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CHANGES OF BASIC INTERMEDIATES IN BLOOD IN MYOCARDIAL INFARCTION

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Abstract: The elucidation of molecular mechanisms of cardiac activity is an important issue. The search for new means of pathogenetic correction of cardiovascular system activity disorders at myocardial infarction of various genesis, angina pectoris based on atherosclerotic process is still actual.

Objective. To determine the main intermediates in arterial and venous blood in norm, acute and subacute phase of myocardial infarction and during scarring.

Materials and Methods. Experiments were carried out in two series with a total of 46 experimental animals. The hearts of 5 experimental and 5 control animals were used in in vitro experiments. In vivo experiments on exogenous enzyme injection were performed on 12 experimental and 7 control animals.

Results. Clearly increased molar concentration of compounds with marked acidic properties creates the preconditions of metabolic acidosis. Fluctuations of the total serum protein at the lower limit of the norm cause the possibility of its development.

Conclusion. The presence of correlation between metabolic shifts in the heart muscle and in peripheral blood, aortic blood in the dynamics of myocardial infarction provides the possibility to use determination of free fatty acids, dioxyacetone phosphate, oxaloacetate content as diagnostic tests.

Keywords. Myocardial infarction, glycerol, oxaloacetate, lactate, α-glycerophosphate, dioxyacetonephosphate.

Introduction

Disability of population due to diseases of cardiovascular system, high percentage of mortality due to ineffective medical care determines the need for new experimental methodological approaches to create a theoretical basis sufficient to build a model of energy, plastic needs of the heart muscle in extreme conditions, which will contribute to the successful solution of a number of biomedical problems associated with survival, reveals the prospects of specific effects on the sick organ.

The elucidation of molecular mechanisms of cardiac activity provision is an important issue, the solution of which will provide medical science with fundamental data necessary for searching new means of pathogenetic correction of cardiovascular system activity disorders in myocardial infarction of

various genesis, angina pectoris based on atherosclerotic process [3,4].

The **aim** of the study was to determine the distribution of the main intermediates in arterial and venous blood in norm, acute and subacute phase of myocardial infarction and during scarring.

Materials and Methods

Experiments were carried out in two series, in which a total of 46 experimental animals were used. Myocardial infarction was reproduced in 23 experimental animals [5]. The control group of this block of studies included 5 animals, both intact and falsely operated. The hearts of 5 experimental and 5 control experimental animalsts were used in in vitro experiments. In vivo experiments on exogenous enzyme administration were performed on 12 experimental and 7 control animals. Experimental animalswere kept in standard vivarium conditions and had weight of 2.5 - 3.5 kg.

The presence of myocardial infarction in experimental animals was documented electrocardiographically on an iMAC300 digital electrocardiograph and histologically. The dynamics of changes in the determined indices was monitored on days 1, 3, 7, 10, 20 and 30 of coronary-occlusive myocardial infarction development [11].

Blood and myocardium were the objects of investigation. Blood sampling was performed from auricular vein, aorta and coronary sinus. To study the content of metabolites in different parts of the heart the anterior wall of the left ventricle (infarction zone), anterolateral wall of the left ventricle (perinfarction zone), posterior wall of the left ventricle and the right ventricle (intact zone) were distinguished.

Cardiac mitochondria were isolated according to the conventional technique by differential centrifugation. The homogenate was sequentially centrifuged twice on a cooled HermleZ 383 K centrifuge (Hermle, Germany) for 5 min at 1500g and 4000g, followed by removal of sediment, then centrifuged at 15000g for 15 min, followed by removal of supernatant. Then it was centrifuged again without cooling at 15000g for 15 minutes [6].

Loading with exogenous substrates by their transaortic administration in the acute period of myocardial infarction and control was carried out so as to obtain in the blood of experimental animals concentration of these compounds 10-15 times higher than the norm. For lactate this amount was 0,954mg, for pyruvate - 31,3mg, for oxaloacetate - 31,2mg, for malate - 497,8mg, for α-glycerophosphate - 176,19mg, for dioxoacetone phosphate - 62,32mg, and for glycerol 0,0865mg. For incubation with cardiac mitochondria 0.006mg pyruvate and 0.955mg malate were used [12].

Lactate dehydrogenase preparation (KF 1.1.1.27) was used as exogenous dehydrogenase, which after release from ammonium sulfate was injected into the ear vein of a experimental animalst at a rate of 5000 U/kg.

Determination of malate, lactate, α-glycerophosphate, glutamate, oxaloacetate, dioxyacetone phosphate, and pyruvate was performed on a RT-1904C biochemical analyzer.

Contents of glycerol, protein, glycogen, urea were determined by conventional methods, glucose by glucose oxidase method, free fatty acids by colorimetric method [12].

Activity of malate dehydrogenase was determined by S.Ochoa method, glutamate dehydrogenase - by G.Hogeboom and W.C.Schneider method, lactate dehydrogenase - by A. Kornberg, aldolase - by M.F. Gulov method, aspartate aminotransferase and alanine aminotransferase - by Bio-Test kit [12].

Assessment of metabolites content and enzyme activity was performed on RT-1904C.

The results were processed by the method of variation statistics on a computer using the STATISTICA 6 package.

Research results

Energy supply of any tissue, organ is the basis for performing the function and restoration of structures in the process of life activity. For a diseased organ, the level and nature of the molecular mechanisms of life support, their coherence provides the current processes, but

also the possibility to get out of the pathological situation. Myocardium is the object of close study not only by cardiologists, but also by specialists of basic sciences, especially biochemists. The interest is caused on the one hand by the prevalence of cardiovascular diseases, occupying the leading place as the cause of population disability and mortality, and on the other hand by a certain autonomy of the heart and the features of metabolism, providing this autonomy.

Normally, lactate can be compared with free fatty acids in terms of oxidation activity, the values of arterio-venous difference for oxaloacetate and glycerol are comparable (Table 1). Given the high concentration of lactic acid in peripheral blood and aortic blood, the role of this metabolite in myocardial metabolic processes is obvious. Note that the concentration of glycerol and free fatty acids in the aortic blood is higher than in the peripheral blood. This is characteristic only for these lipid components: the content of glucose, malate, oxaloacetate, α-glycerophosphate is lower, and dioxyacetone phosphate and protein are almost similar. It can be assumed that the source of glycerol, free fatty acids found in increased concentration in the aortic blood may be abundantly vascularized pulmonary tissue. Glycerol and higher fatty acids formed as a result of lipoprotein lipid cleavage are partially used in pulmonary tissue metabolism and along with it enter the left ventricle into the aorta with the bloodstream.

The study was continued by determining the above integral metabolites in the dynamics of myocardial infarction development both in the blood and in different myocardial sites.

Table I Metabolites content in peripheral blood, aortic blood and coronary sinus of intact experimental animals (M±m)

Metabolites (μmol/ml)	Peripheral blood	Aortic Blood	Coronary Sinus	Arterio-venous difference (%)
Malate	1,43±0,03	0,82±0,01	0,78±0,03	4,9
Oxaloacetate	0,09±0,03	0,08±0,01	0,07±0,01	16,3
Lactate	3,92±0,14	3,24±0,17	2,53±0,11	21,9
Pyruvate	0,14±0,02	0,14±0,01*	0,13±0,01	4,9
α-glycerophosphate	0,39±0,01	0,32±0,02	0,30±0,01	4,7
Dioxyacetone phosphate	0,14±0,01	0,14±0,01*	0,12±0,01	14,8
Glycerol	0,46±0,02	0,54±0,03	0,44±0,02	18,9
Free fatty acids (mmol/L)	0,44±0,02	0,54±0,04	0,83±0,02	29,3
Glucose (mmol/L)	4,72±0,14	3,85±0,12	3,71±0,21*	3,7
Protein (mg/ml)	78,14±4,08	77,41±3,11*	76,18±5,12*	1,6

*- P>0.05 relative to control values

Assessment of the results obtained by blood studies in the acute period of the disease showed that with the exception of malate, whose content decreased compared with control by 15,2% (P<0,01), the concentration of dioxyacetone phosphate, oxaloacetate, lactate, glycerol, α-glycerophosphate, pyruvate increased significantly by 158,1%, 135,1%, 89,7%, 50,2% and 39,4% respectively. At the same time, the level of compounds important for tissue energy supply, such as fatty acids and glucose, also changes upward by 151.0% and 76.2% (P<0.001), respectively.

The use of cardiac muscle metabolites in the dynamics of myocardial infarction can be judged by the data given in Table 2.

Table 2. Distribution of main intermediates in arterial and venous blood at different terms of myocardial infarction (M±m)

Metabolites (μmol/mL	Days after occlusion	Peripheral blood	Aortic blood	Coronary sinus	Arterio-venous difference (%)
Malate	1 day	1,22±0,02	0,68±0,01	0,61±0,02	1,4
	3 day	1,21±0,05	0,64±0,02	0,57±0,02	13,2
	10 day	1,33±0,03	0,71±0,02	0,70±0,03	4,8*
	20 day	1,40±0,03	0,79±0,03	0,57±0,07	5,0*
	30 day	1,39±0,04	0,82±0,03	0,77±0,02	5,4
Oxaloacetate	1 day	0,21±0,01	0,17±0,02	0,17±0,01	2,7
	3 day	0,19±0,02	0,19±0,01	0,18±0,02	4,6
	10 day	0,14±0,01	0,10±0,01*	0,10±0,01*	0,4
	20 day	0,09±0,01*	0,07±0,01	0,05±0,01	26,0
	30 day	0,09±0,02*	0,06±0,01	0,05±0,01	10,6
Lactate	1 day	7,47±0,23	5,14±0,21	7,12±0,22	-38,3
	3 day	7,64±0,32	6,09±0,10	7,70±0,21	-26,3
	10 day	7,14±0,21	5,46±0,19	6,71±0,11	-22,8
	20 day	6,98±0,12	3,94±0,07*	4,70±0,12	-19,2
	30 day	7,06±0,21	4,00±0,12*	4,62±0,04	-15,6
Pyruvate	1 day	0,19±0,01	0,20±0,00	0,23±0,02	-16,3
	3 day	0,18±0,01	0,19±0,01	0,24±0,02	-22,2
	10 day	0,15±0,01	0,14±0,01*	0,16±0,00	-8,05
	20 day	0,13±0,01	0,12±0,00	0,13±0,01	-0,77
	30 day	0,14±0,01*	0,13±0,01	0,14±0,01*	-1,44
α-glycero-	1 day	0,59±0,03	0,97±0,02	0,43±0,01	24,7
phosphate	3 day	0,56±0,02	0,54±0,02	0,40±0,02*	25,4
	10 day	0,46±0,01	0,42±0,01	0,37±0,01	11,0
	20 day	0,42±0,01	0,41±0,02*	0,40±0,02*	2,1
	30 day	0,40±0,02*	0,40±0,02*	0,38±0,02*	4,4*
Dioxyacetone	1 day	0,32±0,03	0,37±0,03	0,35±0,03	5,6
phosphate	3 day	0,36±0,02	0,36±0,03	0,37±0,03	-2,4
	10 day	0,29±0,01	0,20±0,01	0,19±0,00	5,4
	20 day	0,21±0,01	0,15±0,01*	0,15±0,00*	1,9
	30 day	0,18±0,00	0,16±0,01	0,15±0,02*	2,4
Glycerol	1 day	0,50±0,03	0,83±0,03	0,74±0,02	10,0
	3 day	0,79±0,05	0,92±0,05	0,88±0,06	4,5
	10 day	0,68±0,03	0,71±0,04	0,59±0,03	16,1
	20 day	0,52±0,02	0,60±0,03	0,51±0,02	15,2
	30 day	0,52±0,03	0,59±0,03	0,44 ±0,04*	25,8
Free fatty acids	1 day	1,04±0,02	0,86±0,06	0,98±0,04	13,7
(mmol/L)	3 day	1,10±0,05	0,93±0,06	1,15±0,05	-24,5
	10 day	0,76±0,03	0,65±0,04	0,72±0,03	10,6
	20 day	0,47±0,03	0,59±0,04	0,62±0,02	-6,7
	30 day	0,49±0,03	0,52±0,03	0,52±0,04	-3,6
Glucose	1 day	6,91±0,20	5,78±0,08	4,84±030	16,3
(mmol/L)	3 day	8,32±0,32	7,23±0,23	5,05±0,10	30,1
	10 day	6,36±0,22	5,84±0,15	4,64±0,34*	20,5
	20 day	5,14±0,11	5,27±0,18	4,65±0,34*	11,6

	30 day	5,19±0,13	5,23±0,24	4,55±0,46*	13,1
Protein (mg/ml)	1 day	76,47±3,29*	86,25±6,52	95,46±6,52	-10,7
	3 day	60,78±5,78	79,74±4,31	89,37±4,24	-12,1
	10 day	65,61±3,64	79,62±7,55	72,22±6,00*	9,3
	20 day	70,71±4,49	77,08±4,85*	65,94±3,11	14,5
	30 day	74,33±5,51	80,37±9,64	74,82±8,65*	6,9

*-P > 0.05 relative to control

Characteristically, the acute period of myocardial infarction is accompanied by hyperglycemia, which reflects the state of the stress period of the body. More stable in time there is an increase in content of free fatty acids, glycerol, oxaloacetate, pyruvate, lactate, α-glycerophosphate and dioxyacetone phosphate. Clearly increased molar concentration of compounds with pronounced acidic properties creates the prerequisites for metabolic acidosis. Fluctuations of the total serum protein at the lower limit of normal causes the possibility of its development

Discussion of results

Cardiac muscle uses a number of intermediates of carbohydrate-lipid-protein origin as an energy source [7]. In our opinion, this deserves special attention in myocardial infarction, when under conditions of necrotic changes of the cardiac muscle the provision of plastic and energy metabolism plays a crucial role. Undoubtedly, the ultimate goal of our scientific research is to find targeted means of correction of impaired cardiac muscle function due to pathological changes on the basis of myocardial infarction. We consider it possible to solve this problem based on a reliable knowledge of the peculiarities of cardiac muscle metabolism in norm and pathology, the specifics of structural-plastic and energy material use in the form of small molecules - natural intermediate products of metabolism. We had to solve this problem before proceeding to the search for means to stabilize cardiac activity. To answer this question, we used a number of methodological approaches, comprising, first of all, assessment of the total concentration of metabolites in the peripheral blood flow, in aortic and coronary sinus blood in intact animals, as well as under loading conditions with exogenous substrates both in norm and in experimental myocardial infarction.

The results allow us to judge about the possibility of metabolite utilization and the intensity of this process over time. In addition, the obtained data may answer the question about the preferential use of carbohydrate-lipid, protein metabolism in the corresponding stage of myocardial infarction. Among the many intermediates, we selected malate, oxaloacetate, lactate, pyruvate, α-glycerophosphate, dioxyacetone phosphate, and glycerol, because they have an integral function in metabolism. Without dwelling on the characteristics of the structure of each of these compounds, it should be noted that they can be divided into two groups by a common feature: protonated substrates with a reduced equivalent in their structure and deprotonated substances serving as hydrogen acceptors in reduction processes. They form a donor-acceptor substrate pair characterized by their own redox potential, acid-base properties providing for the optimal charge, medium reaction, conformational state of macromolecules in the corresponding microcompartments of the cell. Dynamic interaction of small molecules of substrates with biopolymers of structural, catalytic, hormonal, receptor functions ensures intracellular and intraorganic homeostasis and adequate metabolic restructuring in response to changing external and internal conditions.

Summarizing the results of these studies, we can note that the first steps in expanding our knowledge about the possibilities of myocardial infarction therapy with dehydrogenases capable of inducing diverse metabolic processes and energy supply of cardiac muscle functions and plastic requirements in myocardial infarction, as well as raising to a new level, the level of relationships between cell life-support systems, have been made. It is noteworthy that the enzyme is a biogenic factor, along with a distinct and

specific action, has no destructive effect on membrane structures, maintaining a balanced relationship of various cellular microcompartments, determining in general cellular homeostasis under new conditions.

Conclusions

In intact animals, the content of a number of intermediates of carbohydrate, carbohydrate-lipid, and lipid exchange in the anterior, anterolateral, and posterior walls of the left ventricle as well as in the right ventricular wall does not differ significantly, indicating a uniform level of basal exchange processes in different areas of cardiac muscle.

It has been revealed that the preferred substrates for cardiac muscle in norm are free fatty acids, glycerol, oxaloacetate, lactate, dioxyacetone phosphate. Experimental estimation of the cardiac muscle need for energy, structural and plastic material of different nature, has established that the concentration of the studied metabolites in the aorta is slightly higher than the level of these metabolites in the coronary sinus.

In the acute period of myocardial infarction in the peripheral blood, in the aortic blood, the content of the studied metabolites increases significantly: the level of dioxyacetone phosphate, free fatty acids, oxaloacetate increases maximally. The presence of correlation between metabolic shifts in the heart muscle and in peripheral blood, aortic blood in the dynamics of myocardial infarction provides an opportunity to use the determination of free fatty acids, dioxyacetone phosphate, oxaloacetate as diagnostic tests.

Assessing the content of malate, oxaloacetate, lactate, pyruvate, glycerophosphate, dioxyacetone phosphate and glycerol in peripheral blood we can determine the character of changes in the level of these metabolites in the heart muscle in the dynamics of myocardial infarction, as well as judge about the staging process - predominance of destructive or reparative processes.

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