression (expressed as mean value of ST segment depression in all electrocardiographic leads) did not differ significantly among groups of patients with symptomatic and silent myocardial ischemia (Figure 4).

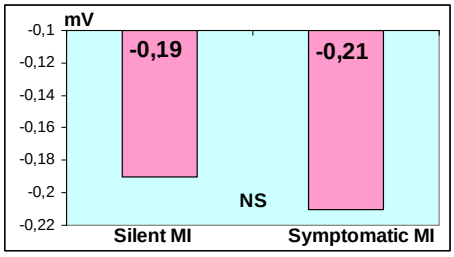

Fig. 4. Mean value of magnitude of ST segment depression in patients with symptomatic and silent myocardial ischemia (MI)

Level of exercise test, when test was terminated, in group of pateinets with silent myocardial ischemia was slightly bigger than in patients with symptomatic myocardial ischemia, but this difference was not statisticaly significant (Figure 5).

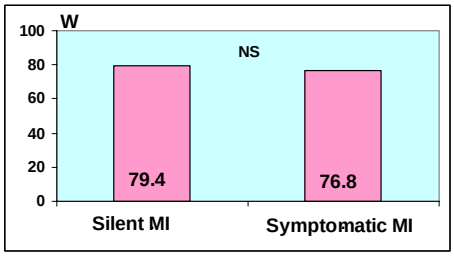

Fig. 5. Exercise tolerance in patients with silent and symptomatic myocardial ischemia (MI)

Other exercise stress test variables: duration of exercise, heart rate (HR) at onset of ST segment depression ≥ 0.1 mV, time to onset of ST segment depression ≥ 0.1 mV and double product (DP) at the end of exercise test, were not significantly different between patients with silent and patients with symptomatic myocardial ischemia (Table 2).

Table 2. Some exercise variables of silent and symptomatic myocardial ischemia on exercise testing

Parameters	Silent myocardial ischemia	Symptomatic Myocardial ischemia	P
Duration of exercise (min)	13.2± 2.8	12.6± 2.3	NS
HR at onset of ST↓ (≥ 0,1 mV)	119.3±12.1	118.2±13.4	NS
Time to onset ST ↓ (≥ 0,1mV)	11.5± 3.5	10.9± 3.8	NS
DP at the end of exercise test	209 ±45.6	211.8±42.3	NS

Wall motion score index (WMSI) was significantly bigger in patients with symptomatic than in patients with silent myocardial ischemia (Figure 6).

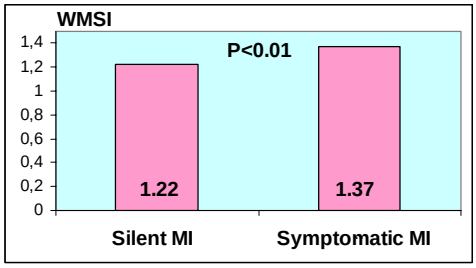

Fig. 6. WMSI in patients with symptomatic and silent myocardial ischemia (MI) on echo stress test

Discussion

Many studies in past two decades showed that silent myocardial ischemia is frequent type of ischemia during exercise test or everyday activities in patients with angina and in patients after myocardial infarction (10,11). Frequency of silent myocardial ischemia in asymptomatic population is not known. Discovering of myocardial ischemia in asymptomatic patients is very important for early prevention of cardiovascular events. Exercise electrocardiogram as the first screening test for myocardial ischemia in asymptomatic population is moderately sensitive and has an unacceptably high false positive rate. Thus, silent myocardial ischemia suspected on the basis of exercise screening must be subsequently confirmed with radionuclide imaging techniques or stress echocardiography. Screening all population by exercise testing is very expensive and theoreticaly, prevalence of myocardial ischemia is more frequent in asymptomatic persons with two or more coronary risk factrors.

In order to detect silent myocardial ischemia in asymptomatic patients with multiple coronary risk factors (more than 20% absolute risk for coronary heart disease over ten years or an absolute risk of fatal cardiovascular

disease more than 5%) we performed exercise electrocardiogram as the first test and if ST segment depression was found, exercise 2D echocardiogram was additionaly performed for confirming myocardial ischemia. On exercise electrocardiogram 290 (81%) patients have no ST-segment depression nor anginal pain, 52 (14%) patients have only ST-segment depression and 18 (5%) have both ST- segment depression and anginal pain (first occurence of pain and first detection of symptomatic myocardial ischemia). Silent myocardial ischemia was confirmed on 2D stress echocardiography in 43 (12%) patients while in 9 patients stress echocardiography was without regional wall motion abnormality (false positive exercise electrocardiogram). Thus both types of myocardial ischemia were recorded in 61 (17%) of examined patients (12% silent and 5% symptomatic myocardial ischemia) and in 299 (83%) patients myocardial ischemia was not found.

Why certain episodes of ischemia are associated with angina, while others are silent, remains unknown. Individual manifestations of myocardial ischemia follow a consistent temporal course with abnormalities of myocardial relaxation occurring first, followed by abnormalities in contraction, ST- segment changes, and ultimately, but not necessarily, the perception of angina. Some studies suggest that episodes of asymptomatic ischemia simply represent less severe ischemia in which the "anginal threshold" is not reached (12,13). Other studies indicate that symptomatic and silent ischemic episodes are similar in all respects, including duration or depth of ST segment depression during ambulatory electrocardiography monitoring, magnitude of reversible thallium defects during exercise testing, and number and severity of coronary obstructions (14,15). In our study, exercise test parameters were not significantly different between patients with silent and symptomatic myocardial ischemia (magnitude of ST segment depression, level of exercise test, duration of exercise, heart rate at onset of ST segment depression $\geq$ 0.1 mV, time to onset of ST segment depression $\geq$ 0.1 mV and double product at the end of exercise test). However, wall motion score index on stress echocardiography was significantly bigger in patients with symptomatic than in patients with silent myocardial ischemia. It can be supposed that bigger wall motion score index represents more severe ischemia.

Differences in the magnitude of ischemia can not adequately account for the presence or absence of anginal pain. Different neurohumoral mechanisms may be responsible for the presence or absence of symptoms associated with myocardial ischemia. Myocardial pain is provoked when afferent nerve fibers are activated by noxious stimuli (16). Afferent impulses travel through the cardiac sympathetic nerves and sympathetic ganglia to the dorsal roots at upper thoracic levels. These impulses, together with some sensory innervation that travels along the vagus nerves, are conducted to the thalamus and cerebral cortex.

Disorders of peripheral autonomic nerves have been considered responsible for silent ischemia in some patients, such as diabetics. There are conflicting observations in diabetic patients. Diabetics are reported to have a higher prevalence of asymptomatic ischemia during exercise testing or holter monitoring than nondiabetics (17,18). However, other experience indicates that diabetics may have similar silent ischemia than nondiabetics (19). Although peripheral neuropathy may be responsible for the lack of angina perception in a small number of patients, it is not responsible for the inconsistency of angina perception in the majority of coronary patients. In our study, in diabetic patients silent myocardial ischemia was more frequently than in those without diabetes.

A number of studies have shown that patients whose myocardial ischemia is silent have a more generalized disorder of pain perception (20). Increased beta-endorphin levels, naturally ocurring opiates, have been demonstrated in patients with asymptomatic myocardial ischemia during exercise (21). However, the failiure of naloxone to initiate chest pain during exercise-induced asymptomatic ST segment depression suggests that endorphins do not have much influence (22).

A recent study using PET brain scanning of nondiabetic patients with exercise induced ischemia may explain why some episodes of ischemia are asymptomatic (23). Bilateral activation of the thalamus was similar both in patients who experienced angina during ischemia, and in those whose ischemia was silent (23). The patients with silent ischemia had significantly less cortical activation, compared to those who experienced angina . These findings showed that afferent stimuli from the heart reach the central nervous system even if ischemia is not perceived as angina. The lack of perception of anginal pain appears to be related to abnormal central processing of afferent pain messages from the heart. According to the "gate theory," nonmyocardial factors may exert a critical influence on the central processing of afferent stimuli. Further investigations are necessary to determine certain factors which are responsible for perception of angina.

Our study clearly confirm that silent myocardial ischemia was common in high coronary risk patients. Nevertheless, silent myocardial ischemia is not benign ischemia and have similar prognostic implication as symptomatic ischemia (24,25). Therefore, it is necessary for searching of silent myocardial ischemia in every patient with multiple coronary risk factors.

Conclusion

This study showed that in asymptomatic "high coronary risk" patients the incidence of silent myocardial ischemia amounted to 12% during the exercise test.

Silent myocardial ischemia was more frequent than symptomatic myocardial ischemia (first occurrence) in asymptomatic patients with multiple coronary risk factors.

There were no significant differences between two types of myocardial ischemia in the exercise electrocardiogram but symptomatic ischemia had a higher degree of wall motion abnormality on stress echo than silent myocardial ischemia.

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ASIMPTOMATSKA MIOKARDNA ISHEMIJA U ASIMPTOMATSKIH OSOBA S MULTIPNIM KORONARNIM FAKTORIMA RIZIKA

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Kratak sadržaj: *Miokardna ishemija koja nije prećena anginoznim bolom ili ekvivalentima anginoznog bola (asimptomatska miokardna ishemija) je česta u bolesnika sa stabilnom i nestabilnom anginom pektoris, kao i u bolesnika s preživljenim infarktom miokarda. Takodje, asimptomatska miokardna ishemija se može otkriti i u asimptomatskih bolesnika s većim brojem faktora rizika za koronarnu bolest.*

Cilj rada je odrdjivanje učestalosti i karakteristika asimptomatske miokardne ishemije u osoba bez simptoma miokardne ishemije i bez ranije dijagnostikovane koronarne bolesti, ali s multipnim koronarnim faktorima rizika.
U grupi od 360 muških osoba (starosti izmedju 35 i 70 godina) sa većim brojem faktora rizika (rizikom većim od 20%) za ishemijsku bolest srca (najčešći faktori rizika su bili arterijska hipertenzija – 74% i pušenje duvana – 60%) uradjen je test fizičkim opterećenjem maksimalnog tipa ili je test bio limitiran pojavom simptoma sa ST depresijom ili samo pojavom ST segment depresije ≥ 0,2 mV. Svim bolesnicima koji su na elektrokardiogramu u testu fizičkim opterećenjem imali depresiju ST segmenta ≥1 mV uradjen je sledećih dana i 2D stress ehokardiografski test radi potvrde postojanja miokardne ishemije.
U grupi od 290 osoba (81%) nije registrovana depresija ST segmenta na elektrokardiogramu, niti se javio anginozni bol u testu fizičkim opterećenjem. U grupi od 52 (14%) bolesnika registrovana je depresija ST segmenta ali bez pojave anginoznog bola ili njegovih ekvivalenata (asimptomatska ST segment depresija) i u grupi od 18 (5%) registrovana je, po prvi put, depresija ST segmenta, koja je praćena angiznim bolom ili njegovim ekvivalentima (simptomatska miokardna ishemija). Svi bolesnici sa simptomatskom miokardnom ishemijom imali su pozitivan stres ehokardiografski test (poremećaj kinetike segmenata leve komore u naporu), dok su u 43 od 52 bolesnika sa asimptomatskom ST segment depresijom u testu fizičkim opterećenjem nadjeni segmentni poremećaji kinetike leve komore (asimptomatska miokardna ishemija), a u 9 bolesnika nisu postojali znaci miokardne ishemije (lažno pozitivan nalaz miokardne ishemije na elektrokardiogramu u opterećenju). Prema tome u 61 (17%) asimptomatskog bolesnika s multipnim koronarnim faktorima rizika nadjena je miokardna ishemia (12% asimptomatska i 5% simptomatska). Nisu nadjene značajne razlike u veličini i trajanju depresije ST segmenta, niti u toleranciji fizičkog napora u bolesnika sa simptomatskom i asimptomatskom miokardnom ishemijom. Medjutim, u bolesnika sa simptomatskom miokardnom ishemijom indeks skora zidne pokretljivosti bio je značajno veći no u bolesnika sa asimptomatskom ishemijom (P<0,01).
U osoba sa "visokim koronarnim rizikom" stres testom asimpotomatska miokardna ishemija je registrovana u 12%. Nema značajnih razlika izmedju simptomatske i asimptomatske ishemije na elektrokardiogramu u testu fizičkim opterećenjem, dok se u bolesnika sa simptomatskom ishemijom stres ehokardiografskim testom otkrivaju veće abnormalnosti u segmentnoj kinetici leve komore.

Ključne reči: *Asimptomatska miokardna ishemija, stres ehokardiografski test, koronarni faktori rizika*