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Shved MI
Ternopil State Medical
University By I.Ya.
Horbachevsky, Ministry of
Health of Ukraine, Ternopil,
Ukraine

Tsuglevich LV
Ternopil State Medical
University By I.Ya.
Horbachevsky, Ministry of
Health of Ukraine, Ternopil,
Ukraine

Heryak SM
Ternopil State Medical
University By I.Ya.
Horbachevsky, Ministry of
Health of Ukraine, Ternopil,
Ukraine

Prokopovich OA
Ternopil State Medical
University By I.Ya.
Horbachevsky, Ministry of
Health of Ukraine, Ternopil,
Ukraine

Correspondence
Shved MI
Ternopil State Medical
University By I.Ya.
Horbachevsky, Ministry of
Health of Ukraine, Ternopil,
Ukraine

Effectiveness of metabolic therapy in patients with acute coronary syndrome (ACS) - myocardial infarction (MI) with dysfunctional liver conditions

Shved MI, Tsuglevich LV, Heryak SM and Prokopovich OA

Abstract

The purpose of this work was to improve the existing therapeutic programs of ACS (myocardial infarction) by differentiated approach to therapy depends of the presence or absence of violations of the liver functional state. There are a violation of central and peripheral hemodynamics, endothelial function of the vessels in patients with myocardial infarction, which leads to a violation of protein synthesis, detoxification, energy-supplying function of the liver, lipid metabolism. At the same time excessive activation of peroxide processes of lipids, suppresses the activity of enzymes of the antioxidant system enhances pathological processes in the heart and liver. Violation of the functional state of the liver in patients with myocardial infarction significantly impairs the clinical course of the basic pathological process, further exacerbates the violation of systolic and diastolic function of the heart and contributes to the more frequent development of complications of ACS (MI). Inclusion in the complex program of patients treatment with acute coronar syndrome (MI) L-arginine and L-carnitine contributes to the restoration of endothelial function of blood vessels, antioxidant protection of the body and increases energy supply of myocarditis, which is accompanied with the improvement of contractile myocardium function and reduction of clinical and laboratory manifestations of cytolytic and cholestatic syndromes in these patients.

Keywords: Acute coronary syndrome, liver, treatment

Introduction

According to our previous studies [8], comparing with the results of international pre-RELAX-AHF and ESCAPE multicentre studies (2014), a violation of the functional state of the liver (FSL) in a myocardial infarction (MI) is associated with its complicated course and manifested by the development of a cytolytic, cholestatic syndromes and decreasing of the synthesizing liver function [6]. Persons who applied for a treatment later than 6 hours after the onset of an angina attack or for other reasons, in particular, comorbidity, are in the risk group and have contraindications to fibrinolytic therapy or percutaneous coronary intervention, that subsequently undergo standard pharmacotherapy of myocardial infarction [15, 16]. However, this protocol therapy does not take into account the functional state of the liver in these patients, which may significantly impair their immediate and distant prognosis [8, 17]. In addition, the treatment of patients with acute coronary syndrome (ACS) - (MI) and liver functional status disorders due to non-alcoholic steatosis is the limited use of statins that can strengthen liver dysfunction [14]. Therefore, priority is given to a differentiated approach to the treatment of patients with acute coronar syndrome (myocardial infarction), considering comorbid pathology [9, 12, 13].

The purpose of this work was to improve the existing therapeutic programs of ACS (myocardial infarction) by differentiated approach to therapy depends of the presence or absence of violations of the liver functional state.

Materials and methods: The study was conducted on the base of the cardiology department of the Ternopil University Hospital during 2012-2018. 149 patients with acute myocardial infarction were selected. General clinical examination, determination of myocardial necrosis biomarkers (troponin I and creatine phosphokinase MB), lipidogram, coagulogram, electrocardiography in 12 common leads were done in the first day of hospitalisation. The patients were divided into 2 groups, depending on the revealed violations of the liver functional state.

The main study group included 107 patients with ACS (myocardial infarction) and violations of the liver functional state. The control group included 42 patients with acute myocardial infarction (MI) who had not been diagnosed atrial fibrillation. 52 patients of the main and 22 - of control group received standard treatment of myocardial infarction, according to the Unify Protocols of the Ministry of Health of Ukraine. Another 55 patients in the main group and 20 patients from control group received modified treatment with an additional of 4.2 g of L-arginine and 2.0 g of L-carnitine (Tivorel) in the 100 ml solution intravenously, once a day, 5 days. For the study of intracardial hemodynamic an echocardiography was performed in the B-mode with the use of the Aloka SSD-2000 (US) apparatus at rest, on the third - fifth, fifteenth and twentieth day of the study. Indicators of activity of lipid peroxidation (LPO) and antioxidant system (AOS) were evaluated by the results of plasma content of malone dialdehyde (MDA) (ID Stalna, TG Garishvili, 1977), concentration of SH groups, activity of dismutase superoxide (SOD) (KF 1.15.1.1) - by degree of inhibition of reduced nitrotetrazolium blue (E .E. Dubinina *et al.*, 1983); catalase activity (CT) in erythrocytes (KF 1.11.1.6) - photocolometric method (MA Korolyuk *et al.*, 1988). The blood cholesterol content was determined by the Ilk method (with the Lieberman-Burhard reagent). The functional state of the liver was evaluated based on the results of clinical and biochemical examination (bilirubin level, total protein, cholesterol, lipid fractions, prothrombin, hepatic alanine (Al-AT), and aspartate aminotransferase (As-AT), gammaglutamyltransferase (GGT), alkaline phosphatase (AIF), and ultrasound liver examination.

The research is conducted in compliance with the provisions of the Council of Europe Convention on Human Rights and Biomedicine, the Helsinki Declaration of Recent Review, as well as the recommendations of the Bioethics Committee at the Presidium of the National Academy of Medical Sciences of Ukraine.

Statistical analysis of data was used by the STATISTICA application package (StatSoft, USA, v 6.0). The T-Wilcoxon standard and the Spirman rank correlations for the determination of the presence and strength of the relationship between the investigated parameters were used as the methods of nonparametric statistics. Statistically significant differences were considered at $p < 0,05$. These surveys were repeated on the 14th and 28th day. The study group included patients with a verified diagnosis of acute myocardial infarction in accordance with the European Society of Cardiologists Recommendations (2016) from the first day of hospitalization. Exclusion Criteria from the study were the presence of chronic liver disease in patients with chronic hepatitis, history of alcohol abuse, prolonged use of hepatotoxic drugs, oncology, severe acute left ventricular failure (IV FK by T.Killip), cardiac decompensation (HF II B-III according to M.D. Strazhesko, V.H. Vasilenko).

Surgical coronary intervention and/or thrombolytic therapy in patients of the main and control groups were not conducted due to contraindications or written refusal.

Results and discussion: The uncomplicated course of myocardial infarction (40%) was noted in 17 patients of the control group. In 84 patients with MI who had a violation of the functional state of the liver, the underlying disease was due to various complications (78,5%). Thus, in 42 (39,3%) patients of the main group, epistenocardiac pericarditis was significantly more prevalent compared with 8 patients (19%) of control group. Violations of rhythm or conduction, manifested by paroxysmal tachyarrhythmias, transient atrioventricular blockades and blockade of the Gissa branch legs, extrasystolic arrhythmia were also more common in patients of the main group (35,5%) and much less frequently in patients with MI without violations of the functional state of the liver (21,4%). In addition, 17 (15,9%) patients with MI were accompanied with the development of the left ventricular aneurysm and only 4 (9,5%) of the examined control groups. Acute left ventricular failure accompanied the course of the MI in all patients of both groups, but the GSN I and II of the FC for Killip et Kimball (1972) were significantly more frequent in patients in the control group, while the GSN III FK was significantly more diagnosed in patients with the main group. It was found that the development of epistenocardiac pericarditis was more characteristic of persons who were in the age group of 45-65 years (in 24 (17,8%) patients), while the left ventricular aneurysm and the development of arrhythmias were significantly more common in persons of the older age group, respectively (in 7 (5,3%) and 19 (13,4%) patients).

At the same time, patients with both the primary and control groups observed a violation of the systolic and diastolic function of the left ventricle (Table 1). Though more significant decrease of the myocardium contractile function (EF - 42, $12 \pm 1,13\%$) compared with the control (EF - 48, $23 \pm 1,16\%$). The indicated changes were closely related to the more pronounced left ventricular remodeling processes in the acute period of myocardial infarction in patients with the main group. In particular, an increase in the diameter of the left ventricular cavity - LV diastolic diameter.

In the main group was $5,62 \pm 0,21$ sm, in the control group it was $4,71 \pm 0,24$ sm ($p < 0,05$). The development of diastolic dysfunction was evidenced by changes in the time of IVRT in the main ($63,23 \pm 0,41$ ms) and in control groups ($68,12 \pm 0,36$ ms), as well as in the time of retardation of the early diastolic transdermal flow (DT) in comparable groups ($178,11 \pm 0,54$ ms and $182,43 \pm 0,37$ ms).

After the standard treatment of MI in patients of the control group there was a significant improvement in hemodynamic parameters, in particular, the left ventricular ejection fraction increased, CDL + was decreased, diastolic function of LV-IVRT and DT improved in comparison with patients with MI, that showed functional impairment of the liver ($p < 0,05$).

Table 1: Dynamics of indicators of systolic and diastolic functions of the heart in patients with myocardial infarction under the influence of proposed treatment programs ($M \pm m$)

Indication	№	Before treatment	Standard treatment	Standard treatment + L-arginine and L-carnitine
LV diastolic diameter, sm	1	5,62±0,21	5,84±0,07	5,23±0,18*
	2	4,71 ±0,24	5,58±0,14	5,53±0,12
E/A	1	1,35±0,03	1,03±0,04	1,31±0,03*
	2	1,41±0,03	1,19±0,05	1,38±0,07
IVRT, ms	1	63,23±0,41	68,13±2,10	76,13±1,11*
	2	68,12±0,36	73,21±1,26	79,27±1,33*
DT, mc	1	178,11±0,54	164,26±4,66	214,22±4,23*
	2	182,43±0,37	184,62±4,35	213,65±4,21*
EF, %	1	42,12±1,13	43,28±0,23	49,68±0,32*
	2	48,23±1,16	48,76±1,36	51,62±1,62*
ST, ml	1	47,14±0,79	49,26±2,29	51,43±1,20
	2	52,88±1,62	59,26±2,15	59,68±1,56

1. 1,2 - accordingly indicators in patients with MI with AF and without AF ;
2. The underlying values are significantly different from those in the control group ($p<0,05$);
3. * - the rates are significantly different from those in patients who received standard treatment.

However, in patients with myocardial infarction with AF, standard treatment implies only an indirect effect to improving the liver function by overall hemodynamics and does not reduce direct hepatocyte-protective effects, which is accompanied with longer activation of oxidative processes and inhibition of the enzymes activity in the antioxidant defense system. As a result, pathological processes are deeper both in the heart and in the liver.

L-arginine and L-carnitine are perspective in this regard, as they pronounce metabolic and energy-producing activity, restore the endothelial function of blood vessels, have antioxidant effects and prevent irreversible ischemic and reperfusion damage, limit the area of myocardial necrosis, improve the processes of adaptation of cells to function in hypoxia conditions, reduce the pathological cardiac remodeling processes. One of the mechanisms of such therapeutic effect is their ability to suppress the formation of radicals in the decomposition of fatty acids and thereby reduce the damaging effects of peroxidation products on the functional state of the ion channels of the body's cell [4, 5].

The hepatoprotective effect of L-arginine and L-carnitine is manifested not only due to cytoprotective effects on the hepatocyte membrane (normalization of phospholipid metabolism, reduction of permeability of the vascular-cellular barrier, inhibition of LPO, and severity of systemic inflammation processes). According to our research, it has been proved that a positive effect based on the contractile function of the myocardium provides improved hepatic hemodynamics, which ultimately leads to a decrease in the negative effects of hypoxia on the integrity and functioning of hepatocytes [1, 9, 10].

Thus, it was found that in patients with the main group of application of a comprehensive program of treatment with the inclusion of Tivorel significantly affected the restoration of systole-diastolic function of the heart: normalization of the parameters of systolic and diastolic functions of the heart came within 28 days of treatment. In this case, the linear dimensions of the cavity of the heart changed insignificantly, so we can assume that the positive dynamics of the parameters of EF, LV diastolic diameter, IVRT and DT compared with the indicators in the initial state were due to remodeling and restoration of the functional state of ischemia zones and myocardial hypertension [7]. In this case, we note the significant difference between all the studied parameters in patients with the main and control groups in the initial state.

Detected violations of the functional state of the liver in patients with myocardial infarction at the beginning of treatment first of all were manifested with the presence of a cytolysis syndrome, which is associated with hepatocyte membranes damage and intrahepatic cholestasis. A moderate decrease of total protein level according to hypoalbuminemia in this group of patients indicates an initial violation of the synthetic liver function. In addition, patients of the main group were more likely to have dyslipidemia, that was manifested by hypercholesterolemia and an increasing of atherogenic fractions of lipoproteins, in particular LDL cholesterol.

In the course of the observation, it was noted that, against the background of the use of traditional therapy during the hospital period of the MI treatment in patients with AF, not only the liver function indicators improved, but also less complications compared with the group of patients, that received standard therapy, marked significantly. Thus, in patients of the main group the incidence of episthenocardic pericarditis was reduced by 33,2%, heart failure - by 63,9% and development of early post-infarction angina - by 22,2% after two weeks of complex treatment with the inclusion of L-arginine and L-carnitine. Significantly the frequency of rhythm and conduction disorders decreased in patients, who had received Tivorel, with myocardial infarction and functional disorders of the liver, In particular, the frequency of sinus tachycardia for 28 days decreased by 63,9%, conduction violations along the His beam legs - by 16,7%, ventricular extrasystoles - by 41,7% and supraventricular extrasystoles - by 52,8% less than the baseline.

A comparative analysis of the efficacy of standard treatment and the proposed modified (using a tourniquet) in patients of the main and control groups showed that in the experimental group of patients the main manifestations of cytolytic and cholestatic syndromes were normalized for the 14th day. At the same time, in patients that received standard treatment, the hepatoprotective effect was not achieved. They maintained a significant difference between the cholestasis, cytolysis and dyslipidaemia before and after the course of treatment.

The obtained results coincide with those of Jin H., Juan J. [12, 13], who found that the liver is extremely sensitive to hypoxia in the body, so it is clear so-called "ischemic hepatitis" as a result of acute MI and acute hemodynamic disorders. Thus, conjunction with the activation of LPO dyslipidaemia is one of the causes of the development of it. Its enzymatic activity, inhibition of processes of biotransformation and functions are

violated. in particular, synthetic, exchange, detoxication is marked under the conditions of cytotoxic influence on hepatocytes of products of Lipid peroxidation. These processes result in the accumulation of a large number of modified lipids in hepatocytes and fatty liver transplantation. As a result, the processes of regeneration in the body slow down, that contributes to pathological remodeling of the heart. In addition, proinflammatory agents directly damage the hepatocyte membranes and increase hepatic dysfunction. Toxic LPO products also damage RNA, DNA, nucleotide phosphates, which leads to mitosis reduction, development of chromosomal aberrations and mutations, and, ultimately, to inhibition of cell regeneration [2, 3, 4].

Thus, the results of the study allow us to conclude that the violation of the functional state of the liver significantly affects the course of acute myocardial infarction and is accompanied by a significantly higher frequency of complications. Such patients experience more profound violations in the system of lipid peroxidation and decrease the activity of antioxidant defense, which in turn violates the endothelial function of blood vessels and contributes to deterioration of hemo-microscopic circulation. Simultaneously, there is a significant decrease in systolic and diastolic function of the myocardium in patients with MI with AF due to the violation of the remodeling processes of the heart chambers and the change of their linear-geometric parameters.

Comprehensive treatment of patients with MI with violations of the functional state of the liver with the inclusion of L-arginine and L-carnitine contributes to the restoration of endothelial function of blood vessels, antioxidant protection of the organism and reduction of clinical and laboratory manifestations of cytolytic and cholestatic syndromes, which, as a result, improves the contractile function of the myocardium.

Conclusions

1. There are a violation of central and peripheral hemodynamics, endothelial function of the vessels in patients with myocardial infarction, which leads to a violation of protein synthesis, detoxification, energy-supplying function of the liver, lipid metabolism. At the same time excessive activation of peroxide processes of lipids, suppresses the activity of enzymes of the antioxidant system enhances pathological processes in the heart and liver.
2. Violation of the functional state of the liver in patients with myocardial infarction significantly impairs the clinical course of the basic pathological process, further exacerbates the violation of systolic and diastolic function of the heart and contributes to the more frequent development of complications of ACS (MI).
3. Inclusion in the complex program of patients treatment with acute coronar syndrome (MI) L-arginine and L-carnitine contributes to the restoration of endothelial function of blood vessels, antioxidant protection of the body and increases energy supply of myocarditis, which is accompanied with the improvement of contractile myocardium function and reduction of clinical and laboratory manifestations of cytolytic and cholestatic syndromes in these patients.

References

1. Аляві АЛ, Кенжаєв МЛ, Аляві БА. Вплив корвітину на зворотню дисфункцію міокарда лівого шлуночка у хворих з гострим коронарним синдромом з елевацією сегмента ST. Практична ангіологія. 2009; 1:55-59.
2. Лутай ЯМ, Пархоменко ОМ, Рижкова НА, Гавриленко ТІ та ін. Вплив терапії внутрішньовенним інгібітором 5-ліпоксигенази кверцетином на функцію ендотелію, вираженість системного запалення і оксидативного стресу при гострому інфаркті міокарда з елевацією ST. Медицина невідкладних станів, 2016, 1(72).
3. Лутай ЯМ, Пархоменко ОМ, Степура АА, Іркін ОІ та ін. Клініко-прогностичне значення результатів проби з потік-залежною вазодилатацією у хворих з гострим коронарним синдромом з елевацією ST. Медицина невідкладних станів. 2014, 3(58).
4. Мойбенко ОО, Пархоменко ОМ. Ефективність водорозчинної форми кверцетину (Корвітину) при лікуванні гострого коронарного синдрому з елевацією сегмента ST. <http://health-ua.com/article/671.html>.
5. Пархоменко АН. Метаболічна терапія, або кардіопротекція при ішемічній хворобі серця: підсумки та перспективи. Укр. мед. журнал. 2008; 4(66):15-19.
6. Пархоменко ОМ, Кожухов СН, Лутай ЯМ. Обґрунтування і дизайн багаточентрового рандомізованого дослідження ПРОТЕКТ - вивчення ефективності та безпеки застосування кверцетину у пацієнтів з гострим інфарктом міокарда. Український кардіологічний журнал. 2016; 3:31-36.
7. Пархоменко АН, Кожухов СН. Результати відкритого рандомізованого дослідження з вивчення переносимості та ефективності препарату Корвітин у пацієнтів із застійною серцевою недостатністю і систолічною дисфункцією лівого шлуночка. Лікарю-практику. 2014, 4(102).
8. Порушення функціонального стану печінки та його корекція у хворих на інфаркт міокарда : автореф. дис. ... канд. мед. наук : 14.01.11 / О. А. Прокопович; ДВНЗ "Івано-Франків. нац. мед. ун-т". - Івано-Франківськ, 2012. - 20 с. - укр.
9. Швед МІ, Прокопович ОА. Лікування хворих на інфаркт міокарда з порушеннями функціонального стану печінки. Галицький лікарський вісник. 2011; 2:130-134.
10. Bartekova M, Carnicka S, Ondrejckova M, Breier A, Rgerova T. Acute treatment with polyphenol quercetin improves postischemic recovery of isolated perfused rat hearts after global ischemia. Can. J. Physiol. Pharmacol. 2010; 88:465-471.
11. Gregory S. Quercetin. AMR 2011; 16(2):172-94
12. Jin H, Song Y, Zhang Y *et al.* Protective roles of quercetin in acute myocardial ischemia and reperfusion injury in rats. Mol. Biol. Rep. 2012; 39:11005-11009.
13. Juan J. Antioxidants decrease reperfusion induced arrhythmias in myocardial infarction with ST-elevation. Frontiers in Bioscience. 2007;12:2029-2037.
14. Kwo Paul Y. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. Am. J Gastroenterol advance. 2016; 20:1-18.

15. Silber S. Evidence-based management of ST-segment elevation myocardial infarction (STEMI). Latest guidelines of the European Society of Cardiology (ESC) Herz. 2010; 35:558-564
16. Van de Werf F, Bax J, Betriu A *et al.* Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Europ. Heart. J. 2008; 29:2909-2945
17. Yellon D, Hausenloy D. Myocardial Reperfusion Injury. N. Engl. J Med. 2007; 357:1121-35.