

THE PHARMA INNOVATION

Analysis Of Cardiovascular Risk Factors Influence On Occurrence And Course Of Silent Form Of Ischemic Heart Disease Of Patients With Postinfarction Cardiosclerosis

Peredruk T.V.^{1*}

1. Department of Internal Medicine No. 2 (Head of Department – Professor Seredyuk N.M.), State university "National Medical University of Ivano-Frankivsk", Ukraine. [Email: t.peredruk@mail.ru]

Special features of silent myocardial ischemia course were examined depending on the presence of cardiovascular risk factors. Data on interdependence of risk factors presence and figures of holter monitoring of electrocardiography was received. It was ascertained that for the patients with silent myocardial ischemia with such risk factors occurrence of complicated course of ischemic heart disease, such as arterial hypertension, diabetes and hyperlipidemia, the following indicators are typical: higher average daily indicators of ischemic episodes per day, higher aggregate daily duration of ST-segment depression, higher aggregate amplitude of ST-segment depression, higher average duration of one ischemic episode, compared to the persons without risk factors. Probability of antinociceptional system activation processes influence on the risk of accrual of acute coronary syndrome was proved.

Keyword: Silent Myocardial Ischemia, Holter Monitoring Of Electrocardiography, Antinociceptional System, B-Endorphines.

Problem stating and analysis of recent researches: Ischemic heart disease (IHD) belongs to one of the most widespread nosologies in the world. According to the data of various authors from 5% to 10% of general public of active working age suffer from IHD [5,8]. Complication of IHD is one of the most important reason of disability of general public in developed countries of the world. Identification of such forms of IHD, which are not accompanied with clinical manifestation, is characterized with asymptomatic course, which is often caused by untimely resort of the patient for medical aid, has great importance. Such form of IHD is silent myocardial ischemia (SMI). It occurs

both as separate nosology and in the form of episodes at other forms of IHD. SMI could be considered as significant predictor of accrual of acute coronary syndrome, sudden cardiac death, acute heart failure [1,7]. Accrual of AMI could be provoked by such factors as physical load, psychoemotional strain: everyday stress and negative emotions, smoking, overcooling, etc. [2]. Increase of duration of SMI episodes at increase of functional class of stenocardia is noted. Among factors, which increase the risk of SMI accrual at relatively healthy people, there could be middle age, male sex, hyperlipidemia [3,4,6].

Aim of research: to examine the peculiarities of the course of silent myocardial ischemia, taking into consideration the indicators of holter monitoring of electrocardiography, indicators of antinociceptive system activation with stratification of risk of complication of ischemic heart disease.

Materials and methods of research: 154 patients were examined with silent form of ischemic heart disease, which has occurred at the persons with postinfarction atherosclerosis. Diagnostic criteria were the following: verified with the help of holter monitoring of electrocardiography and tests with dosed physical load of AMI episodes. Diagnostics and medication of the patients were conducted according to existing standards of treatment of the persons with IHD, which are based on clinical protocol of provision of medical aid to the patients with IHD. Diagnosis of SMI was put forward according to the data of holter monitoring of electrocardiography, using the rule of "three units", defined by working party of National Institutes of Health (USA): deviation of ST-segment with amplitude of 1 mm and more with duration not less than 0,08 sec from point j, with duration of 1 min and more, with interval between the episodes not less than 1 min.

Average age of the patients was $53,5 \pm 1,2$ years: male – $51,2 \pm 1,2$ years, female – $56,9 \pm 1,5$ years. The most numerous was age group of the patients of age 40-49 and 50-59 years, accordingly 42,9% and 37,0% examined.

All examined patients were randomized to 5 groups depending on the presence of risk factors: I) – patients with silent form of IHD at the absence of risk factors (n=11); II) – patients with silent form of IHD with lipid metabolism (n=34); III) – patients with silent form of IHD with accompanying arterial hypertension (n=29); IV) – patients with silent form of IHD with accompanying diabetes (n=38); V) – patients with silent form of IHD at presence of two and more risk factors (n=42).

Traditional clinical methods were applied:

study of claims, anamnesis of disease and anamnesis of life, common physical examination, and electrocardiography. The following were included to scientific program of examination of the patients: transthoracic echocardiography from parasternal and apical approaches, holter monitoring of electrocardiography, veloergometry test, daily monitoring of blood pressure. Level of β -endorphins was examined, as marker of activation of antinociceptive system of organism, lipid range of blood was defined. Registration of electrocardiogram was conducted on electrocardiograph "Cardiofax" (Electrokardiograph, ECG 8820G, Germany). Holter (outpatient, daily) monitoring of electrocardiography was conducted with the help of the system "Cardiolab", produced by the company "ХАИ-МЕДИКА" (Kharkiv, Ukraine). At analysis of the data of holter monitoring of electrocardiography the following indicators were assessed: average frequency of heart rate, factor, which provokes ischemia, quantity of ischemia episodes and time of their occurrence during the day, average amplitude of depression / elevation of ST-segment (in mm), average frequency of ischemic episode, average duration of one ischemia episode (in minutes), aggregate duration of ischemia during the day (minutes per day); mentioned indicators of day and night periods were compared. As criteria of myocardial ischemia were considered the changes on electrocardiography in form of dislocations of ST-segment against isoline. The following symptoms of ischemic depression of ST-segment at the patients with IHD were distinguished: horizontal or obliquely downward character of ST-segment dislocation, displacement of ST-segment lower than isoline not less than for 0,1 mV in the point, which is located 80 ms from point J, duration of episode of ST-segment depression not less than 1 minute, time interval between the two similar episodes not less than 1 minute.

Results of research and their discussion. In our study the frequency of accrual of acheless forms of myocardial ischemia was analyzed, taking into consideration the presence of risk factors of complicated course of IHD. It was

ascertained that at the persons with hyperlipidemia, arterial hypertension, diabetes and presence of two or more risk factors the formation of asymptomatic options of myocardial ischemia were observed more frequently, in comparison to the patients at the absence of risk factors. At the same time it is worth mentioning that the frequency of occurrence of ventricular tachycardia, syncope states was not dependent from the presence of risk factors (Table 1). Obtained results could be explained by the different degree of sensitivity of individual persons to efferent nociceptive stimulation, which is partially defined by individual peculiarities of the patient and by the conduct of life. Interconnectedness of risk factors of IHD and probability of formation of asymptomatic

myocardial ischemia affirms great influence of external factors on the sensitivity to myocardial ischemia.

Significant aspect of study was examining of peculiarities of conduct of life of the patients, which increase the risk of hyperlipidemia or impairment of carbohydrate metabolism. It was ascertained that diabetes is more frequently observed at the persons with hypodynamia and excessive weight. Influence of smoking and durable distress syndrome on lipid and carbohydrate metabolism was also noted. Hereby, our study proves the importance of modified risk factors on the characteristic of clinical picture and on individual pathogenetic aspects at the patients with IHD.

Table 1: Peculiarities of course of silent myocardial ischemia, taking into consideration the risk factors of ischemic heart disease

Symptoms	Patients with acheless form of IHD, depending of the risk factors				
	Absence of risk factors (n=11)	Hyperlipidemia (n=34)	Diabetes (n=29)	Arterial hypertension (n=38)	Presence of 2 and more risk factors (n=42)
Asymptomatic myocardial infarction	1(9,1%)	3 (8,8%)	2(6,7%)	5(13,2%)	10 (23,8%) p<0,05
Clinically manifested myocardial infarction	10(90,9%)	31(91,2%)	27(93,3%)	33(86,8%)	32 (76,2%) p<0,05
Ventricular tachycardia	2(18,2%)	1(2,9%)	-	2(5,3%)	3(7,1%) p>0,05
Transient ischemic attack	-	-	-	1(2,6%)	1(2,4%) p>0,05
Syncope history	-	-	1(3,4%)	-	-

Note: mentioned percent from the total quantity of the persons in the group, p-authenticity of difference between the group of patients with two or more risk factors, in comparison to the patients with one risk factor.

Clinical and instrumental analysis was conducted at the patients with AMI with postinfarction cardiosclerosis. Assessment of obtained electrocardiography data at 12 standard abductions demonstrated that at patients with SMI, in comparison to the examined persons of controlled group, rhythm

disturbance of supraventricular and ventricular type, as well as sinus tachycardia were discovered more frequently (Table 2).

Results of standard electrocardiography examination determined the necessity of conducting of holter monitoring of electrocardiography. At analysis of the indicators of holter monitoring of electrocardiography it was ascertained that for the patients with SMI with such risk factors of accrual of complicated course of IHD as arterial hypertension, diabetes and hyperlipidemia the following indicators are

typical: higher average daily quantities of ischemic episodes during the day, higher aggregate daily duration of ST-segment depression, higher aggregate amplitude of ST-segment depression, average duration of one ischemic episode in comparison to the persons without risk factors ($p < 0,05$). As can be seen from Table 3, average figure of the quantity of ischemic episodes in the group of

examined patients without risk factors equaled $3,8 \pm 0,2$ per day, at patients with hyperlipidemia it equaled $5,4 \pm 0,5$ per day, and at examined patients with accompanying diabetes and present arterial hypertension – $5,9 \pm 0,31$ per day and $4,8 \pm 0,43$ per day, accordingly. At patients with two or more risk factors the average value of similar indicator was the highest and equaled $6,3 \pm 0,46$ per day.

Table 2: Results of electrocardiography of examined patients with acheless form of IHD

Results of electrocardiography of examined patients with acheless form of IHD						
Results of electrocardiography	Without risk factors (n=11)	Hyperlipidemia (n=34)	Diabetes (n=29)	Arterial hypertension (n=38)	Presence of 2 and more risk factors (n=42)	All patients (n=154)
Rhythm disturbance:						
- sinus tachycardia	1 (9,1%)	2 (5,9%)	4(13,8%)	2(5,3%)	6(14,3%)	15 (9,7%)
- sinus bradycardia	1 (9,1%)	3(8,8%)	1(3,4%)	1(2,6%)	2(4,8%)	8 (5,2%)
- ventricular extrasystole	1(9,1%)	5(14,7%)	13(48,3%) $p < 0,05$	7(18,4%)	24(57,1%) $p < 0,01$	49(31,8%)
- supraventricular extrasystole	1 (9,1%)	6(17,6%)	2(6,9%)	5(13,2%)	9(21,4%)	23(14,9%)
Asequence:						
- complete blockage of the left leg of bundle of His	-	-	1(3,4%)	1(2,6%)	-	2 (1,3%)
- incomplete blockage of the left leg of bundle	1 (9,1%)	6(17,6%)	5(17,2%)	2(5,3%)	11(26,2%)	25 (9,7%)
- complete blockage of the right leg of bundle	3 (27,3%)	-	-	1(2,6%)	-	4 (2,6%)
- incomplete blockage of the right leg of	1 (9,1%)	1(2,9%)	2(6,9%)	-	3(7,1%)	7 (4,55%)
Symptoms of	-	1(2,9%)	-	2(5,3%)	1(2,4%)	4(2,6%)
Focal cicatricial changes in the myocardium	1 (9,1%)	26(76,5%) $p < 0,001$	19(65,5%) $p < 0,01$	16(42,1%) $p < 0,05$	37(88,1%) $p < 0,001$	99 (64,3%)
Inversion of the T wave	2 (18,2%)	5(14,7%)	6(20,7%)	9(23,7%)	9(21,4%)	31 (20,1%)
Depression of ST-segment	3 (27,3%)	6(17,6%)	5(17,2%)	7(18,4%)	11(26,2%)	32 (20,8%)
Elevation of ST-segment	1 (9,1%)	-	-	-	1(2,4%)	2(1,3%)
Syndrome of early ventricular repolarization	-	1(2,9%)	3 (10,3%)	-	2(4,%)	6 (3,9%)
Hypertrophy of left ventricular	1 (9,1%)	-	-	27(71,1%) $p < 0,001$	31(73,8%) $p < 0,001$	59 (38,1%)

Note: mentioned percent from the total quantity of the persons in the group; p- authenticity of difference between the group of patients with one risk factor, in comparison to the patients without risk factors.

Average value of aggregate duration of ST-segment depression for the day in the group with impairment of lipid metabolism equaled

$57,7 \pm 3,52$ minutes per day. Similar figure at patients at presence of diabetes equaled $58,4 \pm 2,9$ minutes per day. Average daily

duration of ST-segment depression at patients with SMI with accompanying arterial hypertension equaled $51,23 \pm 1,09$ minutes per day. It was examined that at patients with two or more risk factors the value of aggregate duration of ST-segment depression was the highest and equaled $62,32 \pm 4,36$ minutes per day ($p < 0,01$). At the same time, at patients with SMI without risk factors the average level of this indicator equaled $42,17 \pm 4,3$ minutes per day.

At analysis of indicators of average value of maximum ST-segment depression, average depth of ST-segment depression, average

indicator of heart rate during ST-segment depression, heart rate at maximum depth of ST-segment displacement reliable differences at various groups of examined patients weren't ascertained ($p > 0,05$). Obtained results proved that risk factors of complicated course of IHD at patients with SMI could negatively influence the condition of myocardial perfusion and could provoke ischaemisation of myocardium. This is manifested by more intensive symptoms of ischemic changes, discovered during holter monitoring of electrocardiography.

Table 3: Indicators of myocardial ischemia according to the data of holter monitoring of electrocardiography at patients for AMI

Risk factors					
Indicators	Absence of risk factors (n=11)	Hyperlipidemia (n=34)	Diabetes (n=29)	Arterial hypertension (n=38)	Presence of 2 and more risk factors (n=42)
Average quantity of myocardial ischemia episodes during the day	$3,8 \pm 0,2$	$5,4 \pm 0,5$ $p < 0,01$	$5,9 \pm 0,31$ $p < 0,001$	$4,8 \pm 0,43$ $p < 0,05$	$6,3 \pm 0,46$ $p < 0,001$
Aggregate duration of ST-segment depression, minutes per day	$42,17 \pm 4,3$	$57,7 \pm 3,52$ $p < 0,01$	$58,4 \pm 2,9$ $p < 0,05$	$51,23 \pm 1,09$ $p < 0,05$	$62,32 \pm 4,36$ $p < 0,01$
Aggregate amplitude of ST-segment	$6,7 \pm 0,63$	$9,02 \pm 0,46$ $p < 0,01$	$7,02 \pm 0,27$ $p > 0,05$	$8,74 \pm 0,32$ $p < 0,01$	$8,6 \pm 0,19$ $p < 0,01$
Average duration of one myocardial ischemia episode, minutes	$8,16 \pm 0,41$	$10,36 \pm 0,52$ $p < 0,01$	$9,37 \pm 0,31$ $p < 0,05$	$10,47 \pm 0,38$ $p < 0,001$	$9,68 \pm 0,46$ $p < 0,05$
Average value of the depth of ST-segment	$1,7 \pm 0,12$	$2,05 \pm 0,1$ $p > 0,05$	$1,8 \pm 0,14$ $p > 0,05$	$1,9 \pm 0,04$ $p > 0,05$	$2,0 \pm 0,8$ $p > 0,05$
Average value of maximum ST-segment	$2,2 \pm 0,09$	$2,4 \pm 0,25$ $p > 0,05$	$2,3 \pm 0,2$ $p > 0,05$	$2,27 \pm 0,26$ $p > 0,05$	$2,4 \pm 0,29$ $p > 0,05$
Average value of heart rate during ST-segment depression, during 1 minute	$74,4 \pm 3,5$	$76,3 \pm 1,6$ $p > 0,05$	$69,2 \pm 2,75$ $p > 0,05$	$70,3 \pm 2,9$ $p > 0,05$	$72,8 \pm 3,4$ $p > 0,05$
Heart rate at maximum depth of ST-segment displacement, during 1 minute	$98,7 \pm 4,4$	$101,37 \pm 3,32$ $p > 0,05$	$89,5 \pm 3,17$ $p > 0,05$	$95,7 \pm 2,85$ $p > 0,05$	$104,21 \pm 2,1$ $p > 0,05$

Note: p - authenticity of average values in comparison to the patients without risk factors.

Performed assessment of results of holter monitoring of electrocardiography proved that the presence of such risk factors as

hyperlipidemia, diabetes and arterial hypertension at patients with SMI with passed myocardial ischemia in anamnesis, are

associated with established increasing of the frequency of accrual of ventricular arrhythmias ($p < 0,05$). Hereby, the feature of risk factors of complicated course of IHD to decrease electrical stability of cardiomyocytes and to induce the rhythm disturbance of ventricular extrasystoles type was proved.

In this study the indicators of activation of antinociceptive system of organism were examined. With this aim the indicators of β -endorphins concentration were analyzed. It was ascertained that at patients with SMI at the absence of perceived pain and clinical manifestation of the disease the level of β -endorphins was significantly higher, in comparison to the control group, which proves the existence at the patients with SMI of pronounced afferent nociceptive stimulation. It was ascertained that average value of β -endorphins concentration at patients with impairment of lipid metabolism equaled to $4,91 \pm 0,02$ ng/ml, at presence of diabetes this indicator equaled to $4,09 \pm 0,03$ ng/ml ($p < 0,01$), and at persons with accompanying Arterial hypertension it equaled to $3,82 \pm 0,02$ ng/ml ($p < 0,05$).

Reliability of average values at patients of the main group with various risk factors was noted, in comparison to the group of practically healthy persons, in which average level of β -endorphins equaled to $0,68 \pm 0,01$ ng/ml ($p < 0,01$).

Correlations between the level of activity of antinociceptive system and the frequency of accrual of instable angina, myocardial infarction, pathological value of HRTO were analyzed at patients with SMI. For this purpose point-dichotomous correlation analysis among between the concentration of β -endorphins in plasma and the risk of occurrence of examined events was conducted, which provides the opportunity to ascertain the correlation interaction between quantitative and qualitative indicators.

Direct correlation interaction of average strength between the level of β -endorphins and accrual of myocardial infarction was ascertained. Coefficient of point-beaded

correlation equaled to 0,52 ($p < 0,05$). At analysis of correlation interaction between the concentration of β -endorphins in plasma of the examined patients and the risk of occurrence of instable angina statistically reliable correlation of medium strength was discovered.

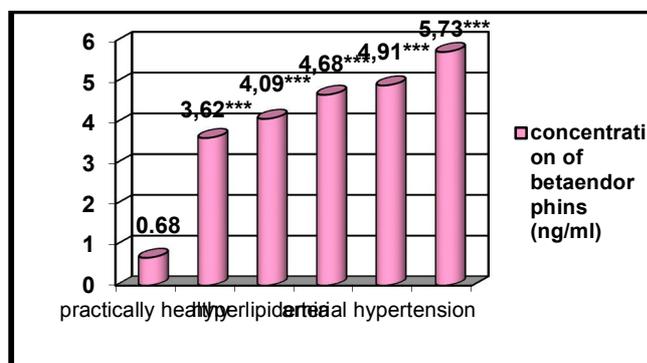


Figure 1. The concentration of β -endorphins in patients with silent myocardial ischemia, depending on the presence of risk factors

Note: The accuracy difference compared with practically healthy individuals- * $p < 0,05$, ** $p < 0,01$; *** $p < 0,001$.

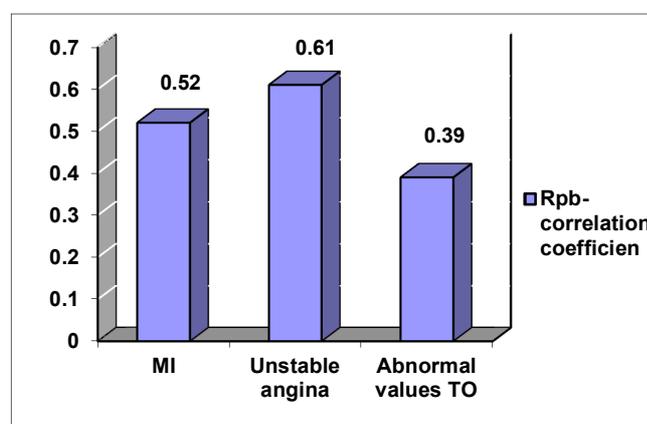


Figure 2. Point-biserial correlation coefficient between the level of β -endorphin and risk of ACS, abnormal heart rate turbulence

Coefficient of point-beaded correlation equaled to 0,61 ($p < 0,05$). Correlation of pathological value of heart rate turbulence with the level of β -endorphins is weak but reliable – coefficient of point-beaded correlation equaled to 0,39 ($p < 0,05$). Performed study of clinical and functional characteristics of SMI allowed to prove that

acheless myocardial ischemia is the disease, which leads to complex pathological changes in organism with affection not only on myocardium, but on vascular system as a whole. We confirmed the fact of presence at patients with Ami of myocardial ischemia, activation of antinociceptive system. Obtained data are extremely important for comprehension of the main links of the course of SMI and provide the possibility to base the approach to the therapy of such patients at differentiated system algorithm, which takes into consideration the inconsistency between clinical manifestations of disease and its real influence on coronary perfusion and state of vascular wall.

CONCLUSIONS:

1. Acheless form of IHD with postinfarction cardiosclerosis occurs at presence of the factors of cardiovascular risk: arterial hypertension, diabetes, hyperlipidemia or their combination.

2. Presence of the risk factors, in turn, complicates the course of silent myocardial ischemia, which manifests in deterioration of clinical state, decrease of tolerance to physical load, significant changes of hemodynamics and vegetative regulation, intensive manifestations of myocardial ischemia, activation of antinociceptive system, in comparison to the persons without risk factors ($p < 0,05$).

3. It was ascertained that the patients with acheless form of IHD have tight correlation link between the presence of the risk factors and indicators of holter monitoring of electrocardiography, especially, average values of quantity of ischemic episodes per day, aggregate daily duration of ST-segment depression and average duration of one ischemic episode.

4. At silent form of IHD reliable increase of β -endorphins in blood takes place. This proves existence at examined patients of expressed afferent nociceptive stimulation, intensity of which, probably, depends on the degree of myocardial ischemia.

5. Among the patients with silent myocardial ischemia the group with high-risk of occurrence of cardiovascular complications should be distinguished.

REFERENCES:

1. Ahmed A.H., Shanka K., Eftekhari H. et al. Silent myocardial ischemia: Current perspectives and future directions. // *Exp Clin Cardiol.* – 2007. – Vol. 12, №4. – P.189-196.
2. Anderson T.J. Assesment and treatment of endothelial dysfunction in humans. *J.Am. Coll.Cardiol.* 1999; 34: 631-638.
3. Brown J.P., Katzel L.I., Neumann S.A. et. al. Silent myocardial ischemia and cardiovascular responses to anger provocation in older adults // *Ind J Behav Med.* – 2007. – Vol. 14, №3. – P.134-140.
4. Callaham P.R., Froelicher V.F., Klein J., Risch M. et al. Exercise-induced silent ischemia: Age, diabetes mellitus, previous myocardial infarction and prognosis // *J. Am. Coll. Cardiol.*— 2009.— N14.— P.1175—1180.
5. Campbell S. Silent myocardial ischemia // *Brit. Med. J.*— 2008.— Vol. 62.— P. 1005—1010.
6. Cottone S., Vadala A., Mangano M.T. Endothelial factors in essential hypertension with microalbuminuria // *Am. J. Hypertens.* 2000. 13. 172-176.
7. Luft F.C. Mechanisms and cardiovascular damage in hypertension // *Hypertension.* 2001. №37. (2). 594-598.
8. Silent myocardial ischaemia in patients with type II diabetes mellitus and its relation with autonomic dysfunction / R. Sukhija, D. Dhanwal, DS. Gambhir [et al.] // *Indian Heart J.* 2000 Sep-Oct;52(5): 540-546.