ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

DOI: 10.21802/artm.2023.1.25.66
UDC 616.127-008.9+616.127-005.8+612.276

PECULIARITIES OF CONNECTIVE TISSUE METABOLISM IN PATIENTS WITH POST-INFARCTION REMODELING AND REPERFUSION SYNDROME

N.M. Seredyuk, I.P. Vakaliuk, Ya.L. Vandzhura, R.V. Denina, I.Yu. Vandzhura, P.P. Zvonar

Ivano-Frankivsk national medical University, Department of internal medicine №2 and nursing, Ivano-Frankivsk, Ukraine,
ORCID ID: 0000-0002-3616-2445,
ORCID ID: 0000-0002-4430-6816,
ORCID ID: 0000-0003-2525-371X,
ORCID ID: 0000-0001-8196-7130,
ORCID ID: 0000-0001-5905-487X,
ORCID ID: 0000-0001-6121-5281,
e-mail: roksolanadoc@ukr.net

Abstract. Early restoration of coronary blood flow in acute myocardial infarction with elevation helps reduce the area of myocardial necrosis, prevent dilatation of the ventricular cavity, and reduce the development of arrhythmias and mortality. However, despite modern technologies in STEMI treatment, the development of reperfusion syndrome, in particular, arrhythmias, is possible after the restoration of blood flow in the infarct-related artery, which is a consequence of acute cellular, metabolic and local electrophysiological changes in the myocardium.

The aim: is to investigate the long-term effects of reperfusion syndrome on the catabolic/anabolic activity of connective tissue and the processes of connective tissue framework formation in the post-infarction period in patients with myocardial infarction.

Materials and methods. The study involved 156 patients with acute myocardial infarction with ST segment elevation (STEMI), and 15 apparently healthy individuals (control of laboratory parameters). The average age of the patients was (57.8±1.2) years. The percent of male patients prevailed (76 %).

All MI patients were divided into two groups: Group I (98 people) – MI patients without clinical signs of reperfusion syndrome during revascularization, Group II (58 people) – MI patients with the signs of reperfusion syndrome in the form of rhythm and conductivity disturbances during revascularization of coronary arteries by percutaneous coronarography intervention (PCI) with prolonged stenting of the infarct-dependent coronary artery.

Peculiarities of connective tissue metabolism were studied by the content of free and bound oxyproline, glycosaminoglycans, and antibodies to atypical collagens (Ig M and Ig G) in blood serum.

Results. The recovery period after myocardial infarction showed an increase in collagen catabolism over collagen synthesizing processes in patients with MI who had reperfusion syndrome. The described patterns were also established by changes in glycosaminoglycans. The study showed an increase in the level of antibodies to atypical collagens. Particularly, the level of Ig M, which was within the norm (0.43±0.18) ng/ml, in patients with MI without reperfusion manifestations was three times higher ($p<0.001$), and in cases of combination of MI and reperfusion syndrome – the highest ($p<0.001$).

Conclusions:

1. Changes in collagen-synthesizing processes are observed in patients with MI, with a tendency to increase the processes of catabolism of the connective tissue matrix.
2. The presence of reperfusion syndrome manifestations in MI patients after revascularization aggravates the processes of catabolism, even in the recovery period after MI.
3. Increase in the activity of catabolic processes stimulates fibrosis and formation of rigid matrix and atypical collagen, to which antibodies are synthesized, thus blocking the pathological circuit of restructuring of the heart connective tissue framework, and accordingly its pathological remodeling.
4. The obtained study results contribute to the identification of more sophisticated approaches to revascularization techniques to avoid negative effects of reperfusion syndrome, as well as new effective medications for collagen synthesis correction, which can increase the effectiveness of rehabilitative management of such patients.

Keywords: myocardial infarction, reperfusion syndrome, connective tissue exchange, free oxyproline.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Introduction. The aim of the research. Recently, the scientists have been involved in detailed study of a phenomenon with profound biochemical and neurohumoral basis, which occurs during the complete or partial restoration of blood flow in ischemic tissue, regardless of how the revascularization took place – spontaneously or artificially. This phenomenon has got the name of reperfusion syndrome, and was based on the process of destruction and dysfunction of primary ischemic tissues caused by the restoration of arterial blood flow, which is manifested by a disintegration of cell membranes, activation of the processes of apoptosis and necrosis of cells due to violation of energy and ion exchange with an increase in the production of toxic forms of oxygen and activation of the local inflammatory reaction [4, 6, 7].

The main pathogenetic components of reperfusion syndrome are: **ischemic tissue reoxygenation syndrome** – excessive oxygen supply to cells under the influence of xanthine oxidase (which is formed in conditions of ischemia) leads to the formation of active forms of oxygen – superoxidanion, which in its turn leads to oxidative stress [12, 13]; **«calcium paradox»** and **«sodium paradox» phenomena** – as a result of ischemic dysfunction of ion pumps and excessive influx of calcium (Ca^{2+}) and sodium (Na^{+}) ions, they penetrate the cells, resulting in increase of intracellular volume with damage to intracellular structures, primarily mitochondria [1, 2, 5], accordingly resulting in the decrease of adenosine triphosphate (ATP) production and formation of cardiomyocyte contracture leading in the future to its death; **mechanical damage to cardiomyocytes** – during the initial stage of blood flow restoration process, an additional (mechanical) factor of cardiomyocyte membrane damage takes place due to their overstretching and ruptures [2, 8]; **block of the microcirculatory bed («no-reflow» phenomenon)** – damage to the endothelium, release of a certain amount of free radicals and paradoxical decrease in oxygen supply to tissues due to swelling of the endothelium and increase in the proportion of arteriovenular shunting, against the background of arterial hemodynamics restoration, the volume of blood entering the microcirculatory channel approaches normal amount, while the volume of the microcirculatory bed does not increase (this is due to the fact that long-term ischemia of the tissues of extremity leads to desolation of the microcirculatory bed with the subsequent reduction of microvessels, which is manifested by a decrease in their number and decrease in tissue blood flow), which leads to a simultaneous increase in the speed of blood flow in all microvessels and an increase in basal blood flow, at the same time, the number of real capillaries is not enough to provide an adequate volume of blood through the nutritional channel, which causes increased arteriolo-venular shunting; direct revascularization is accompanied by the progression of regional venous hypertension and profound disorders in tissue blood flow [4, 5, 10, 12, 13]; **activation of polymorphonuclear leukocytes,** which can produce a large amount of superoxide anions and are a source of proteinases, in particular elastinase, collagenases and lipoxygenases, which are secreted into the extracellular medium during degranulation and have a potent alterative effect on cell membranes; activated leukocytes promote the release of biologically active substances (thromboxane, leukotrienes that activate platelet factor), which participate in the local inflammatory reaction, in addition, the importance of neutrophils in the pathogenesis of reperfusion injury of the myocardium is due to their ability to clog capillaries in the area of ischemia/reperfusion zone being the basis for «no-reflow» phenomenon [3, 5, 9 ,12].

Profound pathogenetic changes occurring in the tissue reperfusion zone are reflected in the form of:

- reperfusion arrhythmias, which are represented by ventricular extrasystole, accelerated idioventricular rhythm, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, etc. [1, 2];

- phenomenon of myocardial «stunning», namely its reversible postischemic dysfunction [1, 10, 12];

- damage to the vessels of the microcirculatory bed and lack of coronary blood flow restoration at the tissue level («no-reflow» phenomenon – lack of dynamics in the resolution of ST segment in acute coronary syndrome (ACS) [4, 5, 12];

- accelerated development of necrosis of cardiomyocytes, the function of which was affected by prior ischemia (manifested by an increase in troponin levels) [1, 7, 13].

However, these pathological changes can be observed straight after myocardial revascularization. Proliferative processes and cell differentiation are also important, especially in patients after myocardial infarction (MI), as they significantly affect the structure and elastic properties of both arterial vessels and connective tissue matrix of the myocardium. The above mentioned factors contribute to functional changes in the left ventricle of the heart, primarily in terms of hemodynamics.

The aim: to investigate the long-term effects of reperfusion syndrome, especially its influence on the catabolic/anabolic activity of connective tissue and the processes of connective tissue framework formation in the post-infarction period in patients with ischemic heart disease.

Materials and methods. The study involved 156 patients with acute myocardial infarction with ST segment elevation (STEMI), and 15 apparently healthy individuals (control of laboratory parameters). The average age of the patients was (57.8±1.2) years. The percent of male patients prevailed (76 %).

All MI patients were divided into two groups: Group I (98 people) – MI patients without clinical signs of reperfusion syndrome during revascularization, Group II (58 people) – MI patients with the signs of reperfusion syndrome in the form of rhythm and conductivity disturbances during revascularization of coronary arteries by percutaneous coronarography intervention (PCI) with prolonged stenting of the infarct-dependent coronary artery.

Peculiarities of connective tissue metabolism were studied by the content of free and bound oxyproline, glycosaminoglycans, and antibodies to atypical collagens (Ig M and Ig G) in blood serum.

The content of free and bound oxyproline in blood serum was determined according to the method of A.A. Krel, A.N. Furtseva, H. Stegemann and K. Stalder, modified by L.A. Utevska by means of colorimetry on photoelectric colorimeter.

Biochemical technique of anion-exchange chromatography on DEAE cellulose was used to determine the levels of glycosaminoglycans. Quantitative immunoenzymometric determination of Ig M and Ig G was carried out using a set of CJSC «Vector-Best» reagents.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Statistical processing of the obtained findings was carried out by means of STATISTICA-10 computer program and Microsoft-Excel statistical software on a personal computer, using the variational statistical method of analysis. P-values less than 0.05 ($p < 0.05$) were considered statistically probable.

Results of the investigation and their discussion. Heart rhythm and conductivity disturbances during PCI were diagnosed in 52 (89.7%) examined patients of Group II, while supraventricular extrasystoles were observed in 28% and ventricular extrasystoles – 19.2% of patients. Paroxysms of atrial fibrillation/flutter were observed in 13.5% of patients, sinus tachycardia was recorded in 9.6%. Ventricular fibrillation and ventricular tachycardia were registered in 11.5% and 5.8% of patients, respectively. III-degree (complete) atrioventricular block occurred in 3.8% of patients, asystole with successful rhythm recovery (3.8%), transient His bundle branch block (3.8%). In 3.8% of patients, reperfusion syndrome developed on the first day after PCI and was manifested in recurrent paroxysms of ventricular tachycardia. The "no-reflow" phenomenon was observed in 6 (10.3%) patients.

The analysis of exchange indicators in connective tissue showed that both MI patients without the development of reperfusion syndrome and patients with previous MI with the development of reperfusion syndrome, had a number of changes which, on the one hand, reflect the activity of collagen metabolism, and at the same time point to the mechanisms stimulating the formation of undesirable «hard» types of collagens (Table 1).

Table 1

Indicators of collagen synthesizing functions in MI patients with and without reperfusion syndrome manifestations (M±m)

Indicator, units of measurement	Healthy (n=7)	Patients with MI (n=98)	Patients with MI and RS (n=58)
Free oxyproline, μmol/l	11.78±0.26	12.48±0.23 $p_1<0.05$	14.80±0.37 $p_1<0.001$ $p_2<0.001$
Bound oxyproline, μmol/l	8.45±0.18	9.46±0.38 $p_1<0.05$	10.25±0.34 $p_1<0.01$ $p_2>0.5$
Glycosaminoglycans, g/l	0.089±0.009	0.204±0.004 $p_1<0.001$	0.226±0.008 $p_1<0.001$ $p_2<0.01$
Antibodies to atypical collagen (Ig M), ng/ml	0.43±0.18	1.48±0.11 $p_1<0.001$	2.03±0.12 $p_1<0.001$ $p_2<0.01$
Antibodies to atypical collagen (Ig G), ng/ml	2.61±0.67	6.83±0.55 $p_1<0.01$	8.14±0.59 $p_1<0.001$ $p_2>0.05$

Note: The difference in probability rates: p1 – as compared to healthy individuals; p2 – as compared to patients with MI.

The activity of metabolism (catabolic and anabolic processes) of collagen is manifested in the increased levels of both free and bound oxyproline, since it is a well known fact that the concentration of free fraction of oxyproline is an indicator of collagen catabolism, and the level of protein-bound oxyproline content reflects its synthetic component. Profound analysis of these indices showed their probable differences in the investigated groups of patients.

Thus, the blood level of free oxyproline in MI patients without reperfusion manifestations significantly exceeded its level in healthy individuals ($p <0.05$), and in case of MI with reperfusion syndrome its level was the highest – (14.8 ± 0.37) μmol/l ($p <0.001$). Similar changes were observed in blood levels of bound oxyproline: (9.46 ± 0.38) μmol/l in MI patients without reperfusion manifestations and (10.25 ± 0.34) μmol/l in MI patients with reperfusion syndrome, as compared to (8.45 ± 0.18) μmol/l in healthy ($p <0.05$) individuals. If we trace the dynamics of these indices in the recovery period after MI, we will observe that the level of free oxyproline in patients with MI, who experienced manifestations of reperfusion syndrome during revascularization in the acute phase, was significantly higher than in MI patients without reperfusion manifestations, while the analysis of bound oxyproline did not show a significant difference ($p> 0.5$). Therefore, even in the recovery period after MI, we observed the prevalence of collagen catabolism over collagen-synthesizing processes in patients with MI who experienced reperfusion syndrome. The above described patterns are also specified by changes in another marker – glycosaminoglycans. Their level in the blood of patients with reperfusion manifestations was (0.226 ± 0.008) g/l, which was significantly higher than in healthy individuals ($p <0.001$) and even higher than in MI patients without reperfusion manifestations ($p <0,01$). This is most likely due to a prolonged reaction of local inflammation in patients with reperfusion syndrome, and therefore the activity of superoxide anions, proteinases and other biologically active substances.

High levels of bound oxyproline in the blood of MI patients with and without reperfusion syndrome, as compared to healthy individuals, indicate a tendency to constant pressure as well as collagenosynthetic processes in such patients.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

However, the study showed an increase in the levels of antibodies to atypical collagen. Thus, the level of Ig M, which in the norm makes up (0.43 ± 0.18) ng/ml, was three times higher ($p<0.001$) in MI patients without reperfusion manifestations and when combined with MI and reperfusion syndrome it reached the highest level ($p <0.001$).

The content of Ig G, as one of the markers of antibodies to atypical collagen, was also significantly higher in MI patients as compared to healthy individuals ($p <0.01$). On the other hand, the increased Ig G values in MI patients with and without the signs of reperfusion did not significantly differ ($p> 0.05$), although the tendency to higher Ig G values was observed in MI patients with reperfusion syndrome, and made up (6.83 ± 0.55) ng/ml and (8.14 ± 0.59) ng/ml respectively. It should be noted that in this case Ig M can be considered an early marker of «rigid» collagen synthesis activation, and Ig G level indicates remote changes in collagen synthesis. Thus, the blood level of free and bound oxyproline, glycosaminoglycans and antibodies to atypical collagen, including Ig M, may be considered the most informative markers to establish peculiar changes in connective tissue in the recovery period after MI.

Therefore, the activation of collagen metabolism on the one hand is aimed at ensuring the formation of connective tissue matrix of the heart, which is adequate to changes in the myocardial mass of the left ventricule as well as complete scarring in the myocardial necrosis zone (after MI), and on the other hand, these prolonged stiffening in catabolism and anabolism of connective tissue processes contributes to the tendency to synthesize atypical collagen (more obvious in patients after MI with reperfusion syndrome). This leads not only to an increase in the «stiffness» of the left ventricle, but also provokes its pathological remodeling.

Conclusions:

1. Changes in collagen-synthesizing processes are observed in patients with MI, with a tendency to increase the processes of catabolism of the connective tissue matrix.
2. The presence of reperfusion syndrome manifestations in MI patients after revascularization aggravates the processes of catabolism, even in the recovery period after MI.

Increase in the activity of catabolic processes stimulates fibrosis and formation of rigid matrix and atypical collagen, to which antibodies are synthesized, thus blocking the pathological circuit of restructuring of the heart connective tissue framework, and accordingly its pathological remodeling.

The obtained study results contribute to the identification of more sophisticated approaches to revascularization techniques to avoid negative effects of reperfusion syndrome, as well as new effective medications for collagen synthesis correction, which can increase the effectiveness of rehabilitative management of such patients.

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ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

УДК 616.127-008.9+616.127-005.8+612.276

ОСОБЛИВОСТІ СПОЛУЧНОТКАНИННОГО МЕТАБОЛІЗМУ У ХВОРИХ З ПОСТІНФАРКТНИМ РЕМОДЕЛЮВАННЯМ ТА РЕПЕРФУЗІЙНИМ СИНДРОМОМ

Н.М. Середюк, І.П. Вакалюк, Я.Л. Ванджура, Р.В. Деніна, І.Ю. Ванджура, П.П. Звонар

Івано-Франківський національний медичний університет, кафедра внутрішньої медицини № 2 та медсестринства, м. Івано-Франківськ, Україна,
ORCID ID: 0000-0002-3616-2445,
ORCID ID: 0000-0002-4430-6816,
ORCID ID: 0000-0003-2525-371X,
ORCID ID: 0000-0001-8196-7130,
ORCID ID: 0000-0001-5905-487X,
ORCID ID: 0000-0001-6121-5281,
e-mail: roksolanadoc@ukr.net

Резюме. Раннє відновлення коронарного кровоплину при гострому інфаркті міокарда з елевацією сприяє зменшенню зони некрозу міокарда, попередженню дилатації порожнини шлуночків, зниженню розвитку аритмій та смертності. Однак, незважаючи на сучасні технології лікування STEMI після відновлення кровоплину в інфарк-залежній артерії можливий розвиток реперфузійного синдрому, зокрема аритмій, які є наслідоком гострих клітинних, метаболічних і локальних електрофізіологічних змін у міокарді.

Мета. З'ясувати віддалені наслідки впливу реперфузійного синдрому на катаболічно/анаболічну активність сполучної тканини та процеси формування сполучнотканинного каркасу в постінфарктному періоді в пацієнтів з інфарктом міокарда.

Матеріали і методи. Проведено клініко-лабораторне обстеження156 хворих на гострий інфаркт міокарда з ознаками та без ознак реперфузійного синдрому. Особливості сполучнотканинного метаболізму вивчали за вмістом у сироватці крові вільного та зв'язаного оксипроліну, глікозаміногліканів, антитіл до атипічних колагенів (Ig M та Ig G).

Результати. У відновному періоді після ІМ спостерігається підвищення колагенового катаболізму над колагенсинтезуючими процесами в пацієнтів з ІМ, у яких мав місце реперфузійний синдром. Описані закономірності констатовані і за змінами – глікозаміногліканів. Спостерігалося зростання рівня антитіл до атипічних колагенів, зокрема рівень Ig M, складаючи в нормі (0,43±0,18)нг/мл, у хворих на ІМ без реперфузійних проявів був втричі вищим ($p<0,001$), а при поєднанні ІМ та реперфузійного синдрому – найвищим ($p<0,001$).

Висновки. Встановлено, що при поєднанні у хворих інфаркту міокарда з наявними клінічними ознаками реперфузії ще в більшій мірі констатують виражені порушення деструктивно-синтетичних процесів сполучної тканини, що веде за собою стимуляцію синтезу атипових колагенів та посилює процеси реструктуризації міокарда.

Ключові слова: інфаркт міокарда, реперфузійний синдром, обмін сполучної тканини.

Стаття надійшла в редакцію 22.02.2023 р.
Стаття прийнята до друку 23.03.2023 р.