EFFECT OF POLYMERS REDUCING HYDRODYNAMIC RESISTANCE ON SYSTEMIC HEMODYNAMICS

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If special polymers, lowering the hemodynamic resistance of the blood, are injected intravenously, the arterial blood pressure (BP) falls in animals of various species [3, 4]. It has been shown [3] that the average BP (ABP) may fall as a result both of an equal lowering of both systolic and diastolic pressure, and of a greater fall of the systolic pressure. Lowering of ABP took place when the heart rate (HR), the rate and amplitude of respiration, hematocrit index, and pH and osmolarity of the arterial blood were all unchanged. Significantly often pO_2 of the arterial blood was raised and its pCO_2 lowered, although not outside normal limits. The local cerebral blood flow was unchanged in both the gray and white matter. No increase was found in permeability of the blood–brain barrier in respect of blood proteins. By contrast with the absence of change in the diameters of the mesenteric vessels in response to injection of polymers [4], vasoconstriction on the brain surface was noted in [3] under these conditions when ABP was lowered and the local cerebral blood flow was unchanged; this effect was evidently connected with a special type of autoregulation of the cerebral vessels, preventing any possible increase of the inflow of blood into the brain in this case. This autoregulatory response of the cerebral vessels, which was first noted in [3], differed from the known response of autoregulation of the cerebral vessels to lowering of ABP by the fact that instead of the vasodilator reaction, usually arising under these circumstances, to maintain the cerebral blood flow at a constant level under these conditions, i.e., during a change in the hydrodynamic properties of the blood (an increase in its flowability), constriction of the pial vessels was observed.

Thus a previously known phenomenon of autoregulation of the cerebral circulation in response to lowering of the hydrodynamic resistance to the blood flow, on account of a change in its rheologic properties [3], was discovered with the aid of special linear high-molecular-weight polymers. Injection of these polymers against a background of severe circulatory cerebral ischemia, induced in rabbits by ligation of the four main arterial trunks to the head in the neck, with the development of a marked phenomenon of reduced circulation [1], led to a sharp increase in the collateral inflow of blood and to disappearance of signs of the reduced circulation. Conversely, the aftereffects of cerebral circulatory disturbances induced by an acute rise of ABP in animals with depressed hydrodynamic resistance of the blood following preliminary injection of the polymer were more severe [2]. In other words, polymers lowering hydrodynamic resistance and increasing the flowability of the blood have a marked influence on certain parameters of the systemic and visceral circulation in animals, including a shift of the upper and lower boundaries of autoregulation of the cerebral blood flow toward lower values of ABP [2]. The effect of lowering of the hydrodynamic resistance of the blood on parameters of the systemic hemodynamics such as cardiac output (CO), total peripheral resistance (TPR), and HR, depending on the time elapsing after intravenous injection of the polymer, has not yet been adequately explained [4, 5].

The aim of this investigation was to determine the effect of polymers lowering the hydrodynamic resistance on the systemic hemodynamics.

EXPERIMENTAL METHOD

Experiments were carried out on normal adult chinchilla rabbits weighing 2-3 kg under pentobarbital anesthesia (40 mg/kg), receiving heparin (500 U/kg, from Richter, Hungary) by

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intravenous injection. The hydrodynamic resistance of the blood was lowered by intravenous injection of polyethylene-oxide WSR-301, a special high-molecular-weight linear polymer, for 2-3 or 15-20 min, in the form of the original solution of the polymer with a concentration of 5×10^{-4} g/ml, with a resultant dose of 2×10^{-6} g/ml blood of each animal. In group 1 (11 rabbits) the polymer was injected and all the parameters measured under acute experimental conditions. Background values of the parameters measured before injection of the polymer served as the control. The animals of group 2 were divided into two subgroups: experimental, consisting of 10 rabbits into which the polymer was injected intravenously 72 h before the acute experiment, and control, consisting of 12 rabbits receiving physiological saline in the same dose (the volume did not exceed 1 ml) by intravenous injection 72 h before the acute experiment. The following parameters were recorded continuously during the acute experiment: systolic and diastolic pressure and ABP (through a catheter in the ascending part of the arch of the aorta), HR from the ECG, the body temperature and respiration rate, by means of appropriate units of a polygraph from "Nihon Kohden" (Japan). Cardiac output was measured by the dye dilution method (Cardio-Green; "Hynson") 6 times during the acute experiment: twice before injection of the polymer (in group 1) and 4 times at different times after injection. The dye was injected through a catheter into the superior vena cava as a "bolus," and samples were taken through a catheter from the ascending part of the arch of the aorta. The circulating blood volume (CBV) was determined by measuring the concentration of the dye Evans' blue in the blood. From values of ABP, CO, and HR the stroke volume (SV) and TPR were calculated. The hematocrit index was determined with a hematocrit centrifuge, arterial blood gases and pH were measured by the micro-Astrup method, and the osmolarity of the arterial blood was determined on a micro-osmometer ("Knauer," West Germany). The diameter of the common carotid artery was measured by means of an MBS-2 microscope (using an ocular with metric scale). The viscosity of whole blood was determined on a capillary viscosimeter without any additional conservation of the blood. In the animals of group 1 background values of all parameters were measured, after which the solution of the polymer was injected and the parameters were monitored for 1-1.5 h. Mean values compared with the initial values for the group as a whole were calculated. Animals of group 2 were used in the acute experiments 72 h after receiving an injection of polymer solution or of physiological saline. All parameters were measured many times in the course of 45-60 min, so that stable values could be obtained to allow comparison of the mean values of all parameters in the experimental and control subgroups. To compare results obtained in the animals of groups 1 and 2, the average initial values of the parameters in group 1 and in control subgroups 2 were taken as 100%, and accordingly the time course of all the parameters could be reduced to relative percentages with corresponding statistical analysis of all the results.

EXPERIMENTAL RESULTS

ABP was considerably reduced 5 min after the beginning of injection of the polymer, and reached minimal values after 30 min. It then rose slowly until the 90th minute, and after 72 h it remained significantly lower than the initial level by 20-10% (Fig. 1a). CO also fell significantly during the first minute after injection of the polymer, but by the 90th minute it was restored to its initial values, and after 72 h it was significantly higher than the initial level by 15-16% (Fig. 1b). In the case of very slow injection of the polymer (over a period of 15-20 min) the initial decline of CO did not take place. No changes were observed in HR and CBV after injection of the polymer. The character of the change in SV as a whole corresponded to changes in CO, but whereas the decrease in CO after 5 and 30 min was significant, although small, the decrease in SV at these times was not significant. By the 60th minute SV corresponded to the background values, but after 90 min and after 72 h it was significantly higher than the background values by 10 and 15% respectively. TPR was increased but not significantly 5 min after injection of the polymer, but later it began to fall, and by the 90th minute it was significantly lower than the initial value by 10-20%. TPR 72 h after injection of the polymer was 20-25% below the background level (Fig. 1c). No changes were observed in the diameter of the common carotid artery, hematocrit index, asymptotic blood viscosity, and pH and osmolarity of the arterial blood. The pO_2 of the arterial blood, although remaining within normal limits, increased significantly, but its pCO_2 fell, as was observed previously [3].

The results are evidence that in the initial period after injection of the polymer (especially if injected relatively quickly in the course of 2-3 min) a decrease in some parameters of the systemic hemodynamics was observed, possibly leading to a small increase in TPR. As was stated above, this short-term worsening of the hemodynamics can be avoided by increasing

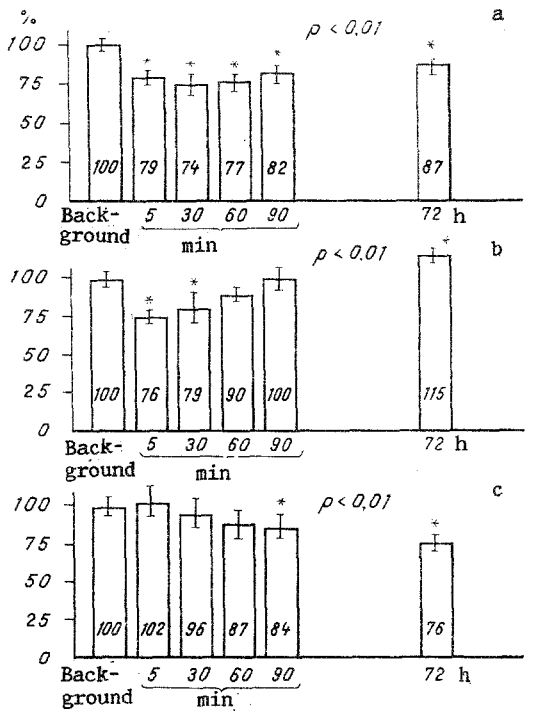

Fig. 1. Changes (in % of initial values) in ABP (a), CO (b), and TPR (c) depending on time elapsing after intravenous injection of polymer solution. Asterisk indicates significance of difference from background value.

the time taken to inject the same dose of polymer. Later there was a stable fall of TPR compared with the initial value without dilatation (as was shown in [3, 4]) of the resistive vessels. In our opinion, the explanation of the initial shifts of these parameters may lie in the fact that the first response of the vascular system to injection of the polymer is a reaction to a sufficiently rapid change in the rheologic properties of the blood and in the structure of the blood flow. If the rate of these changes was reduced about tenfold by slower injection of the same quantity of polymer (over a period of 15-20 min), these changes evidently lay outside the threshold of sensitivity of the vascular system.

It has to be pointed out that polymers lowering the hydrodynamic resistance of the blood reduce TPR, lower ABP, and increase CO simultaneously, collectively and, for a fairly long time (in the present experiments — not less than for 3 days). Meanwhile treatment with drugs can lower ABP in hypertension (vasodilators or adrenoblockers), can increase CO in heart failure (corglucon, strophanthin, etc.), and reduction of TRP (papaverine, adrenoblockers) do not give a prolonged therapeutic effect if administered in a single dose or even intravenously, for the duration of their action is measured in minutes or, at most, in hours.

Thus special high-molecular-weight linear polymers, capable of reducing the hydrodynamic resistance of the blood, if injected intravenously can change parameters of the systemic hemodynamics such as ABP, CO, and TPR substantially and for a sufficiently long time. Meanwhile they can reveal the sensitivity of the vascular system to changes in the rheologic properties of the blood (its rheosensitivity) and they suggest the existence of special rheoreceptors.

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