5. N. N. Mikhailovskii, G. S. Gorkovenko, and N. I. Mezheritskii, in: Electrical Stimulation of Organs and Tissues [in Russian], Kiev (1979), p. 355.
6. L. A. Skurikhina, Physical Factors in Treatment and Rehabilitation of Patients with Diseases of the Cardiovascular System [in Russian], Moscow (1979).
7. I. G. Sokovets and G. F. Plekhanov, in: Clinical Application of Magnetic Fields [in Russian], Izhevsk (1977), p. 8.
8. K. V. Sudakov, Zh. Vyssh. Nerv. Deyat., No. 5, 899 (1976).
9. K. V. Sudakov and G. D. Antimonii, in: Development of a General Theory of Functional Systems. Third Seminar [in Russian], Moscow (1977), p. 212.
10. É. D. Tykochinskaya, Fundamentals of Needle Reflex Therapy [in Russian], Moscow (1979).
11. V. A. Frolov, in: Physico-Mathematical and Biological Problems of the Action of Electromagnetic Fields and Ionization of the Air [in Russian], Vol. 1, Moscow (1975), p. 313.
12. D. Constantin, Rev. San. Milit., 79, 315 (1976).

VALUE OF REPEATED DEXTRAN INFUSIONS IN THE TREATMENT OF POSTRESUSCITATION STATES AFTER LETHAL BLOOD LOSS IN DOGS

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An important place among the combination of resuscitation measures adopted after lethal blood loss at the present time is occupied by blood transfusion in conjunction with various blood substitute solutions. Infusion therapy of this type is aimed not only at restoring an adequate volume of circulating fluid, but also to creating artificial hemodilution in order to improve the rheologic properties of the blood, to abolish or reduce peripheral circulatory disturbances, and to restore the microcirculation [1, 4].

The object of the present investigation was to study the effect of repeated dextran infusion in the recovery period on the state of the central hemodynamics and the oxygen balance in animals after hypovolemic hypotension lasting 4 h. The survival rate of the animals and the completeness of their neurologic recovery after resuscitation were evaluated at the same time.

EXPERIMENTAL METHOD

Experiments were carried out on 25 dogs of both sexes weighing 15-20 kg. After premedication with trimeperidine (8 mg/kg), rapid exsanguination of the animals was carried out from the femoral artery for 5-8 min under superficial pentobarbital anesthesia combined with local anesthesia, to reduce the arterial blood pressure (BP) on average to 40 mm Hg, and pressure was maintained at this level for 4 h. The total blood loss was 41 ± 4 ml/kg body weight. BP was restored by fractional (50-150 ml) intraarterial reinfusion of blood into the femoral artery. Immediately after restoration of the blood volume the animals were given dextran (20-30 ml/kg for 1 h) by intravenous drip. Dextran infusion therapy (10 ml/kg for 2 h) was repeated on the 1st, 3rd, and 4th-6th days after resuscitation. During the study of the recovery period, the heart rate, the presence or absence of disturbances of the cardiac rhythm, the time course of the pressure in the aorta and pulmonary artery, and the hematocrit index were analyzed. BP and the ECG were recorded on a San-Ei (Japan) polygraph. Meanwhile the cardiac output was determined in the postresuscitation period by Fick's method, and the total oxygen consumption of the animal, and the oxygen concentration in the arterial and mixed venous blood (from the pulmonary artery) were determined by means of a GKhL-2 gas chro-

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TABLE 1. Effect of Prolonged Dextran Infusions on the State of the Circulation and Oxygen Budget in the Blood of Animals during the Postresuscitation Period (M ± m)

Parameter investigated	Initial state	Postresuscitation period							
		first hour		first day		third day		4th-6th day	
		before infusion of dextran	after infusion of dextran	before infusion of dextran	after infusion of dextran	before infusion of dextran	after infusion of dextran	before infusion of dextran	after infusion of dextran
Cardiac index, ml/kg · min	152,2±16,2 (15)	127,1±15,8 (10)	157,9±21,7 (5)	70,1±10,8 (5)	116,6±7,5 (5)	118,8±23,7 (6)	145,5±12,7 (6)	130,1±15,6 (7)	184,1±15,9 (7)
P		>0,5	>0,5	<0,005	<0,05	>0,5	>0,5	>0,5	>0,5
Stroke index, ml/kg	1,98±0,16 (15)	1,00±0,17 (10)	0,76±0,08 (5)	0,45±0,09 (5)	1,03±0,27 (5)	1,15±0,05 (6)	1,01±0,08 (6)	1,21±0,27 (7)	1,54±0,14 (7)
P		<0,05	<0,05	<0,05	<0,05	<0,05	<0,05	>0,5	>0,5
Heart rate, beats/min	77±3,4 (15)	137±13 (10)	213±9 (5)	149±30 (5)	115±13 (5)	130±31 (6)	146±13 (6)	112±13 (4)	125±11 (7)
P		<0,05	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05
Arterial pressure, mm Hg	108,0±3,2 (15)	108,0±8,0 (10)	130,0±6,0 (10)	94,0±5,0 (5)	110,0±2,0 (5)	99,0±6,5 (6)	103,0±3,0 (6)	101,0±5,5 (7)	106,0±3,0 (7)
P			<0,05	>0,5	>0,5	>0,5	>0,5	>0,5	>0,5
Pressure in pulmonary artery, mm Hg	13,1±0,8 (15)	13,1±1,7 (9)	14,2±0,9 (9)	15,0±2,5 (5)	15,0±1,1 (5)	13,3±0,9 (6)	13,5±1,0 (6)	15,0±0,3 (7)	15,4±0,9 (7)
P			>0,5	>0,5	>0,5	>0,5	>0,5	>0,5	>0,5
Total peripheral resistance, dynes·sec·cm^{-5}	3362±364 (15)	4413±241 (10)	2981±127 (5)	5793±371 (5)	3844±310 (5)	4271±254 (6)	3177±252 (6)	3494±435 (7)	2641±232 (7)
P		0,05	>0,5	<0,05	>0,5	>0,5	>0,5	>0,5	>0,5
Oxygen concentration in arterial blood, vols.%	20,9±0,5 (15)	21,5±1,3 (10)	20,8±0,9 (5)	22,3±1,0 (5)	19,2±0,9 (5)	17,0±0,6 (6)	15,5±0,7 (6)	15,0±0,8 (7)	13,0±0,7 (7)
P			>0,5	>0,5	<0,05	<0,05	<0,05	<0,05	<0,05
Arteriovenous oxygen difference, Vols.%	4,6±0,4 (15)	8,0±0,5 (10)	6,5±0,7 (5)	9,4±1,6 (5)	7,8±0,8 (5)	6,3±1,3 (8)	6,2±0,6 (6)	6,4±0,5 (7)	5,7±0,4 (7)
P		<0,05	<0,05	<0,05	<0,05	>0,5	0,05	<0,05	>0,5
Total oxygen consumption, ml/kg	5,2±0,6 (15)	6,8±1,1 (10)	7,3±0,7 (5)	7,6±1,1 (5)	8,1±2,0 (5)	7,9±1,6 (6)	9,4±1,6 (6)	8,2±0,7 (7)	10,1±0,8 (7)
P		>0,5	0,05	>0,5	>0,5	>0,5	<0,05	<0,05	<0,05
Hematocrit index, liter/liter	0,48±0,02 (15)	0,56±0,01 (9)	0,44±0,02 (9)	0,49±0,03 (5)	0,40±0,02 (5)	0,36±0,01 (6)	0,33±0,07 (6)	0,32±0,01 (7)	0,28±0,01 (7)
P		<0,05	≤0,05	>0,5	>0,5	<0,05	<0,05	<0,05	<0,05
Oxygen transport, ml/kg·min	30,8±0,7 (15)	27,3±1,1 (10)	32,9±0,9 (5)	16,7±1,0 (5)	22,0±0,5 (5)	20,1±1,2 (6)	22,8±1,6 (6)	19,6±1,9 (7)	23,8±1,3 (7)
P			≥0,05	<0,05	<0,05	<0,05	<0,05	<0,05	<0,05

Legend. Number of animals shown in parentheses.

matograph. On the days following resuscitation observations were kept on the general state of the animals, the intake of water and food, posture, coordination of movements, the state of the skin, and responses to various stimuli. The state of all the functions mentioned above served as an indicator of external recovery of the corresponding divisions of the central nervous system.

EXPERIMENTAL RESULTS

At the end of the first hour of the postresuscitation period after reinfusion of blood and dextran infusion the cardiac index, the total peripheral resistance, and the hematocrit index of the animals were close to their initial values (Table 1). By contrast, the writers found previously that in cases when no dextran infusion was given and treatment was confined to reinfusion of blood, the cardiac output was reduced, the peripheral resistance was increased, and hemoconcentration developed [2]. Consequently, a combination of blood transfusion with dextran infusion after prolonged hypovolemic hypotension enables the volume velocity of the blood flow to be maintained at a sufficiently high level during the first hours of resuscitation.

However, it follows from the data in Table 1 that after 1 h the cardiac index of all animals had fallen on average by 55.6% ($P < 0.05$) compared with the first hour after resuscitation, but the oxygen concentration and hematocrit index were substantially unchanged. Oxygen transport toward the end of the first day of the recovery period was reduced. The decrease in the quantity of transported oxygen was accompanied by a compensatory increase in oxygen utilization. Under these circumstances the total oxygen consumption of the animal did not differ significantly from its initial value.

A single course of fractional infusions of dextran in the early recovery period after hypovolemic hypotension thus did not lead to prolonged stabilization of the circulation, and by the end of the first day the cardiac index was considerably depressed so that the tissue perfusion consequently was reduced.

It will be clear from Table 1 that dextran infusions on the 1st, 3rd, and 4th-6th days of the recovery period, in a volume of 10 ml/kg body weight, were accompanied mainly by similar changes in the parameters of the circulation: an increase in cardiac output and aortic pressure, a decrease in the total peripheral resistance. The only difference was that the degree of hemodilution increased (hematocrit index on the 4th-6th day 0.32-0.28 liter/liter), but the cardiac index before each successive infusion was higher and came close to the initial values or even exceeded them. A gradual increase in the oxygen consumption was discovered equally clearly, for on the 4th-6th day it was 10.1 ml/kg, which was twice the level before blood loss. This last fact was evidence of improvement in the oxygen supply to the tissues. Prolonged dextran infusion therapy thus prevented the development of secondary disturbances of the hemodynamics and of the oxygen supply to the body, and promoted stabilization and gradual normalization of the parameters of the circulation. The transport function of the blood with respect to oxygen, although depressed because of the reduction in the oxygen capacity of the blood because of hemodilution during the infusion therapy, nevertheless remained much higher than the critical values, which lie within the range of 9-10 ml/kg·min [7].

The beneficial effect of dextrain infusion therapy on the state of the hemodynamics is evidently associated with the correction of the relative and absolute hypovolemia, prevention of aggregation of blood cells in the small vessels, and maintenance of adequate perfusion in the tissue.

Of the 25 animals subjected to hypovolemic hypotension 20 (80%) survived. Outwardly complete neurologic recovery occurred in 93.7% of cases. As was shown previously [3], only single small foci of death of nerve cells were observed in the cerebral cortex of the animals treated with repeated dextran infusion. At the same time we know that in animals subjected to prolonged hypovolemic hypotension and subsequent reinfusion of blood, but not treated with repeated dextran infusion, foci of pathologically changed neurons are larger [5, 6]. The increase in the volume of effectively circulating fluid and improvement of the microcirculation in the postresuscitation period following dextran therapy evidently prevent the development of profound degenerative changes in the cerebral cortex, potentiate the protective functions of the organism, and increase the survival rate of the animals.

Prevention of secondary circulatory disorders by repeated fractional infusions of dex-

TABLE 1. Changes in Blood Serum Lipid Levels and Severity of Atherosclerosis in Experimental Rabbits Kept on Atherogenic Diet after Partial Iliac Shunting and in Control Animals after Laparotomy (M ± m)

Group of animals	Indicator of blood lipid spectrum, mg %	Initial values	Duration of experiment, weeks				Area of involvement of aorta by atherosclerosis, percent
			4	8	12	16	
Exptl. ($n = 15$)	Total cholesterol	23±3,8	48±6,4	43±5,2	115±16,2	163±28,9	0
	Triglycerides	81±16,2	76±15	65±8,5	84±17	81±16,8	
	α-cholesterol	9,4±2	14±3,1	13,8±1,8	14,8±4,5	15,6±3,7	
Control (n = 15	Total cholesterol	32±4,7	605±97	1045±46	1101±75	1176±87	24±6
	Triglycerides	30±3,4	55±11,8	147±15,5	178±24,8	179±19,4	
	α-cholesterol	8,7±3,2	9,1±3,1	9,8±1,9	11±4,2	12,2±3,9	

teries [6, 9, 10]. This method may prove effective in the treatment of obesity and of certain forms of atherosclerosis in man.

The object of the present investigation was to study the effect of the operation of partial iliac shunt on certain biochemical indices and on digestion as a whole, and also to determine whether surgical correction of marked hyperlipidemia is possible in rabbits kept on an atherogenic diet.

EXPERIMENTAL METHOD

In the experiments of series I, 18 dogs of different sexes were used. Under anesthesia, a midline laparotomy was performed. The length of the small intestine was measured and it was then divided at a distance of one-third of its length from the iliocolic valve. The distal end of the small intestine was closed by sutures and the proximal end was anastomosed with the cecum at the iliocecal angle by an end-to-side method.

In the experiments of series II 30 male chinchilla rabbits weighing from 2.5 to 3 kg were used. Partial shunting of the ileum was performed on the animals of group 1 (15 rabbits) under anesthesia, whereas the animals of control group 2 (15 rabbits) underwent laparotomy alone. The animals of both groups were transferred to an atherogenic diet one month after the operation.

Experimental atherosclerosis was produced by Anichkov's method by peroral administration of 5 ml of 10% cholesterol solution in sunflower oil (200 mg cholesterol/kg body weight) five times in the course of a week. The duration of the experiment was 16 weeks. Before the beginning of the experiment and during its course at 4-weekly intervals the concentration of total cholesterol, and of cholersterol of α-lipoproteins and triglycerides, was determined in the blood serum of all the rabbits. Lipids were determined by a standardized method on an AA-II automatic analyzer (from Technicon) [2].

At the end of the experiment the atherosclerotic index in the aorta of all the experimental rabbits was determined by Avtandilov's method [1] after preliminary staining of the blood vessels *in toto* with Sudan III. For histological investigation sections were stained with Sudan III and hematoxylin by Van Gieson's method; for elastic fibers by the Weigert–Hart method and impregnated with silver by Foot's method.

EXPERIMENTAL RESULTS

Observations on the dogs during 6 months after Buchwald's operation showed that it produced no marked biochemical or pathological changes in the animals apart from moderate hypokalemia during the first month after the operation. During the three months after the operation the animal became completely adapted to the new conditions of digestion. For example, whereas in the first month after the operation the dog lost about 8% of its normal body weight, by the 3rd month it was completely restored. Diarrhea ceased by the end of the first month, except in one dog in which it persisted for 2.5 months. The serum cholesterol level five months after the operation was lowered on average by 15.6%.

When the rabbits of both groups were kept on an atherogenic diet it was observed that four weeks after the beginning of the experiment the blood serum cholesterol concentration in animals of the control group was 19 times higher than initially, whereas in the experimental animals it was only twice as high (Table 1). The same ratio persisted later during the experiment. At the end of the experiment the blood cholesterol concentration in rabbits of the control group was 7.2 times higher and the triglyceride concentration 2.2 times higher than in the experimental animals undergoing Buchwald's operation.

In the experimental rabbits cholesterol of α-lipoproteins accounted for 10% of the total cholesterol compared with only 1% in the control rabbits. This fact is important in light of modern views on the role of hypo-α-cholesteremia in the risk of development of atherosclerosis.

The results of the biochemical investigation of the serum cholesterol concentration thus confirmed previous observations [6, 8] showing that Buchwald's operation prevents the development of hypercholesteremia. This last effect is linked with the exclusion from the digestive process of that portion of the small intestine where cholesterol is absorbed most rapidly, with the result that the excess cholesterol is excreted by the animal.

The results of morphological investigation agreed with those of biochemical lipid analysis. In the animals of the control group, kept for 16 weeks on an atherogenic diet, lipid stains and atherosclerotic plaques were observed to be formed in all parts of the aorta. The area of aorta involved (the atherosclerotic index) averaged 24 ± 6%. In 14 of the 15 rabbits previously undergoing Buchwald's operation, no atherosclerotic changes were observed to develop in the arterial wall even after total staining of the aorta with Sudan III (Table 1). Only in one rabbit were lipid stains observed to be formed above the aortic valve and in the region of the arch, and in this case the atherosclerotic index was only 5%.

On histological investigation of the aorta of the rabbits of the control group we observed atherosclerotic plaques with a well-developed connective-tissue membrane and with deposition of lipids in foam cells, their destruction and the beginning of an atheromatous focus in the depth of the tissue. As alredy mentioned, in the rabbits of the experimental group atherosclerosis was not seen to develop, and the process was limited to moderate edema of the subendothelial layer. It is possible that the mechanism preventing the development of atherosclerotic lesions in the arterial walls of the animals undergoing partial iliac shunting comprised not only the basic cause, namely prevention of absorption of cholesterol, but also a number of contributory factors. In particular, in experiments to study regression of atherosclerotic lesions in pigeons undergoing the operation at the height of development of experimental atherosclerosis, not only was rapid normalization of the blood lipid level found, but also activation of lysosomal hydrolytic enzymes [10]. Evidently during moderate hypercholesteremia after Buchwald's operation lipoproteins enter the cells of the intima by a process of receptor-dependent endocytosis [7]. As a result of this process foam cells are not formed or destroyed, there is no tissue necrosis, and no hypertrophy of the connective tissue in the cells.

The results of this investiagion with a comparison of data in the literature thus show that the operation of partial iliac shunting can evidently have a beneficial effect on normalization of lipid metabolism, and may possibly lead to reabsorption of lipids from the plaques. The result can be regarded as providing a basis for the development of methods of surgical correction of atherosclerosis.

LITERATURE CITED

1. G. G. Avtandilov, Morphometry in Pathology [in Russian], Moscow (1973).
2. V. F. Tryufanov and S. I. Suchkov, in: Dyslipoproteinemia and Ischemic Heart Disease [in Russian], Moscow (1980), p. 151.
3. A. M. Khil'kin and V. V. Zemlyanikov, Kardiologiya, No. 4, 141 (1976).
4. H. Buchwald, Circulation, 28, 649 (1963).
5. H. Buchwald, R. B. Moore, and R. L. Varco, in: Atherosclerosis, New York (1980), p. 462.
6. H. Buchwald, R. B. Moore, I. Bertish, et al., Ann. Surg., 173, 311 (1972).
7. J. L. Goldstein and M. S. Brown, Arch. Pathol., 99, 181 (1975).
8. L. Lorenzini, F. Tani, F. Papi, et al., G. Aterioscler., 2, 95 (1979).
9. M. T. Ravi Subbiah, B. A. Dicke, B. A. Kottke, et al., Artheriosclerosis, 31, 117 (1978).
10. G. R. Thomson and A. M. Gotto, Lancet, 2, 35 (1973).