the sorption capacity of serum albumin suggests that this protein plays a part in the detoxication of the GABA-lytic. For aspirin, however, another mechanism is also possible: alteration of the functional state of the GABA-benzodiazepine receptor complex.

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Substrate Supply to the Heart during Myocardial Infarction: Selectivity and Time Course of Utilization of Metabolites

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Myocardial infarction is experimentally modeled in rabbits. The blood content of metabolites in intact and experimental animals is measured at different times of infarction. An inverse utilization of the substrates by the myocardium is found: an enhanced utilization of glucose and reduced utilization of fatty acids. The emergence of metabolic acidosis and of an arrhythmogenic effect, and the aggravation of ischemia are substantiated by the accumulation of oxaloacetate, pyruvate, lactate, glycerophosphate, and dihydroxyacetone phosphate. During the repair period a tendency toward a normalization of substrate utilization by the myocardium is noted.

Key Words: *carbohydrate and lipid metabolism; myocardial infarction*

The contractile, self-regulating, and secretory functions of the myocardium are governed by intensive metabolic processes. Higher fatty acids have proved to be the primary substrate which supplies the myocardium with energy, endogenous water, and equivalents for the reactions of reductive synthesis [5]. At the same time, under certain conditions free fatty acids (FFA) are able to aggravate ischemia and exert an arrhythmogenic effect [7].

Being an intermediate in carbohydrate, lipid, and protein metabolism, oxaloacetate acts as an energetic precursor and assists (as a component of the malate-aspartate shuttle) the transport of cytoplasmic NADH into mitochondria. The acidic properties and polarity of the molecule are responsible for the electric balance of the medium, while two possible con-

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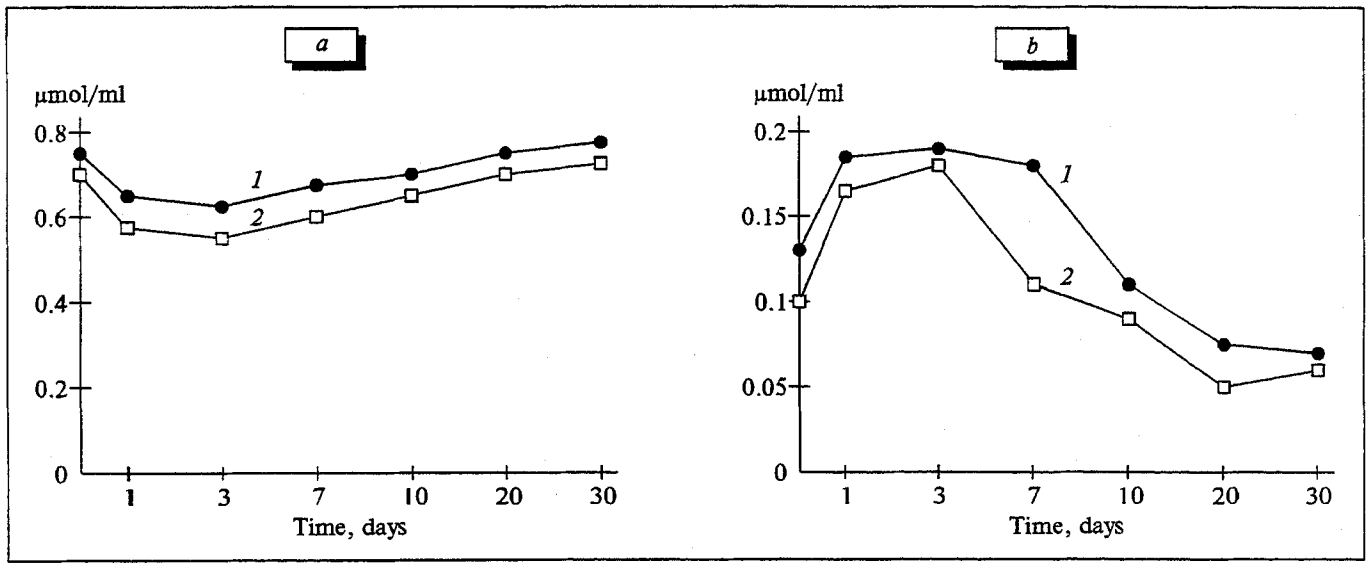

Fig. 1. Content of malate (*a*) and oxaloacetate (*b*) in arterial and venous blood in acute and subacute myocardial infarction during scarring. Here and in Figs. 2 and 3: *1*) aorta; *2*) coronary sinus.

figurations determine the pattern of its utilization by enzymes competing for this substrate [6]. The human myocardium contains 0.76±0.24 μmol oxaloacetate per gram of tissue. It has been shown that hyperpyruvatemia and hyperoxaloacetatemia, whether experimentally modeled or observed in the blood of patients with myocardial infarction, provoke rhythm disturbances, primarily supraventricular extrasystoles.

In this context the constancy of the life-supporting substrates utilized by the myocardium is of indubitable interest. Is it determined solely by the specificity of heart metabolism or does it also depend on the nature and stage of such a critical state as myocardial infarction? This was the subject of the present study.

MATERIALS AND METHODS

The experiments were carried out on 75 nonpedigree rabbits weighing 2.5-3.5 kg. Myocardial infarction was reproduced by occlusion of the left coronary artery. The study of metabolites was performed in intact animals and immediately after ligation of the coronary artery and 1, 3, 7, 10, 20, and 30 days postinfarction. Blood samples from the aorta and the coronary sinus were taken after the thorax was opened under narcosis. Peripheral blood was drawn from the ear vein.

The blood content of malate, oxaloacetate, lactate, pyruvate, α-glycerophosphate, and dihydroxyacetone phosphate was measured using a unified method [2], and the concentration of glycerol [3], glucose [1], FFA [4], and protein was also determined. The arteriovenous difference was calculated by the formula:

$$(Ca\text{-}Ccs)/Ca \times 100\%,$$

where *Ca* and *Ccs* are the blood content of the substance in the aorta and the coronary sinus, re-

TABLE 1. Content of Metabolites in Peripheral Blood, Aorta, and Coronary Sinus in Rabbits

Metabolites	Peripheral blood	Coronary sinus	Aorta	Arteriovenous difference, %
Malate, μmol/ml	1.43±0.03	0.82±0.01	0.78±0.03	4.9
Oxaloacetate, μmol/ml	0.09±0.03	0.08±0.01	0.07±0.01	16.3
Lactate, μmol/ml	3.92±0.14	3.24±0.17	2.53±0.11	21.9
Pyruvate, μmol/ml	0.14±0.02	0.14±0.01	0.13±0.01	4.9
α−Glycerophosphate, μmol/ml	0.39±0.01	0.32±0.02	0.30±0.01	4.7
Dihydroxyacetone phosphate, μmol/ml	0.14±0.01	0.14±0.1	0.12±0.01	14.8
Glycerol, μmol/ml	0.46±0.02	0.54±0.03	0.44±0.02	18.9
FFA, mmol/liter	0.44±0.02	0.54±0.04	0.38±0.02	29.3
Glucose, μmol/liter	4.72±0.14	3.85±0.12	3.71±0.21	3.66
Protein, mg/ml	78.14±4.08	74.1±3.11	76.18±5.12	1.58

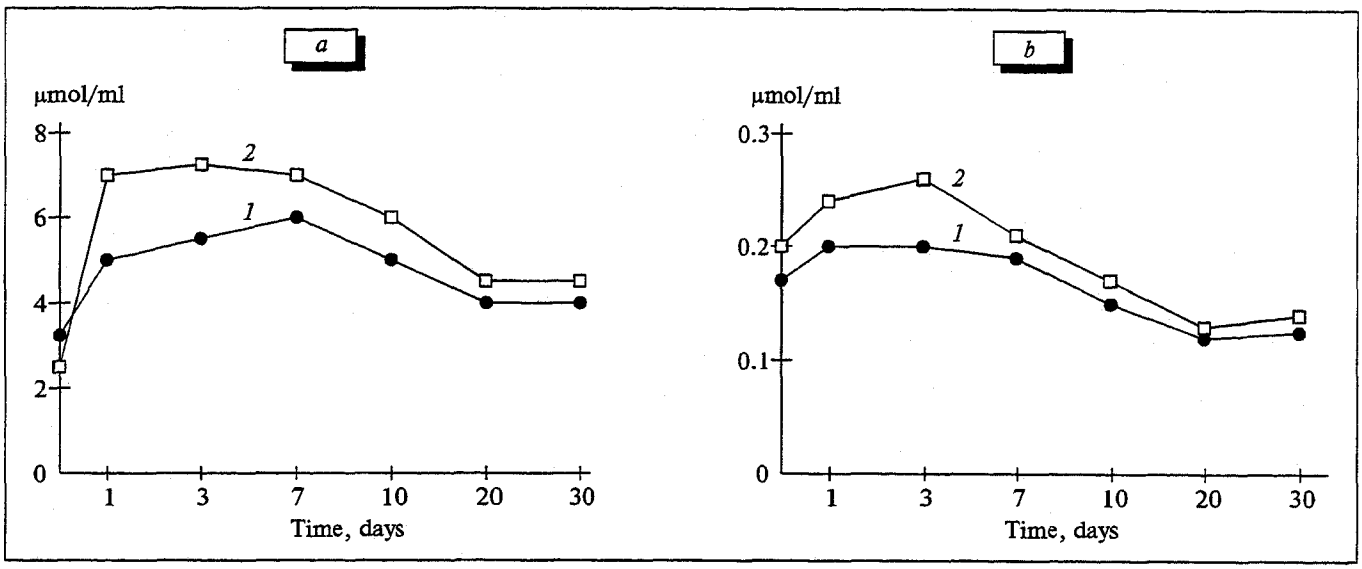

Fig. 2. Content of lactate (*a*) and pyruvate (*b*) in arterial and venous blood in acute and subacute myocardial infarction during scarring.

spectively. A positive difference implies consumption, while a negative difference suggests production of the substance.

RESULTS

Table 1 presents data on the intensity of utilization of carbohydrate-lipid and protein metabolites by the myocardium. Normally, the activity of oxidation of FFA is similar to that of lactate, the arteriovenous differences for oxaloacetate and glycerol are also comparable. The high concentration of lactate in peripheral and aortal blood suggests its important role in metabolic processes in the myocardium. It should be noted that the concentration of glycerol and FFA is higher in the aorta than in the peripheral blood, a feature which is specific to these lipid components. The content of glucose, malate, oxaloacetate, and α-glycerophosphate in the aorta is lower, while the content of dihydroxyacetone phosphate and protein is practically equal to that in peripheral blood. Glycerol and FFA detected in the aorta in high concentrations may be assumed to originate from richly vascularized pulmonary tissue. Glycerol and higher fatty acids, products of lipoproteinlipolysis, are partially metabolized in pulmonary tissue and are partially delivered to the left ventricle and then to the aorta with the blood flow.

Table 2 illustrates the utilization of metabolites by the myocardium in the course of acute

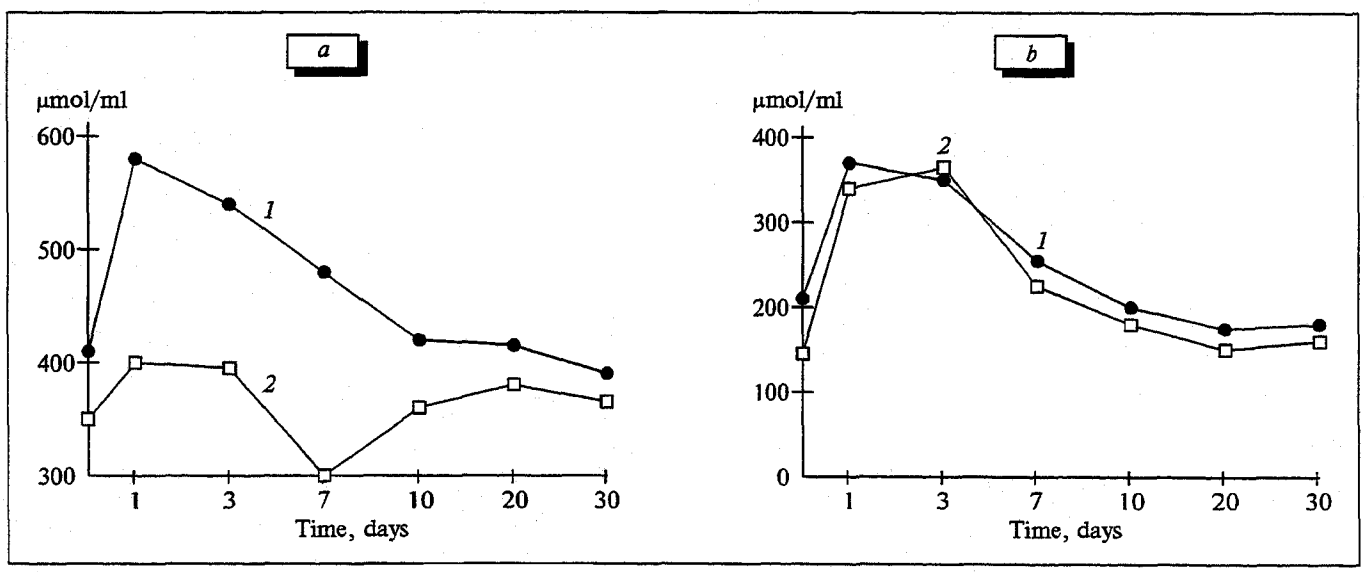

Fig. 3. Content of α−glycerophosphate (*a*) and dihydroxyacetone phosphate (*b*) in arterial and venous blood in acute and subacute myocardial infarction during scarring.

TABLE 2. Distribution of Main Intermediates in Aortal and Venous Blood at Different Times of Myocardial Infarction

Days after occlusion	Peripheral blood	Aorta	Coronary sinus	Arteriovenous difference, %
		Glycerol, μmol/ml		
1	0.50±0.03*	0.83±0.03	0.74±0.02	10.0
3	0.79±0.04*	0.92±0.05	0.88±0.06	4.0
10	0.68±0.03*	0.71±.04	0.59±0.03*	16.1
20	0.52±0.02*	0.60±0.03*	0.51±0.02*	15.2
30	0.52±0.03*	0.59±0.03*	0.44±0.04*	25.8
		FFA, μmol/ml		
1	1.04±0.02*	0.86±0.06*	0.98±0.04*	−13.7
3	0.11±0.05*	0.93±0.06*	1.15±0.05*	−24.5
10	0.76±0.03*	0.65±0.04*	0.72±0.03*	10.6
20	0.43±0.03	0.58±0.04	0.62±0.02*	−6.7
30	0.49±0.03	0.52±0.03	0.54±0.04*	−3.6
		Glucose, μmol/ml		
1	6.91±0.20*	5.78±0.08*	4.84±0.30*	16.3
3	8.32±0.32*	7.23±0.23*	5.05±0.10*	30.1
10	6.36±0.22*	5.84±0.15*	4.64±0.34*	20.5
20	5.14±0.11*	5.27±0.18*	4.65±0.33*	11.6
30	5.19±0.13*	5.27±0.24*	4.55±0.46*	13.1
		Protein, mg/ml		
1	76.47±3.29	86.25±6.52*	95.46±6.52*	−10.7
3	60.78±5.78*	79.74±4.31	89.37±4.24*	−12.1
10	65.71±3.64*	79.62±7.55	72.22±6.00	9.3
20	70.71±4.49	77.08±4.85	65.94±3.11*	14.5
30	74.33±5.51	80.37±9.64	74.82±8.65	6.9

Note. *$p<0.01$ in comparison with the control (Table 1).

myocardial infarction. It is characteristic for the acute period of myocardial infarction to be accompanied by hyperglycemia, which reflects the strained state of the organism. A more stable increase is noted in the content of FFA, glycerol, oxaloacetate, pyruvate, lactate, α-glycerophosphate, and dihydroxyacetone phosphate (Figs. 1-3). A markedly increased concentration of acidic compounds provides the prerequisites for metabolic acidosis, while the possibility of its development is determined by fluctuations of the concentration of total serum protein around the lower boundary of the norm.

A striking feature is the observed inversion in utilization of the substrates by the myocardium. The arteriovenous difference suggests a prevailing realization of glucose in metabolic processes in the myocardium during 30 days postocclusion. It is particularly remarkable that this parameter, though maximal from the 3rd to the 10th day, surpasses the control value and the level observed in the peripheral blood 4.5- and 1.5-fold, respectively, starting from the first day.

In our opinion, it is of interest that over the entire observation period the content of FFA in the coronary sinus markedly exceeds that in the aorta. Thus, the metabolic supply of the myocardium in the modeled critical situation is primarily accomplished by carbohydrates rather than higher fatty acids. The accumulation of lactate and pyruvate is indicative of active anaerobic oxidative processes. The energy supply of the myocardium is evidently effected through a phylogenetically more ancient mechanism, which is realized in hypoxia via glycolysis. The accumulation of oxaloacetate and pyruvate attests to hindered utilization of these substrates in aerobic conversion and in transamination reactions.

Parallelly recorded electrocardiography demonstrated that the peak blood concentration of oxaloacetate, lactate, and pyruvate coincides with the disturbances of the cardiac rhythm and the development of arrhythmia. In the aortal blood the concentration of glycerol is sharply increased in comparison with the control and peripheral blood by 52.9% ($p<0.01$) and 64.1% ($p<0.01$), respectively, attaining the maximum on day 3 and remaining at this level during the subacute and repair period. On the other hand, utilization of glycerol by the myocardium is lower than in the control. The arteriovenous difference is minimal on day 3, which coincides with its maximal concentration in the aortal blood. The existence of a functional interrelation between the heart and lungs

probably allows for parallel metabolic shifts in the pulmonary tissue. The reduced utilization of glycerol results in its elevated concentration in the arterial blood. A dissonance arises between the demand of the myocardium for this substrate and its utilization and concentration. Due to intense glucose oxidation, dihydroxyacetone phosphate originating from carbohydrates and lipids competes for common paths of further transformation. This is confirmed by the sharp increase in the content of dihydroxyacetone phosphate on day 3, when the utilization of glucose is maximal (Fig. 3). Normalization of the level of dihydroxyacetone phosphate proceeds in parallel with the increase in the utilization of glycerol by the myocardium. On day 30 we observe the maximal utilization of glycerol together with the lowest (over all 30 days) utilization of glucose.

Thus, in the repair period a trend becomes evident toward a normalization of the utilization of substrates to meet the demands of the myocardium.

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