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## THE INFLUENCE OF XENOBIOTICS ON THE COURSE OF ST-ELEVATION MYOCARDIAL INFARCTION AND THE STRUCTURE OF INTRACORONARY THROMBI

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Xenobiotics are significant risk factor for the development of acute myocardial infarction. To elucidate the influence of xenobiotics on the course of ST segment elevation myocardial infarction and the peculiarities of intracoronary thrombi structure. 100 patients (mean age  $57.81 \pm 10.26$  years) with ST segment elevation myocardial infarction were included. All participants underwent manual thromboaspiration during percutaneous coronary intervention. Thrombi were evaluated morphologically. Patients with exposure to xenobiotics were significantly younger ( $55.29 \pm 10.86$  vs.  $61.25 \pm 11.14$  years;  $P < 0.008$ ), more often had male gender (48 [92.3 %] vs. 34 [70.8 %];  $P = 0.005$ ), and were smokers (35 [67.3 %] vs. 22 [45.8 %];  $P = 0.03$ ). Intracoronary thrombi of these patients less frequently demonstrated peripheral inflammation (22 (44 %) vs. 31 (66 %),  $p = 0.030$ ). Patients with occupational exposure to xenobiotics were more often males of younger age. The intracoronary thrombi of these patients rarely demonstrated signs of inflammation.

**Key words:** myocardial infarction, blood clot, percutaneous coronary revascularization, xenobiotics.

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## ВПЛИВ КСЕНОБІОТИКІВ НА ОСОБЛИВОСТІ ПЕРЕБІГУ ІНФАРКТУ МІОКАРДА З ЕЛЕВАЦІЄЮ СЕГМЕНТУ ST ТА БУДОВУ ІНТРАКОРОНАРНИХ ТРОМБІВ

Ксенобіотики є вагомим фактором ризику розвитку гострого інфаркту міокарда. Вивчити вплив ксенобіотиків на перебіг гострого інфаркту міокарда з елевацією сегменту ST та будову інтракоронарних тромбів. В дослідження увійшло 100 пацієнтів віком  $57,81 \pm 10,26$  роки з гострим інфарктом міокарда з елевацією сегменту ST. Усім їм було проведено первинне черезшкірне коронарне втручання із застосуванням мануальної тромбоаспірації. Отримані тромби аналізували морфологічно. Пацієнти, які мали професійний контакт з ксенобіотиками, були молодшого віку ( $55,29 \pm 10,86$  проти  $61,25 \pm 11,14$  років;  $p < 0,008$ ), частіше чоловічої статі (48 [92,3 %] проти 34 [70,8 %];  $p = 0,005$ ) та курили (35 [67,3 %] проти 22 [45,8 %];  $p = 0,03$ ). Запальна інфільтрація по периферії тромбу встановлена суттєво частіше в таких пацієнтів 22 (44 %) і 31 (66 %) пацієнтів ( $p = 0,030$ ). Пацієнти з гострим інфарктом міокарда з елевацією сегменту ST та професійним контактом з ксенобіотиками частіше чоловічої статі та молодшого віку. Отримані у них інтракоронарні тромби рідше мають ознаки запалення.

**Ключові слова:** інфаркт міокарда, тромби, черезшкірна коронарна рекануляція, ксенобіотик.

*The study is a fragment of the research project "The influence of arterial hypertension, type 2 diabetes, overweight, smoking, and subclinical hypothyroidism on the occurrence of acute and chronic forms of coronary heart disease", state registration No. 0120U105778.*

For many years, cardiovascular diseases have been one of the main causes of death and disability worldwide [13]. According to WHO data, this pathology leads to the annual loss of more than 17 million lives [14]. About half of deaths caused by cardiovascular diseases are due to coronary artery disease (CAD). The main cause of death in patients with CAD is acute myocardial infarction with ST segment elevation (STEMI) [13]. Most frequently, this is a type 1, the direct cause of which is coronary artery thrombosis caused by the rupture of an atherosclerotic plaque [12]. In recent years, the recommendations of the European Society of Cardiology (ESC) have been developed regarding unified approaches to the treatment of this pathology. According to them, the most effective method of revascularization in such patients is percutaneous coronary intervention (PCI) [6]. In recent years, significant progress has been observed in the treatment of STEMI, which is largely related to the introduction and improvement of PCI [6]. Since 1977, when this procedure was performed for the first time, PCI technologies have undergone constant improvement [4]. Along with the technology improvement, there was a rapid increase in the frequency of their application in everyday cardiology practice of all countries, including Ukraine [2]. The widespread implementation of this treatment method contributed to a significant mortality reduction, as well as the number of acute and chronic complications of myocardial infarction [6]. At the same time, there is an ongoing research for ways to improve the PCI technique and expand the arsenal of possibilities that would increase its efficacy. At the same time, it should be noted that timely use of PCI does not always lead to adequate reperfusion. One of the main reasons for this phenomenon is the development of distal embolism, which in turn results in microvascular obstruction, which leads to an increase in the frequency of early

post-infarction complications. In recent years, a number of measures have been proposed to prevent distal embolization during PCI, including mechanical thromboaspiration [5, 7].

Nowadays of particular importance is the analysis of various risk factors that can affect the specifics of intracoronary thrombi formation and the course and prognosis of STEMI. There is considerable scientific interest in the study of the state of the environment and its connection with various pathologies. The recent publications state that the increase in the frequency of CAD and the mortality caused by them is more frequently registered among people who in their professional or everyday life are exposed to harmful substances (xenobiotics) [3].

The occupation of the patient is important, moreover, there are data that representatives of working professions are more likely to suffer from STEMI at a young age [1].

In this context, the study of xenobiotics influence on the course of STEMI, the intracoronary thrombi morphological structure and the long-term outcome of patients deserves special attention. Currently these issues are insufficiently studied and require the in-depth analysis.

**The purpose** of the study was to establish the relation of xenobiotics explosion on the course of STEMI and morphological features of intracoronary thrombi structure.

**Materials and methods.** The research was carried out in three medical institutions: the National Scientific Center “M.D. Strazhesko Institute of Cardiology” in Kyiv, Communal Non-Profit Enterprise “Clinical Emergency Care Hospital” in Lviv and Communal Non-Profit Enterprise of Lviv Regional Council “Lviv Regional Clinical Medical and Diagnostic Cardiology Center”. The study included 100 patients aged  $57.81 \pm 10.26$  years with STEMI (22 % women, 78 % men), who in the first 12 (average 7.00 [4.75;10.00]) hours from the onset of symptoms underwent primary PCI with the use of manual thromboaspiration. The use of the latter was carried out based on the decision of the doctor who performed the procedure. The initial coronary angiography of each patient showed massive thrombosis or occlusion of the infarction-related coronary artery. Sufficient aspiration material for histological examination was obtained in 97 patients, who were included in the further stages of the study. All of them gave informed consent to participate in the study. The intracoronary thrombi obtained were analyzed macroscopically and were divided into three groups: white, red, and mixed. Later they were fixed in a neutral formalin solution, then embedded in resin and following the standard technique were stained with hematoxylin-eosin, as well as by the orange-red-blue method (Zerbino-Lukasevych methodology). The latter makes it possible to estimate fibrin age by color. In particular, if fibrin becomes red or pink, then less than 24 hours have passed since its formation. Blue or purple fibrin indicates that it was formed more than 24 hours prior fixation. When the share of such fibrin was more than 30 %, the thrombus was considered to be old.

In the process of thrombi detailed analysis, a number of their characteristics were studied. In particular, the age of the thrombus – whether it was old or fresh (according to the staining method by Zerbino-Lukasevych), its structure (presence or absence of a layered structure), presence of microchannels and peripheral infiltration with neutrophilic leukocytes. In addition, presence of eosinophilic leukocytes and atherosclerotic plaque components in blood clots was analyzed.

On the basis of a specially developed questionnaire, a detailed anamnesis was collected with clarification of xenobiotics exposure. Particular attention was paid to the identification of occupational or household contact with xenobiotics. The group of patients who were in contact with xenobiotics included persons who during their professional life for more than 2 years had regularly worked with welding, soldering, varnishes, paints, acids, alkalis, solvents, toxic chemicals, fertilizers, lubricants and other compounds harmful to human bodies.

In order to evaluate the effectiveness of treatment, a comparison of the short-term and long-term prognosis of patients was carried out. The short-term prognosis was determined based on the following indicators: achievement of TIMI 3 blood flow, myocardial blush MBG 3 level and ST segment resolution by at least 50 % one hour after the intervention, as well as evaluation of left ventricular ejection fraction, myocardial contractility index, signs of left ventricular post-infarction aneurysm formation, QS wave formation at the time of hospital discharge. The long-term prognosis was determined 6, 12 and 24 months after primary PCI with manual thromboaspiration. It provided for the study of the frequency of major cardiac events (death, myocardial infarction and repeated revascularization) and appearance and progression of angina symptoms severity.

**Results of the study and their discussion.** The cohort under study included 52 patients who exposed to xenobiotics, 48 patients with no exposure. The average age of patients in contact with xenobiotics was  $55.29 \pm 10.86$ , while among non-contact patients it was  $61.25 \pm 11.14$  ( $p < 0.008$ ). The time from the onset of pain to primary PCI in young patients was 6.00 [3.00; 9.00], in older – 5.00 [3.00; 9.25]

( $p=0.667$ ) hours. The obtained results confirm the existing data that representatives of working professions much more frequently suffer from STEMI at a younger age.

Table 1 presents the initial clinical and anamnestic characteristics of the patients participating in the study. Among them the groups differed significantly only in terms of gender and prevalence of smoking. All the other characteristics of the participants were similar.

Table 1

**Comparative analysis of initial clinical and anamnestic characteristics of patients depending on professional exposure to xenobiotics**

Indices	Exposure to xenobiotics		No exposure		p
	abs	%	Abs	%	
Male	48	92.3	34	70.8	0.005
CAD in the anamnesis	23	44.2	19	39.6	0.638
History of myocardial infarction	9	17.3	5	10.4	0.321
Pain more than 24 hours prior the infarction	20	38.5	22	45.8	0.456
Cardiogenic shock at hospitalization	7	13.5	5	10.4	0.640
Thrombolytic therapy before PCI	6	11.5	2	4.2	0.175
Diabetes	12	23.1	11	22.9	0.985
Arterial hypertension	29	55.8	29	60.4	0.638
Smoking	35	67.3	22	45.8	0.03
Obesity	25	48.1	16	33.3	0.134
Dyslipidemia	17	32.7	16	33.3	0.880
Anemia	6	11.52	11	23.4	0.118
Leukocytosis	35	67.3	21	43.8	0.018
Chronic kidney failure	12	23.1	8	16.7	0.423
Hyperglycemia at hospitalization	24	46.2	20	42.6	0.719
Left ventricle dilatation	27	52.9	18	37.5	0.123

In the course of the study, the analysis of initial angiographic characteristics and features of interventions was carried out depending on the professional contact of patients with xenobiotics (Table 2).

Table 2

**Comparative analysis of initial angiographic characteristics and features of interventions depending on the professional contact of patients with xenobiotics**

Indices	Exposure to xenobiotics		No exposure		p
	abs	%	abs	%	
Infarction-related left coronary artery	28	53.8	13	27.1	0.007
Usage of balloon	26	50	23	47.9	0.835
Other blood vessels lesions except for the infarction-related	23	44.2	17	35.4	0.369
Blood flow TIMI 0 prior the intervention	41	78.8	41	85.4	0.393
MBG 0 prior the intervention	45	86.5	43	89.6	0.640

In both groups of patients, the left coronary artery was less frequently infarction-related. However, the comparison of the study groups showed that this situation was recorded significantly more often in people who were exposed to xenobiotics (28 [53.8 %] vs. 13 [13 %] respectively;  $p=0.007$ ). Among them, the probability of detecting a two- or three-vessel lesion of the coronary arteries was somewhat higher, though the difference did not reach statistical significance (23 [44.2 %] vs. 17 [35.4 %] respectively;  $p=0.369$ ). The other characteristics under research had similar frequency among the groups.

In the course of the study, thrombi were obtained in 50 xenobiotics-exposed and 47 non-exposed patients. Thrombi morphological analysis revealed old thrombi in 29 (58.0 %) patients who were in contact with xenobiotics and 31 (66.0 %) non-contact patients ( $p=0.42$ ). The thrombi color characteristics are presented in Fig. 1.

The layered structure of thrombi was established in 31 (52 %) and 28 (59.6 %) patients of the comparison group respectively ( $p=0.807$ ). The presence of microchannels was observed in 16 (32 %) patients in contact with xenobiotics and 22 (46.8 %) of the comparison group,  $p=0.135$ . Inflammatory infiltration along the thrombus periphery was established in 22 (44 %) and 31 (66 %) patients respectively ( $p=0.030$ ). Elements of atherosclerotic plaque in thrombi were found quite rarely, in particular, in 4 (8 %) of individuals exposed to xenobiotics and 4 (8.5 %) of the comparison group,  $p=0.927$ . Eosinophilic

leukocytes were found in 40 (80 %) intracoronary thrombi of people in contact with xenobiotics and 42 (89.4 %) from the comparison group ( $p = 0.203$ ). Thus, the conducted studies did not confirm the increased role of inflammation in the pathogenesis of thrombus formation in patients that were in contact with xenobiotics.

Special attention in the research was paid to the study of short- and long-term prognosis of patients using a number of clinical and instrumental indices.

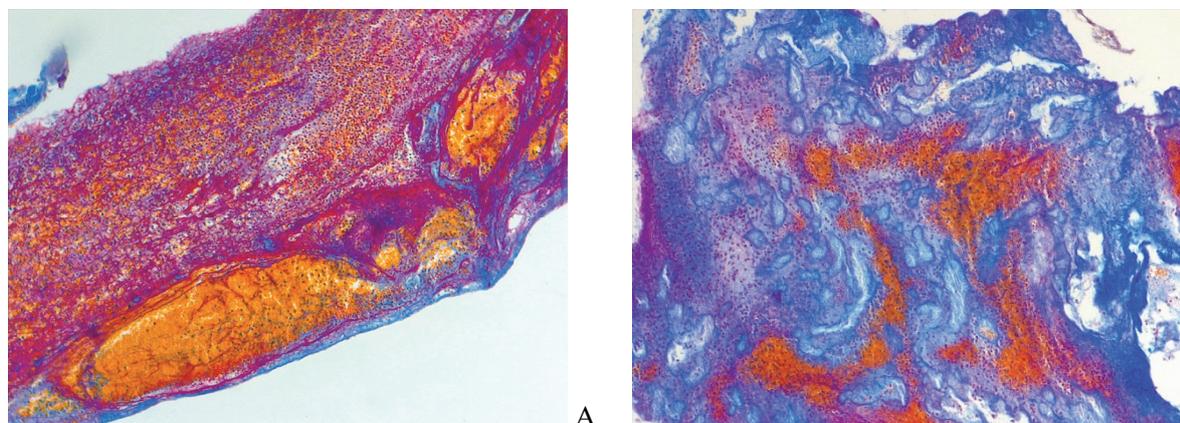


Fig. 1. Staining of intracoronary thrombi using the orange-red-blue method (by Zerbino-Lukasevych). A. Fresh thrombus, x100 magnification; B. Old thrombus formed more than 24 hours ago, x100 magnification.

Blood flow after the intervention was evaluated by the frequency of reaching TIMI 3 and MBG 3 after the intervention. It was possible to achieve TIMI 3 after the intervention in 42 (80.8 %) patients who were in contact with xenobiotics and, somewhat less often, in 37 (77.1 %) patients of the comparison group ( $p = 0.651$ ). A similar situation was observed regarding the achievement of the target level of myocardium staining with MBG 3 contrast, which reflects the state of microcirculation. Specifically, after the intervention MBG 3 was diagnosed in 34 (65.4 %) and 29 (60.4 %) patients respectively ( $p=0.607$ ).

An indisputable feature of the efficacy of the PCI is the presence of the ST segment resolution, which was confirmed when it decreased by at least 50 % one hour after the intervention. Such results were obtained in 33 (63.5 %) patients with harmful working conditions and 37 (77.1 %) patients of the comparison group ( $p=0.138$ ). The QS wave on the ECG at discharge from the hospital was observed in 28 (53.8 %) and 18 (37.5 %) patients respectively ( $p = 0.101$ ). Signs of left ventricular aneurysm formation upon discharge from the hospital were observed in 12 (23.8 %) patients who were in contact with xenobiotics, and in 4 (8.3 %) of the comparison group ( $p = 0.045$ ). Thus, the positive dynamics of electrocardiographic changes was better in the group of patients who were not in contact with xenobiotics, although the difference did not reach reliable values.

To study the myocardium condition at the moment of discharge from the hospital, the echocardiography parameters were analyzed, in particular the left ventricle ejection fraction and the total myocardium contractility index. The left ventricle ejection fraction in persons with occupational hazards was on average  $47.24 \pm 10.47$ , and in the control group it was  $49.52 \pm 8.04$  ( $p=0.2246$ ). The total left ventricle contractility was  $1.38 [1.25; 1.75]$  and  $1.38 [1.24; 1.56]$  ( $p=0.3339$ ).

Analysis of clinical endpoints was performed 6, 12, and 24 months after the intervention. Information was obtained about 47 (90.4 %) patients with occupational hazards and 45 (93.8 %) from the comparison group. Among them, 6 months after the follow-up alive were 46 (95.8 %) patients who were in contact with xenobiotics and 41 (91.1 %) patients from the comparison group,  $p = 0.354$ . The combined endpoint (death, myocardial revascularization, myocardial infarction, or anginal pain restart) was observed in 10 (20.8 %) participants of the study with occupational hazards and 5 (11.6 %) from the comparison group ( $p=0.237$ ). At the same time, major cardiac events (death, myocardial revascularization or myocardial infarction) were recorded in 5 (10.4 %) and 5 (11.4 %) patients respectively ( $p = 0.884$ ).

In the process of the study, certain components of the end points were studied among living patients with whom it was possible to come into contact. In particular, 1 (2.2 %) patient in contact with xenobiotics and none from the comparison group ( $p=0.342$ ) developed myocardial infarction within 6 months after the initial hospitalization. Repeated revascularization was performed in 2 patients from each group ( $p=0.906$ ). The restart or appearance of anginal pains was also observed in the same number of patients (7 patients from each of the groups,  $p=0.249$ ).

In recent years great importance has been attached to the study of patients' treatment compliance, as it is absolutely clear that no matter how correct the lifestyle and treatment recommendations given by

the doctors are, they do not work if a patient does not follow them. Despite significant progress in the treatment of patients who participated in the study, lifestyle modification and drug therapy still were of great importance. It is these factors that have a serious impact on the patient outcome. The results of treatment compliance study among our patients during the first 6 months after PCI showed high compliance to medical treatment in 87.0 % of patients exposed to xenobiotics and 90.2 % in the comparison group. Our observations prove that therapy compliance increases in patients in case they have high trust in the doctor, if the treatment scheme is effective according to objective and subjective indices, and side effects do not exceed the effect of the prescribed treatment.

Analysis of the long-term outcome of the patients during 12-month follow-up period has shown that alive were 45 (93.8 %) participants of the study who were exposed to xenobiotics and 40 of the comparison group (88.9 %),  $p=0.403$ . The combined point (death, myocardial revascularization, myocardial infarction, or restart of anginal pain) was noted in 14 (29.8 %) and 11 (24.4 %) patients respectively ( $p=0.565$ ). And major cardiac events (death, myocardial revascularization or myocardial infarction) occurred in 5 (11.1 %) persons with existing occupational hazards and 7 (17.5 %) of the comparison group ( $p=0.386$ ). Individual components of the endpoints were investigated among living patients who we managed to come into contact with. Repeated myocardial infarction within 12 months after the initial hospitalization developed in 1 (2.2 %) patient with occupational hazards and 1 (2.4 %) of the comparison group ( $p=0.934$ ), revascularization in 2 (4.3 %) and 3 (7.3 %) respectively, ( $p=0.553$ ) and angina pains started again in 8 (17.4 %) and 6 (14.6 %) respectively ( $p=0.727$ ).

High compliance to medication therapy was observed in 35 (76.1 %) of people exposed to xenobiotics and 31 (75.6 %) from the comparison group,  $p = 0.959$ .

24 months after the follow-up alive were 44 (93.6 %) patients who were in contact with xenobiotics, and 39 (86.7 % of those with whom it was possible to get in touch) without proven contact ( $p= 0.262$ ). A combined point (death, myocardial revascularization, myocardial infarction, or anginal pains restart) was observed in 21 (47.7 %) persons exposed to harmful substances at the workplace, and 16 (41.0 %) without such contact ( $p=0.148$ ). And major cardiac events (death, myocardial revascularization or myocardial infarction) occurred in 16 (32 %) and 8 (18.2 %), respectively ( $p=0.125$ ). Individual endpoint components were investigated for living patients whom it was possible to contact. Repeated myocardial infarction 24 months after the initial hospitalization developed in 2 (4.5 %) persons with xenobiotics exposure and 1 (2.5 %) without it ( $p=0.614$ ), revascularization in 3 (6.8 %) and 5 (12.5 %) respectively ( $p=0.376$ ), and angina pains started again in 12 (27.3 %) and 11 (27.5 %) persons respectively ( $p=0.981$ ).

High drug therapy compliance after 24-month follow-up period was observed in 32 (72.7 %) patients with occupational hazards and 30 (75 %) without them,  $p=0.813$ . Thus, one can conclude that compliance is affected by the duration of treatment. The longer the therapy, the lower the treatment compliance of the patients is.

This study is based on real practice and recruitment was conducted prospectively among all the patients subject to the inclusion criteria. That is why there are certain differences between groups in some initial characteristics.

When planning the research, we proceeded from the existing literature data, which note the increase in the incidence of cardiovascular diseases and associated mortality more often among people who in their professional or everyday life are exposed to harmful substances (xenobiotics). Moreover, some researchers state that exposure to xenobiotics can provoke the development of myocardial infarction at a younger age [1]. Our results confirm these facts, since the average age of patients who were in contact with xenobiotics was  $55.29 \pm 10.86$ , while among non-contact patients it was  $61.25 \pm 11.14$  ( $p < 0.008$ ). Analyzing the generally recognized risk factors for the development of CAD, we managed to find a significant difference between the groups regarding the frequency of smoking, which was significantly more common among patients who had professional contact with xenobiotics.

Comparative analysis of the thrombi morphological structure did not show a significant difference among patients of both groups. In recent years, there are literature publications stating that professional exposure to xenobiotics is a significant risk factor for the development of acute myocardial infarction [2, 10]. At the same time, our data have not confirmed the direct impact of harmful environmental substances on the composition, age and structure of intracoronary thrombi. So, it's possible that xenobiotics haven't a direct connection to clot formation.

Interesting results were obtained regarding the assessment of post-intervention blood flow, which was evaluated based on the frequency of achieving TIMI 3 and MBG 3 after the intervention. Somewhat better results were achieved among people who were in contact with xenobiotics, but there was no

statistically significant difference. At the same time, the positive dynamics of electrocardiographic changes was more significant, although it did not show a significant difference in the group of patients who were not in contact with xenobiotics. Such data have some discordance with previous study [2, 10], where they possess influence on the disease course.

The results of a long-term dynamic study of patients' compliance to treatment showed high compliance to drug therapy in both groups during the first 6 months after PCI, however, with prolonged duration of follow-up observations (after 12 and 24 months), we obtained a decreasing tendency. This situation is observed by many researchers [8]. At the same time, therapy compliance among patients increases in case there is high trust in the doctor, if the treatment scheme is effective according to objective and subjective criteria, while patients participate in rehabilitation programs [9]. The last one can significantly improve patients' prognosis [11].

### Conclusions

1. Patients with acute STEMI and occupational exposure to xenobiotics were more often males (48 [92.3 %] vs. 34 [70.8 %];  $P=0.005$ ) and have younger age ( $55.29\pm 10.86$  vs.  $61.25\pm 11.14$  years;  $P<0.008$ ).
2. The intracoronary thrombi obtained in these patients less often demonstrated signs of inflammation (22 [44 %] vs 31 [66 %];  $p=0.030$ ).
3. The short-term and long-term prognosis in patients with or without occupational exposure to xenobiotics did not differ significantly.

Patients' adherence to drug treatment had decreased over time (87.0 % vs 90.2 % 6 months after STEMI and 72.7 % vs 75 % 24 months after)

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Стаття надійшла 13.12.2022 р.