EFFECT OF CARDIOPLEGIA ON THE NITROGEN AND ENERGY METABOLISM OF THE HUMAN HEART

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Considerable changes take place in the structure of metabolism of some amino acids and ammonia in the heart muscle with a fall in the ATP level caused by ischemia or anoxia [4, 9]. However, there is no information in the contemporary literature on the effect of cardioplegia on myocardial metabolism of nitrogen compounds in man. Yet we know that despite the anti-ischemic protection of the myocardium, which is usual during open heart operations, when the heart is disconnected for long periods from the circulation ischemic injuries may develop, with the result that the level of high-energy phosphates may fall [2, 5]. It will be evident that under these conditions changes in the structure of amino acid and ammonia metabolism usually observed experimentally may arise.

The aim of this investigation was to study changes in the concentrations of glutamic and aspartic acids, glutamine, alanine, and ammonia in the human heart during its ischemic arrest and to compare these changes with the energy state of the myocardium.

EXPERIMENTAL METHOD

The investigation was conducted on material removed from patients undergoing radical correction of Fallot's tetrad (FT) (12 patients) and ventricular septal defects (VSD) (five patients) under assisted circulation conditions. The heart was disconnected from the circulation on average for 35 min (from 15 to 91 min). Anti-ischemic protection of the myocardium was effected by a combined method, including general systemic hypothermia, local cooling of the heart, and reperfusion with a blood-based perfusion fluid [1]. Biopsy of the right ventricle was performed during the first 1-2 min of disconnection of the heart from the circulation and at the end of ischemia (before removal of the clamp from the aorta). The biopsy material was quickly frozen in liquid nitrogen. Metabolites were extracted with cold 6% $HClO_4$ [9]. The ATP concentration in the tissue extracts was determined by an enzymic method using hexokinase and glucose-6-phosphate dehydrogenase [6]. To determine amino acids and ammonia, a Liquimat-III amino-acid analyzer (West Germany) with FFM-31 fluorometric cell was used. Elution was carried out on a column (0.4 × 30 cm) packed with DC-4A resin ("Pierce," USA) and lithium-citrate buffers ("Durrum," USA). Solutions for biochemical determinations were made up in deionized water.

EXPERIMENTAL RESULTS

The initial ATP concentration in the right ventricle of the patients varied from 5.90 to 2.45 μmoles/g wet weight of tissue, despite the fact that the time of clamping the aorta until the first biopsy was virtually identical (1.2 ± 0.2 min). The ATP concentration in all samples taken at the end of cardioplegia was below the initial level and varied from 4.40 to 1.10 μmole/g wet weight of tissue. The glutamic acid concentration in samples from the first biopsy varied from 8.63 to 3.18 μmoles/g wet weight of tissue (mean 5.75 ± 0.36 μmole/g). The amino acid concentration showed a decrease in biopsy specimens taken from the majority of patients (16 persons) at the end of ischemic cardiac arrest. Its value was independent of the

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TABLE 1. Distribution of Patients by Groups Depending on Loss of ATP during Cardioplegia (M ± m)

Group of patients	Correction of	Number of patients	Mean duration of ischemia, min	ATP, μmoles/g wet weight of tissue	
				first biopsy	second biopsy
1	VSD	3	38±7	4,26±0,32	2,34±0,21*
	FT	6	—	—	—
2	VSD	4	32±4	3,98±0,31	3,75±0,31
	FT	4	—	—	—

Legend. *p < 0.02 compared with first biopsy.

TABLE 2. Changes in Concentration (in %) of Nitrogen Compounds in Myocardium of Patients during Cardioplegia (M ± m)

Group of patients	Nitrogen compound			
	glutamic acid	aspartic acid	alanine	ammonia
1	−17,42±3,79	−17,57±5,94	+61,44±12,50	+92,41±26,34
2	−7,59±2,69*	−4,65±8,61*	+22,40±7,39*	+33,42±8,25

Legend. −) Decrease, +) increase in concentration of compound in right ventricle compared with initial value. *p < 0.05 compared with group 1.

duration of ischemia and of the initial level. The mean aspartic acid concentration at the beginning and end of cardioplegic arrest was 1.64 ± 0.29 and 1.28 ± 0.32 μmole/g wet weight of tissue respectively. Toward the end of cardioplegia a fall in the aspartic acid level was observed in 13 patients, a rise in three patients, and no change in one. The alanine concentration in samples obtained at the first biopsy averaged 1.99 ± 0.13 μmole/g wet weight of tissue. In the period of cardioplegia the alanine level rose on average to 2.68 ± 0.24 μmole/g wet weight of tissue ($p < 0.02$). In all patients the ammonia level in the heart was raised during cardiac arrest. The mean ammonia concentration toward the end of cardioplegia was significantly increased from 1.24 ± 0.40 μmole in the initial state to 2.06 ± 0.33 μmole/g wet weight of tissue. Changes in the glutamine concentration in the heart under the influence of cardioplegia were variable in direction. In nine patients its level was raised, in the rest it was lowered. The mean glutamine concentration was the same at the initial and final periods of cardiac arrest, namely 12.49 ± 0.87 μmole/g wet weight of tissue.

To detect correlation between changes in the energy state of the myocardium and nitrogen metabolism taking place during cardioplegia, the patients were divided into two groups. Group 1 consisted of patients whose ATP concentration in the right ventricle fell by more than 20% of its initial level (nine persons), whereas group 2 consisted of patients with smaller losses of ATP (eight persons). The mean duration of myocardial ischemia in the patients of the two groups was virtually identical (Table 1). It follows from Table 2 that the loss of ATP in the myocardium during cardioplegia is combined with a fall in the myocardial glutamic and aspartic acid levels, a rise of the alanine concentration, and a tendency for ammonia production to increase.

The increase in ammonia formation in the ischemic myocardium is usually linked with degradation of adenine nucleotides [8, 13]. This hypothesis is in good agreement with the greater rise of the ammonia level in the myocardium of the patients of group 1, in whom a marked fall of ATP concentration was observed (Tables 1 and 2). Despite the increase in ammonia production, the glutamine concentration in the patients' myocardium did not increase during cardiac arrest. This is evidence that ammonia binding in the glutamine synthetase reaction is not sufficiently effective under ischemic conditions. The most likely cause of this is the lowered glutamic acid and ATP concentration.

A fall in the levels of glutamic and aspartic acids in the ischemic myocardium was observed previously [4, 9]. The loss of these amino acids was equimolar to the increase in the alanine concentration and took place under the influence of coupled aspartate- and alanine-aminotransferases [10]. The result of degradation of glutamic and aspartic acids is the formation of α-ketoglutarate and oxaloacetate and intensification of substrate phosphorylation in the mitochondria [12, 14]. Thus the use of cardioplegic solutions containing these amino acids ought to reduce their losses during ischemia, facilitate fuller binding of the excess of ammonia and, most important, maintain ATP at a higher level during cardiac arrest. These conclusions are based on the protective effect of these two amino acids during cardioplegia and reperfusion of the heart in animals [3, 7] and in man [11] and they are in agreement with the results of the present investigation.

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EMOTIONAL–BEHAVIORAL DISORDERS IN RATS ON CREATION OF A GENERATOR OF PATHOLOGICALLY ENHANCED EXCITATION IN THE BASOMEDIAL NUCLEI OF THE AMYGDALOID BODY

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The theoretical basis of this investigation was the theory of determinant and generator mechanisms of neuropathological syndromes [3, 4], according to which a neuropathological syndrome is the clinical expression of activity of a pathological system arriving under the influence of a hyperactive determinant structure; the working basis of such a structure is a generator of pathologically enhanced excitation (GPEE). By creating such generators in certain parts of the CNS, corresponding neuropathological syndromes can be reproduced. Since the

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