THROMBORESISTANT PROPERTIES OF HYDROPHILIC GELS

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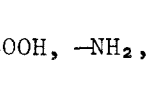
The thromboresistant properties of hydrophilic gels based on copolymers of nitrogen-containing heterocyclic vinyl compounds with vinyl monomers were investigated. The hydrophilic gels were shown to prevent adsorption of fibrinogen, activation of procoagulants, and adhesion of platelets. Hydrogen surfaces possess selective affinity for plasma albumin. The authors consider that the thromboresistant effect of hydrophilic gels is due to the competitive action of plasma albumin. Modification of hydrophilic gels increases their thromboresistant properties.

KEY WORDS: hydrophilic gel; heparin; platelets; albumin; fibrinogen; thromboelastogram; thrombosis.

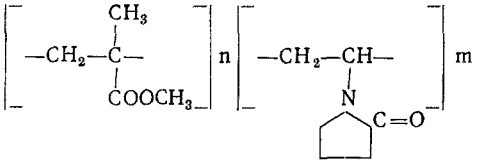
Data have recently been published which show that hydrophilic gels are promising polymers for the formation of endoprostheses [9, 10]. Some workers state that the tendency toward thrombosis during contact between blood and hydrophilic gels is lower than that observed with other polymers used in medicine [8, 12, 14, 15].

Hydrophilic gels are disperse systems formed from microheterogeneous colloidal solutions during their total or partial coagulation. The following functional groups occur in the structure of hydrophilic gels: —COOH, —NH_2, C≡N, and  [3, 4]. Hydrophilic gels can retain up to 10-20% H_2O [8, 9]. In their mechanical and physicochemical properties they correspond much more closely to the natural tissues of the body than other known polymers [14, 15]. This is because hydrophilic gels have low free surface energy, contain the minimal quantity of residual polymerization products, and are distinguished by their hydrophilicity and high elasticity [10, 14].

In the investigation described below the thromboresistant properties of hydrophilic gels synthesized on the basis of methyl methacrylate and N-vinylpyrrolidone were investigated.

EXPERIMENTAL METHOD

Hydrophilic gels were obtained on the basis of copolymers of nitrogen-containing heterocyclic vinyl compounds with vinyl monomers. The original components were methyl methacrylate and N-vinylpyrrolidone. The general structure of the synthesized hydrophilic gels was as follows:



The hydrophilic gels were formed as films measuring 50×50 mm, as test tubes with an internal diameter of 10 mm, and as catheters. The hydrogen products were modified with heparin by the adsorption method, i.e., the article was kept in a 0.1% aqueous solution of heparin (20,000 units) for 6 h at 20°C. Rabbit blood, stabilized with sodium citrate in the ratio of 4:1,

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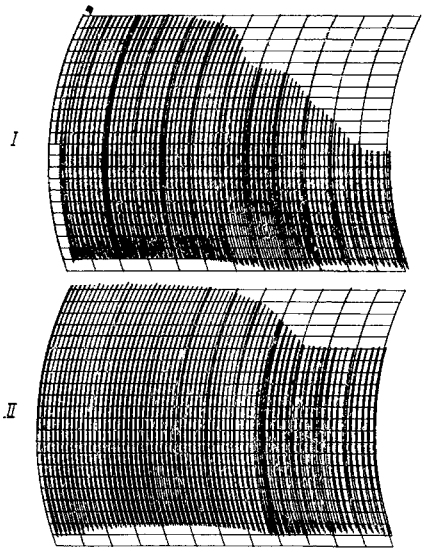

Fig. 1

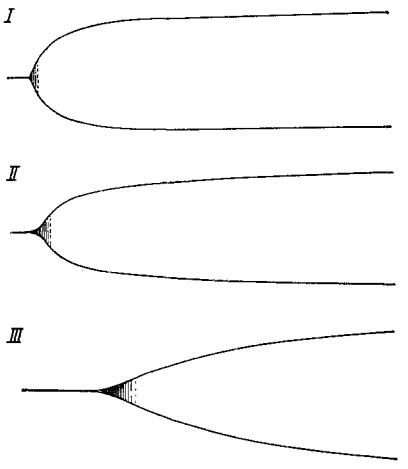

Fig. 2

Fig. 1. Blood heparin tolerance after contact of blood with hydrophilic gel surface. I) Glass surface; II) hydrophilic gel surface.

Fig. 2. Thromboelastogram after incubation of blood with hydrophilic gel surface. I) Glass surface; II) surface made from hydrophilic gel; III) surface from hydrophilic gel modified by heparin.

was used for investigation. Blood clotting indices in test tubes made from hydrophilic gel were studied after incubation of the citrated blood in them for 1 h. A glass surface was used as the control. The blood clotting indices tested included the clotting time of the blood [7], thromboelastography, blood heparin tolerance [11], concentration of factors of the prothrombin complex [2], fibrinogen concentration [1], free heparin concentration [5], index of platelet adhesion [3], platelet spreading time [6], and platelet sedimentation rate [13]. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The thromboresistant properties of hydrophilic gels with different proportions of the original components (methyl methacrylate and N-vinylpyrrolidone) were investigated. Hydro-

TABLE 1. Indices of Hemostasis Following Contact of Blood with Surface of Hydrophilic Gel (M±m)

Blood clotting index	Character of surface		
	glass	hydrophilic gel	hydrophilic gel + heparin
Clotting time, sec	392±17	923±96	1220±27
Concen. of factors of prothrombin complex, sec	10,4±0,12	33,7±2,2	51,7±0,38
Blood heparin tolerance, sec	418±8,3	593±12	—
Fibrinogen concen., mg %	438±12	248±9	184±8,9
Concentration of free heparin, mg %	1,21±0,06	2,49±0,27	2,75±0,33
Platelet adhesion index, %	57,25±1,7	12±1,02	6,3±0,68
Platelet sedimentation rate	0,89±0,0002	0,88±0,008	—

philic gels containing 14 moles % N-vinylpyrrolidone were found to have optimal thromboresistant properties. Changes in the blood coagulation indices following contact of blood with the hydrophilic gels are given in Table 1.

The clotting time of the blood after incubation in tubes made from hydrophilic gel was reduced on average by 531±79 sec, but if the hydrophilic gel was modified by heparin, it was reduced by 828±10 sec compared with that for a glass surface ($P<0.001$). The Quick time (concentration of factors of the prothrombin complex) increased on average by 23.3±2 sec for the hydrophilic gel and by 41±2 sec for the hydrophilic gel modified by heparin ($P<0.01$). The fibrinogen concentration was reduced after contact of the blood with the hydrophilic surfaces. For instance, the fibrinogen concentration after incubation of the blood with the hydrophilic surface, either plain or modified by heparin, was reduced by 190±31 and 254±10 μg % respectively ($P<0.02$). On contact of the blood with the hydrophilic gel surface an increase in the heparin activity of the blood was observed compared with the control. This was shown by a decrease in the blood heparin tolerance (Fig. 1). An increase in the free heparin concentration also was observed. In particular, the free heparin concentration after incubation of the blood for 1 h with the hydrophilic gel surface was increased by 1.28±0.21 mg %, whereas after incubation with the hydrophilic gel surface modified by heparin it was increased by 1.54±0.27 mg % ($P<0.001$). It can be tentatively suggested that during contact of blood with the hydrophilic gel surface for 1 h, less marked inactivation of heparin took place than in the control (glass surface). The hypocoagulation effect of contact of blood with the hydrophilic gel surface was also confirmed by thromboelastography (Fig. 2); whereas the hydrophilic gel surface led mainly to a decrease in the maximal amplitude of the thromboelastogram, modification of the hydrophilic gel by heparin caused an increase in the reaction time and in the coagulation time of the thromboelastogram.

The platelet adhesion index was significantly reduced after contact between blood and the hydrophilic gel surface (Table 1). The platelet sedimentation rate was reduced a little after contact with the hydrophilic gel surface. Investigation of platelet adhesion by the spreading method also showed that hydrophilic gel surfaces cause a distinct decrease in the number of adherent platelets in the absence of any visible morphological changes in them.

The results are evidence that hydrophilic gels have marked thromboresistant properties. This is shown by the hypocoagulation changes in blood after contact between it and a hydrophilic surface and by a decrease in platelet adhesion. The thromboresistant effect of hydrophilic gels must be explained on the grounds that plasma albumin which effectively competes for ability to undergo adsorption on the hydrophilic surface with fibrinogen and other plasma procoagulants [10], is selectively adsorbed on their surface. Adsorption of plasma albumin on the hydrophilic gel surface also prevents adhesion of platelets, which is an important factor in the triggering mechanism of thrombosis on an implanted polymer surface [4]. Additional investigations showed that of all the plasma proteins it is mainly the albumins that are adsorbed on the surface of synthetic hydrophilic gels. The quantity of fibrinogen and other globulins adsorbed is very small. This effect may perhaps be attributable to the inhibitory influence of the hydrophilic gel surface on fibrinase activity and on the quantitative formation of fibrin polymer. Modification of hydrophilic gels by heparin enhances their thromboresistant properties.

Hydrophilic gels based on methyl methacrylate and N-vinylpyrrolidone thus possess thromboresistant properties, and they can therefore be used to modify the surfaces of articles made from polymers which are in direct contact with blood.

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BIOPHYSICAL HEART–BODY MODEL

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A biophysical heart–body model consisting of a liquid bulk conductor, filling a hollow transparent vessel shaped like a human torso, and with an isolated perfused dog's heart immersed in it, is described. Metal electrodes for the various ECG leads are distributed on the inner surface of the vessel. The bulk conductor consists of NaCl solution. The amplitude of the derived signals was shown to depend on the NaCl concentration. With NaCl in a concentration of 0.004% the amplitude of the ECG obtained on the model was similar to that of the human ECG in the same leads. With an increase in the concentration of the solution the amplitude of the ECG falls rapidly, and with a 0.9% NaCl concentration it becomes almost indistinguishable. To protect the heart from injury by the hypotonic solution, an artificial pericardium made of electrically conducting rubber film is used. The method of placing the heart in the model of the torso also is described. It is suggested that the heart–body model can be used to study problems connected with the experimental investigation of ECG changes in different leads associated with intentionally induced injuries to or changes in the state of the heart.

KEY WORDS: electrocardiography; biophysical model.

The distinctive geometric shape of the thorax in animals and its great differences from the human thorax impose severe limitations on the extrapolation of experimental ECG interpretations to clinical electrocardiography. In the history of electrocardiography there is a well-known error connected with the careless transfer of electrocardiographic signs of branch block of the bundle of His obtained in experiments on dogs to clinical practice [3]. As a result of this mistake, an incorrect idea of the electrocardiographic features of these disturbances to conduction was held for more than 10 years. The cause of this error was the difference between the shape of the thorax of the dog and man.

Attempts to surround an animal's heart by a bulk conductor shaped like the human body have been undertaken now for a long time. However, the use of the cadaver as a model of the human body has several important disadvantages and can be very difficult to organize. It is preferable to use artificial models of the thorax, consisting of a hollow vessel shaped like the human torso, filled with an electrolyte, and with electrodes distributed over the thorax to record the electrocardiogram. Such models have been used to study the properties of electrocardiographic leads, by introducing a physical dipole [2, 4, 6, 7] and also for biological experiments [8].

The heart–body model to be described below consists of a hollow cast of the torso of an adult man of normosthenic constitution, filled with NaCl solution, in which the isolated, perfused heart of a large dog weighing 20-35 kg was immersed (Fig. 1A). The heart was isolated and perfused by the method described in [1]. So that during the use of the model

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