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PATHOGENESIS OF THE LOW CARDIAC OUTPUT SYNDROME IN POSTRESUSCITATION STATES

I. E. Trubina and A. V. Volkov

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Acute hypervolemia induced in experiments on dogs by infusion of dextran, did not produce decompensation of the circulation in animals whose cardiac output was sharply depressed in the postresuscitation period after circulatory arrest lasting 15 min. The increase in the venous return and change in the conditions of the peripheral circulation as a result of dextran administration temporarily increased the central venous pressure, caused a lasting increase in the arterial pressure, cardiac output, stroke volume, work of the left ventricle, and total oxygen consumption by the body, and lowered the peripheral vascular resistance. In model experiments on dogs subjected to isolated compression ischemia of the brain for 20 min, a low cardiac output syndrome also developed.

KEY WORDS: hypoxia; postresuscitation period; cardiac output; hemodynamics.

In the postresuscitation period after various types of terminal state, similar phasic changes in the central hemodynamics have been found [6, 7, 11]. The period of hyperperfusion, at a time of extremely intensive work of the heart at the beginning of resuscitation, is gradually replaced after 2-3 h by the onset of a low cardiac output syndrome which may continue for up to 24 h. Among the factors responsible for its development injury to the myocardium as a result of hypoxia and toxemia and a decrease in the absolute circulating blood volume may be distinguished [4, 5, 12]. However, there is as yet no general agreement regarding the nature and functional significance of this phenomenon.

The two objects of this investigation were as follows: first, to investigate the functional reserves of the cardiovascular system in the period of maximal depression of the cardiac output during resuscitation after circulatory arrest in vivo, and second, to determine the role of disturbances of neurohumoral regulation in the development of the low cardiac output syndrome after resuscitation.

EXPERIMENTAL METHOD

Two groups of experiments were carried out on 17 anesthetized (pantopon 4-6 mg/kg, pentobarbital 8-10

Laboratory of Experimental Physiology of Resuscitation, Academy of Medical Sciences of the USSR, Moscow.

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TABLE 1. Changes in Indices of Central Hemodynamics and Oxygen Budget of the Body in Postresuscitation States (M ± m)

Index	Stage of experiment							
	initial state		postresuscitation period					
			1 h		3 h		1 h after loading	
			group of experimental animals					
	2nd	1st	2nd	2nd	1st	1st	1st	1st
					before loading			
Cardiac index (in ml/kg·min)	135,0±6.9	153.9±12,4	169,5±19,0	94,5±10, 2*	90, 0±8,5*	124,6±15,3	243,4±30,0‡	292,0±77,4
Stroke index (in ml/kg)	2.44±0.22	2,22 ± 0, 31	1,20±0,08*	0,92±0, 06*	0,84±0,11*	1,28 ± 0 , 11	1,73±0,33 ‡	2,02 ± 0 .39
Working index of left ventricle (in kg·m/kg·min)	0, 19±0,01	0,21 ±0, 01	0,30±0,04*	0, 14±0, 02	0,15±0,02*	0,19 ± 0 , 03	0,42±0,06‡	0,55 ± 0 , 15
Heart rate (beats/min)	63±3	74 ± 8	144 ± 10*	113 ± 15*	113 ± 13*	98 ± 15	145 ± 9‡	139 ± 12
BP (in mm Hg)	106±2	107 ± 4	128 ± 5*	126 ± 4*	126 ± 6*	109 ± 11	137 ± 11‡	139 ± 1*
CVP (in mm water)	—12,5±9,2	+4.1 ± 6 , 9	—44,0±12,8	—36,0±14,6	—13,6±14,5	—20,0±16,0	+32, 0± 30, 1	+11,0±15,5
Total peripheral vascular resistance (in dynes · sec · cm^{-5})	4822±524	3827 ± 661	4746 ± 551	8229±1256*	7971±1612*	4401 ± 115	2913 ± 201†	2949±1213
Oxygen consumption (in ml/kg·min)	5,5±0.6	5, 4 ± 0, 5	8, 4 ± 1, 4	6, 8 ± 0, 5	8, 4 ± 1 , 5	4, 8 ± 0 .4	13,9 ± 3, 4*	6, 0 ± 0, 4
Arterio-venous O_2 difference (in vols. %)	3, 6 ± 0 , 5	3, 6 ± 0, 3	5, 5 ± 0 , 8	7, 6 ± 0, 8*	8, 5 ± 0, 9*	4, 0 ± 0 , 5	5 , 5 ± 1 . 4‡	2, 5 ± 0 , 9
Hematocrit index (in %)	49 ± 3	50 ± 1	46 ± 3	46 ± 3	49 ± 2	57 ± 3	33 ± 3†	39 ± 1*
Circulating blood volume (in ml/kg)	—	79 , 5 ± 2 , 7	—	—	76,5 ± 3 , 2	—	—	—
Plasma volume (in ml/kg)	—	44 , 1 ± 4 , 1	—	—	41,9 ± 3 , 8	—	—	—

*P ≤ 0.5 compared with corresponding index in initial state.

† P ≤ 0.05 compared with corresponding index before loading (groups 1 and 1c).

‡ P ≤ 0.05 compared with corresponding index in initial state and before loading.

mg/kg) and heparinized (200 units/kg) dogs. In the seven dogs of group 1 circulatory arrest was induced for 15 min by ventricular fibrillation resulting from electric shock. The animals were resuscitated by external cardiac massage, intra-arterial infusion of 30-60 ml dextran with adrenalin, electrical defibrillation of the heart, and artificial ventilation of the lungs with oxygen. During the period of maximal depression of the minute volume of the heart and of strain on the compensatory mechanisms 3 h after resuscitation, a load was applied: Dextran (36-37°C) in a volume of about 40 ml/kg (50% of the blood volume) was injected intravenously at the rate of 100 ml/min [10, 11, 15]. In three control experiments (group 1c) dextran loading was applied to intact animals. In experiments on seven animals in group 2 the brain was completely ischemized for 20 min by increasing the intracranial pressure to 360-400 mm Hg as a result of injection of physiological saline (37°C) into the cisterna magna [9]. During cerebral ischemia and until the restoration of effective spontaneous respiration, the lungs were artificially ventilated with oxygen. If necessary ephedrine solution was injected intravenously to prevent the arterial pressure (BP) from falling below 100 mm Hg.

In the initial state and 1-4 h after resuscitation the principal parameters of the central hemodynamics were determined: the minute volume of the heart (by the Fick method), the heart rate, the central venous pressure (CVP), BP, and the circulating blood volume [2]. The cardiac and systolic indices, the working index of the left ventricle; and the total peripheral vascular resistance were calculated. The oxygen balance of the body and the acid-base state of the blood were determined [8, 13].

EXPERIMENTAL RESULTS

During resuscitation of the animals of group 1, stable cardiac activity was restored on the average after 3.7 ± 0.5 min (M ± m), and respiration and the corneal reflexes appeared after 5.6 ± 0.9 and 22.6 ± 3.0 min, respectively.

Three hours after resuscitation and immediately before loading, significant decreases were observed compared with their initial values in the cardiac (by 42%) and systolic (by 62%) indices and the working index of the left ventricle (by 30%), together with a simultaneous increase in the total peripheral vascular resistance (by 108%), the heart rate (by 53%) and BP (by 15%). In all experiments except one the CVP was lowered. No significant changes were found in the oxygen consumption of the body or the circulating blood volume and its constituents at that time (Table 1).

The maximal increase in CVP during infusion of dextran and the rate of its decrease after the end of infusion were on the average similar in groups 1 and 1c: the end of infusion corresponded to +156 ± 38 and +150 ± 17 mm water, and after 1 h the corresponding values were 32 ± 30 and 11 ± 15 mm water. Only in one experiment of group 1, when clear signs of heart failure were present, did the CVP remain high (+145 mm water) for a long time.

Dextran loading caused a lasting increase in BP, the cardiac index, and the working index of the left ventricle and a decrease in the total peripheral vascular resistance (Table 1). The absolute values of the hemodynamic indices after loading in groups 1 and 1c did not differ significantly although the severity of the changes in group 1 was greater. The increase in oxygen consumption in the animals of group 1 was much greater than in the control. It is also important to note that the outcome of resuscitation in group 1 (five of the seven dogs survived) was better than after the corresponding terminal state but without administration of dextran [1], when seven of 19 animals survived ($P = 0.05$).

The results of the experiments of group 1 demonstrate the preservation of considerable functional reserves of the cardiovascular system during the maximal decrease in cardiac output in the postresuscitation period. By contrast with the anticipated decompensation of the circulation [14-17] at a time of sharp increase in the venous return, the heart was able to increase its minute volume considerably and persistently and to improve the supply of oxygen to the resuscitated organism. This indicated that one cause of the gradual reduction in the cardiac output after resuscitation could be a limitation of the return of blood to the heart as a result of a decrease in the circulating blood volume. Such a decrease evidently arose because of hypoxic disturbances in the system of capacitive vessels and the peripheral circulation, and also because of disturbances of neurohumoral regulation of the circulation.

The role of disorders of nervous regulation in the postresuscitation disturbances of the hemodynamics was studied in experiments in which isolated cerebral ischemia was produced for 20 min, when the severity of the morphological and functional brain injuries was the same as after circulatory arrest in the body as a whole for 12-15 min [3]. During resuscitation of the animals of group 2 respiration and the corneal reflexes reappeared after 5.5 ± 1.2 and 14.5 ± 2.8 min respectively, and all seven dogs survived. Compared with the initial level, the hemodynamics 1 h after resumption of the circulation was characterized by a decrease in the stroke index (by 51%) and an increase in the working index of the left ventricle (by 53%), in the heart rate (by 28%), and in BP (by 21%). The cardiac index did not differ significantly from the initial values (Table 1). A low cardiac output syndrome developed after 3 h, showing that it was connected with the disturbances of neurohumoral regulation and with the general pathological reactions arising in the body during cerebral hypoxia.

Despite the substantial depression of the circulation, the oxygen consumption of the body at this time was indistinguishable from initially in the animals of group 2 as well as of group 1. The supply of oxygen to the tissues was maintained through its increased utilization from the inflowing blood, in which the oxygen concentration at all stages of the investigation was close to its initial value. Although, according to the data for the acid–base balance and the level of organic acids in the blood, the decrease in cardiac output was not accompanied by the development of secondary hypoxia of the body as a whole, hypoxia of individual vitally important organs and tissues cannot be ruled out.

The decrease in cardiac output in postresuscitation states is thus due to a combination of factors among which, besides myocardial injury, absolute and relative hypovolemia, etc., an important role is played by disturbances of the peripheral circulation and of neurohumoral regulation. The development of the low cardiac output syndrome reflects the end result of their interaction. The role of each of these factors will certainly vary depending on the specific nature and severity of the terminal state, the effectiveness of the therapeutic measures, and the individual resistance of the organism.

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ROLE OF THE STRIATUM IN THE MECHANISM OF SEROTONINERGIC EFFECTS ON THE COURSE OF METRAZOL CONVULSIONS IN RATS

R. M. Avakyan

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The effect of 5-hydroxytryptophan (5-HT) and parachlorophenylalanine (PCPA) on behavioral and electroencephalographic manifestations of metrazol convulsions during electrical stimulation and destruction of the striatum was studied in freely moving rats. The effect of the compounds on the seizures, the myoclonic spasms, and the spike-and-wave activity evoked by metrazol did not depend significantly on the functional state of the corpus striatum. Meanwhile the ability of 5-HT to ameliorate, and of PCPA to aggravate the course of the generalized convulsion and the post-convulsive state was potentiated by stimulation and abolished by destruction of the striatum. It is suggested that activation of the serotoninergic mechanisms may be responsible for the abolition of the convulsions that is observed in the case of excitation of the corpus striatum.

KEY WORDS: metrazol convulsions; serotoninergic substances; striatum.

Serotoninergic agents are known to affect the course of metrazol convulsions: the serotonin precursor 5-hydroxytryptophan (5-HT) blocks, whereas the inhibitor of serotonin synthesis parachlorophenylalanine (PCPA), on the other hand, intensifies convulsions of this sort [4-6]. As the writer showed previously [1-3], a change in the functional activity of the striatum, which has a high concentration not only of dopamine and acetylcholine, but also of serotonin, has a distinct influence on the character of metrazol convulsions.

It was therefore decided to study the effect of electrical stimulation and blocking of the striatum on the ability of 5-HT and PCPA to modify the various indices of convulsions evoked by metrazol.

EXPERIMENTAL METHOD

Experiments were carried out on 65 albino rats of both sexes weighing 180-300 g. The pharmacological agents 5-HT (100 mg/kg) and PCPA (300 mg/kg twice at an interval of 24 h) were injected intraperitoneally 0.5 and 48 h respectively before provocation of the convulsions. In the experiments of series I the effect of serotoninergic drugs on behavioral (30 rats) and electroencephalographic manifestations (four rats) of metrazol convulsions were studied in intact animals; in series II the action of the drugs was assessed on the anticonvulsive

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