EFFECT OF GUTIMIN ON THE CARDIOHEMODYNAMICS AFTER BLOOD LOSS

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Many workers [6, 15] now consider that disturbance of the cardiohemodynamics is the principal pathogenetic component in the development of shock. Data on the antihypoxic action of gutimin in various forms of experimental oxygen deficiency [10] and its therapeutic effect in clinical practice on patients with chronic coronary insufficiency [9], and on protection of the myocardium from ischemia during open heart operations [5] are evidence that this substance is a promising possible candidate for the task of increasing the resistance of heart muscle to hypoxia in hemorrhagic shock. The object of this investigation was to study the action of gutimin (guanylthiourea) on the cardiovascular system and to compare it with its concentration in the blood and myocardial tissue and mitochondria in circulatory-hemic hypoxia caused by blood loss.

EXPERIMENTAL METHOD

Experiments were carried out on 54 adult mongrel dogs weighing 10-27 kg. Premedication with trimeperidine and atropine was given. Hypotension was produced in the animals by free bleeding from the femoral artery. The arterial pressure was maintained at 40 mm Hg for 60 min by Wiggers' method. The volume of blood lost was 32% of the total blood volume. Against this background, without replacing the lost blood, the dogs were given gutimin intravenously in a dose of 35-40 mg/kg and changes in the chosen parameters were observed for the next 60 min. The heparinized blood was reinfused into the femoral vein 120 min after the beginning of bleeding, under a pressure of 80-120 mm Hg [1]. During the experiments the ECG was recorded in lead II, the systemic arterial pressure (SBP), the central venous pressure (CVP), and the peripheral venous pressure (PVP), and the cardiac output (CO) was determined by Fick's method followed by calculation of parameters of the pumping function of the heart and the total peripheral vascular resistance (TPVR). The gutimin concentration in the blood and myocardial tissue and mitochondria was determined by gas chromatography [8] in intact and experimental dogs.

EXPERIMENTAL RESULTS

Gutimin was injected intravenously into intact dogs in a dose of 40 mg/kg body weight. The highest gutimin concentration in venous blood was found after 5 min (Fig. 1). After 10 and 15 min the gutimin concentration was reduced by two-thirds compared with its level during the first 5 min of the experiment, after 60 min it was lowered by 95%, and after 120 min only traces could be detected in the blood. Further investigations showed that a gradual fall in the gutimin concentration in the blood was accompanied by its gradual accumulation in the tissue and mitochondria of the heart. The highest levels of gutimin were found 10 and 15 min after its injection. The gutimin concentration in the tissues and mitochondria of the heart after 120 min corresponded to its values determined 5 min after the beginning of its injection.

During circulatory-hemic hypoxia caused by blood loss the time course of the gutimin concentration in the blood and myocardial tissue and mitochondria of the dogs (which received equal doses of gutimin) differed from those in the control. In venous blood, 5 min after the

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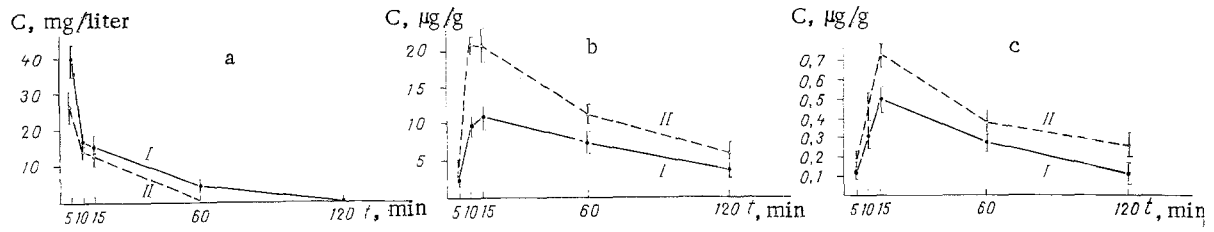

Fig. 1. Time course of gutimin concentration in blood (a) and myocardial tissues (b) and mitochondria (c) of intact dogs (I) and animals after blood loss (II).

beginning of injection, the gutimin concentration was 1.6 times less than that observed in intact dogs at the same time of observation. After 10 and 15 min the blood gutimin concentration was the same in both series. At the 60th minute gutimin could no longer be determined in the blood. The gutimin concentration in the myocardial tissue and mitochondria at this time was much higher than in intact animals.

The lower blood gutimin concentration at the 5th minute of the experiment, its rapid disappearance from the blood stream, and the considerable accumulation of the compound in the myocardial tissue and mitochondria after blood loss are convincing evidence in support of the high rate of utilization of the compound convincing evidence in support of the high rate of utilization of the compound by the heart, under conditions of oxygen deficiency.

As a result of the acute blood deficiency 60 min after bleeding the venous return of the animals was considerably reduced (Table 1). Lowering of CVP by half and quickening of the pulse led to a decrease in the filling pressure of the chambers of the heart. This resulted in a decrease in the stroke volume (SV) and cardiac output (CO). The ECG changes indicated myocardial ischemia. As a result the power and work developed by the ventricular myocardium during systole were reduced. The results given in Table 1 and those obtained previously under similar experimental conditions [7, 15] are evidence of considerable disturbance of capillary perfusion and of metabolism in the organs and tissues.

The use of gutimin during hypotension lasting 60 min almost doubled the cardiac output during the first 10 min. This was probably due to changes in metabolism of the heart muscle as a result of the corrective action of the gutimin which accumulated in the mitochondria, the "power houses" of the myocardium. The observed blocking of the right branch of the bundle of His in four dogs at the 60th minute of hypotension could not be detected after injection of gutimin. Lengthening of diastole was acccompanied by an increase in the power and work of the heart muscle. The beneficial action of gutimin on the cardiohemodynamics, incidentally, did not cause any increase in TPVR. This response of the vessels, against the background of a marked rise in CO and SBP, helped to improve the peripheral circulation, for if the cardiac output is high and TPVR is low, the tissues are perfused by much greater volumes of blood per unit time [12]. This is confirmed by data obtained during a study of the effect of gutimin on the microcirculation in blood vessels of the mesentery [7].

The gutimin concentration in the myocardial tissue and mitochondria 60 min after the beginning of its injection was lower than when determined after 15 min. Meanwhile there was a marked fall in the parameters of the cardiohemodynamics, but they were still much higher than before administration of gutimin.

Selective accumulation of gutimin in the heart tissues and mitochondria, and the positive effect of the drug on the cardiohemodynamics point to the possible role of its mitochondrial effects in the mechanism of the antihypoxic action and they confirm data showing that it not only activates glycolysis in heart muscle, but also improves further oxidation of its products [11, 14] and, as a result of the realization of these mechanisms, it prevents destruction of the cardiomyocyte membranes in hypoxia [4, 15].

During the first minutes after intravenous injection of heparinized blood and during the next 60 min of observation, normalization and stabilization of the parameters of the ECG and cardiohemodynamics and of the systemic circulation were observed. In the control series of experiments, under similar conditions, SBP increased only to 88 mm Hg after correction of the blood loss, and 60 min after reinfusion it fell to 55 mm Hg. The parameters of the cardiohemodynamics corresponded to those determined after 60 min of hypotension [15].

TABLE 1. Parameters of Cardiohemodynamics and Systemic Circulation during Period of Hypotension and after Injection of Gutimin and Reinfusion of Blood (M ± m)

Parameter	Initial state	60 min of hypotension	Period of action of gutimin, min		Recovery period, min	
			10—15	60	10—15	60
CO, ml/min	2838±427	981±222*	1511±326*	1220±206*	2710±518	2041±303
SV, ml	15±1,5	4,6±0,3*	8±0,8*,**	6±0,5*,**	17±2,8	14±3,0
HR, beats/min	187±7	211±6*	200±9	205±11	153±7*	150±10*
CI, liters/m^2/min	5±0,4	0,9±0,1*	2,1±0,4*,**	1,6±0,1*,**	3,7±0,3*	2,6±0,2*
SI, ml/m^2	26±3,0	4,1±0,6*	11,5±1,8*,**	7,3±0,3*,**	24±4,0	18±1,5*
SBP, mm Hg	129±5	42±1*	84±5*,**	83±6* **	123±7	127±7
Power of left ventricle, kg·m/min	5,903±0,43	0,301±0,05*	1,914±0,32*,**	1,508±0,20*,**	4,438±0,46*	3,678±0,40*
Work index of left ventricle, kg·m/min/m^2	10,4±0,6	0,4±0,04*	2,5±0,5*,**	1,7±0,1*,**	5,9±0,7*	4,5±0,4*
Stroke work index of left ventricles, kg·m/m^2	49±4	1,9±0,2*	11,8±2,0*,**	7,9±0,4*,**	41±0,7	31±3*
N, W	0,963±0,090	0,049±0,009*	0,312±0,050*,**	0,246±0,086*	0,724±0,063*	0,597±0,063*
E, J	0,300±0,028	0,013±0,002*	0,090±0,010*,**	0,069±0,012*,**	0,300±0,044	0,253±0,055
CVP, mm water	63±3	32±4*	31±7*	41±8*	45±3*	44±5*
PVP, mm water	114±7	95±8	101±5	99±7*	115±4	116±4
TPVR, dynes·sec·cm^{-5}	3457±514	4155±133	4030±539	4952±225*,**	4010±704	4188±218
Specific peripheral resistance, conventional units	27±3	51±6*	42±6*	48±4*	37±6	48±5*
ECG intervals, sec						
P—Q	0,08±0,005	0,08±0,003	0,08±0,003	0,08±0,05	0,09±0,004	0,09±0,006
QRS	0,05±0,005	0,038±0,009*	0,04±0,002*	0,04±0,002*	0,05±0,003	0,04±0,002*
S—T	0,14±0,009	0,14±0,006	0,13±0,005	0,14±0,009	0,19±0,01*	0,18±0,01*
Q—T	0,21±0,007	0,18±0,006*	0,19±0,007*	0,19±0,006*	0,24±0,009*	0,23±0,01*
T—P	0,05±0,009	0,04±0,008	0,06±0,01**	0,06±0,01**	0,11±0,01*	0,13±0,01*
Amplitude of ECG waves, mV						
R	1,9±0,17	1,30±0,20*	1,50±0,23	1,45±0,26	2,02±0,14	2,1±0,26
T	0,27±0,03	0,30±0,05	0,40±0,06	0,40±0,06	0,30±0,04	0,34±0,04

*Significance of differences of parameters compared with initial state.
**Significance of differences of parameters during hypotension and during period of action of gutimin (differences statistically significant at the $P < 0.05$ level).

Later the animals were kept under observation for 1 month. The survival rate was 66.6% in the experimental series whereas in the control group the mortality was 83.3%.

The investigations thus showed that gutimin, injected intravenously in circulatory-hemic hypoxia due to blood loss, passes quickly through the membrane of the cardiomyocyte organelles and, accumulating in the tissue and mitochondria of the myocardium, it corrects the metabolism of the heart muscle and thereby increases electrical diastole and stimulates the pumping function of the heart and increases the power, energy, and work of the myocardium and SBP, without, however, increasing TPVR under these circumstances. The beneficial action of the compound on the cardiohemodynamics is exhibited during the first minutes after the injection and continues at a stable level for 1 h, which corresponds to maintenance of a high gutimin concentration during this period in the myocardial tissue and mitochondria. Realization of the antihypoxic effect of gutimin at the cellular level [2] enables the reversible phase of the pathological process in the heart muscle and other organs to be prolonged [3], the resistance of dogs to hypoxia and the effectiveness of inevitably delayed treatment to be increased, and the survival rate of the animals to be improved.

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EFFECT OF CAROTID SINUS DENERVATION ON THE DEVELOPMENT OF HIGH-ALTITUDE ACUTE PULMONARY EDEMA

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Chemoreceptor modes, which react precisely to changes in the gas composition of the blood and which have an important influence on parameters of the hemodynamics and gas exchange in the pulmonary circulation in various hypoxic states are located in the carotid bodies [1-3, 5, 8]. The elucidation of the effect of their level of function on the oxygen balance of the body would shed light on the mechanisms of the course of pathological processes in the lungs in a hypoxic environment.

In this investigation an attempt was made to study the effect of denervation of the carotid bodies on the development of high-altitude acute pulmonary edema (HAAPE) and on the various disturbances of function in this condition.

EXPERIMENTAL METHOD

Experiments were carried out on 12 male chinchilla rabbits weighing 3.2-4.2 kg. The animals were used in the experiment 6-8 days after surgical pericarotid denervation. The rabbits were kept in a climatic pressure chamber, in which the pressure corresponded to an altitude of 5.5-6 km and the appropriate meteorological factors (temperature, air humidity, UV irradiation, velocity of the air flow, etc.) were reproduced. To study the function of the cardiovascular systems the right and left sides of the heart, aorta, and pulmonary artery were catheterized. Pressure was measured by means of a Mingograf-81 electromanometer (Elema, Sweden); the ECG was recorded in standard lead II on a 6NEK-401 instrument (East Germany). The cardiac output (CO), central blood volume, velocity of the blood flow between the right heart and ear, and the circulating blood volume (by a dye method) also were determined. The respiratory minute volume (RMV), quantity of absorbed oxygen, and respiration rate were studied at the same time.

To determine the diffusion capacity of the lungs, the blood gases and O_2 and CO_2 concentrations in the expired and alveolar air were studied.

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