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ПРОБЛЕМИ ФУНДАМЕНТАЛЬНИХ І ПРИКЛАДНИХ НАУК

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THE SUBSTANTIATION OF THE PARAMETERS OF THE ROTARY-FILM CONTACTOR FOR EXTRACORPOREAL PROCESSING OF LARGE VOLUMES OF BLOOD USING OZONE

Т.А. Глуханька, В.В. Єгоров, Н.О. Каніщева, Є.І. Назаров, А.В. Кіпенський. **Обгрунтування параметрів роторно-плівкового контактора для екстракорпоральної обробки озоном великих об'ємів крові.** Розвиток і вдосконалення методів озонотерапії тісно пов'язані з оптимізацією технічних засобів, які забезпечують вирішення різних клінічних завдань. ***Мета:*** Метою роботи є розробка нового методу екстракорпорального озонування й оксигенування великих об'ємів крові, а також розробка нового типу контактора «озон – кров». ***Матеріали і методи:*** Кінетика реакції взаємодії озону з цілісною кров'ю вивчалася методом «зупиненого потоку» з використанням проточної комірки. В якості комірки використовували трубу прямокутного перерізу, утворену паралельними скляними пластинами, яку заповнювали цілісною кров'ю піддослідного і термостатували при температурі 37 °С. Уздовж комірки з контрольованою швидкістю через щілинний отвір продували озоно-киснева суміш. Концентрацію озону вимірювали за допомогою проточного фотометричного аналізатора. ***Результати:*** На основі порівняльного аналізу методик озонотерапії розроблено новий метод екстракорпорального озонування й оксигенування великих об'ємів крові. Дослідження кінетики хімічної реакції взаємодії цільної крові з озоно-кисневої сумішшю дозволило побудувати математичну модель, що описує процес гетерофазної реакції взаємодії озон-кров в роторно-плівковому контакторі. З урахуванням розробленої моделі побудовано установку для екстракорпоральної обробки озоном великих об'ємів крові. Отримані експериментальні результати показали хорошу кореляцію з теоретичною моделлю, що підтверджує можливість практичного застосування запропонованого методу.
Ключові слова: озоно-киснева суміш, аутогемоозонотерапія, екстракорпоральна обробка крові, роторно-плівковий контактор.

T.A. Glukhenkaya, V.V. Egorov, N.O. Kanischeva, E.I. Nazarov, A.V. Kipenskiy. **The substantiation of the parameters of the rotary-film contactor for extracorporeal processing of large volumes of blood using ozone.** Development and improvement of methods of ozone therapy is closely related to the optimization of the technical tools providing solutions to a variety of clinical applications. ***Aim:*** The aim of the research is to develop a new method of extracorporeal ozonation and oxygenation of large volumes of blood, as well as the development of a new type of "ozone – blood" contactor. ***Materials and Methods:*** The kinetics of the interaction of ozone with whole blood was studied by the "stopped flow" method using a continuous-flow cell. The cell was a rectangular tube formed by parallel glass plates. The cell was located strictly horizontally, filled with the whole blood of the volunteer and thermostated at 37 °C. Ozone-oxygen mixture was blown through the slotted hole along the cell at a controlled velocity. The concentration of ozone was measured with a flow-through photometric analyzer. ***Results:*** A comparative analysis of ozone therapy techniques has allowed to develop a new method of extracorporeal ozonation and oxygenation of large volumes of blood. The study of the chemical reaction kinetics of whole blood interaction with the ozone-oxygen mixture made it possible to construct a mathematical model describing the process of the heterophase reaction of ozone-blood interaction in a rotor-film contactor. An experimental copy of the plant for extracorporeal treatment of large volumes of blood with ozone was developed based on the model. The experimental results obtained on the developed hardware-software system showed good correspondence with the theoretical model, thereby confirming the possibility of practical application of the proposed method.
Keywords: ozone-oxygen mixture, auto-haemo-ozone therapy, extracorporeal blood processing, rotary-film contactor.

Introduction. Ozone therapy is a modern non-medicamentous way of treating a wide range of diseases [1]. Extracorporeal treatment of the blood with ozone (auto-haemo-ozone therapy (AHOT)) is

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one of the most common methods of ozone therapy [2...3]. However, the generally accepted methods of AHOT allow the treatment of no more than 200 ml of blood in one procedure. For the treatment of a number of diseases, viral, for example, it is necessary to perform the treatment of the entire volume of circulating blood (VCB) [4…6]. The work of Italian scientists shows the advantage of the procedure of extracorporeal ozonation and large-volume oxygenation (EOOB) in front of AHOT in the treatment of peripheral arterial diseases and in the rehabilitation of stroke patients, as well as in the treatment of patients suffering from heart attacks [7].

For the first time, the EOOB procedure for large volumes of blood was used in cardiosurgical practice in 1992 by S.P. Peretyagin using the apparatus of artificial circulation [8]. Such a procedure generally consists of the following steps: the assembly of a perfusion scheme, including lines of blood sampling-return, venous catheters, perfusion pump, oxygenator, ozonator, oxygen source; filling perfusion lines with a solution with an anticoagulant; release of the EOOB procedure (ozonation of the patient's blood in the oxygenator, the performance of the procedure is evaluated by the perfusion pump readings, the total dose of ozone is determined by the volume of perfusate and the ozone concentration supplied to the oxygenator); completion of the EOOB procedure.

At present, there are three main methods that allow the EOOB procedure to be carried out [2, 7, 9]. Analyzing these methods, the following shortcomings can be noted:

– a complexity of preparing the procedure for medical personnel at the stage of preparation of the perfusion system (all surfaces having contact with blood were covered with antifoam to ensure defoaming), a high probability of injuring formed blood cells during ozonation-oxygenation by bubbling [2];

– a treatment of the blood with ozone is accompanied by the loss of part of the blood plasma (plasmapheresis), the treatment of blood with ozone is carried out in membrane filters made from non-ozone-resistant materials [7];

– a high cost (> 700 euros) of a gas-blood polypropylene contactor [10].

The development of a heterophasic gas-blood contactor is required for the technical implementation of extracorporeal treatment of large volumes of blood with ozone. Existing ozone-blood contactors, as defined above, have a number of disadvantages. One of the possible variants of a gas-liquid contactor is a rotating glass container connected to the supply and selection lines of blood and ozone-oxygen mixture (OOM). Such design of the contactor preserves the advantages of the first EOOB technique (low cost of the procedure) and eliminates its shortcomings (blood foaming is excluded, so no additional non-contact resistant coatings of the contactor are required).

The aim of this research is to develop a new method of extracorporeal ozonation and oxygenation of large volumes of blood, as well as the development of a new type of "ozone – blood" contactor.

To achieve this goal it is necessary to solve the following tasks:

– to develop a mathematical model describing the process of heterophase reaction of ozone interaction with blood components;

– to create a hardware and software system that provides the correct extracorporeal procedures for processing of large volumes of blood.

Materials and Methods. The kinetics of the interaction of ozone with whole blood was studied by the "stopped flow" method using a continuous-flow cell [11] (Fig. 1). A cell is a tube of rectangular section with sides $b = 20$ mm, $h = 10$ mm, formed by parallel glass plates. The length of the cell was 200 mm. The cell was located strictly horizontally, filled with the whole blood of the volunteer and thermostated at 37 °C. Height of the blood layer $h_1 = 7$ mm. Thus, at an air gap height $\Delta h = h - h_1 = 3$ mm the area of the flowing part of the cell will be $S_{FA} = 60$ mm^2.

OOM was blown along the cell in the direction of the x axis at a controlled velocity v_x through the slot hole (not shown in the figure). The measurement of the ozone concentration profile in the OOM stream was carried out through the holes in the upper plate of the cell. To measure at a given time, only one hole was used. The others were blocked by traffic jams. Ozone concentration was measured using a flowing photometric DFG analyzer (measurement range 0.1...100 mg/l, relative error

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of measurement is no more than 5%, production of SPE "Econika"). To measure the ozone concentration, no more than 5% of the gas flow in the cuvette was directed to the analyzer.

Results. The possibility of creating a contactor based on the reaction of ozone interaction with the renewed surface of a blood film on the inner surface of a rotating glass tube was preliminarily tested. For this purpose, a continuous-flow cell simulating the process of the heterophase reaction "ozone – easily oxidized blood components" was used. The cell is used in the "stopped flow" mode, which makes it possible to calculate such important characteristics as the order and the reaction rate constant.

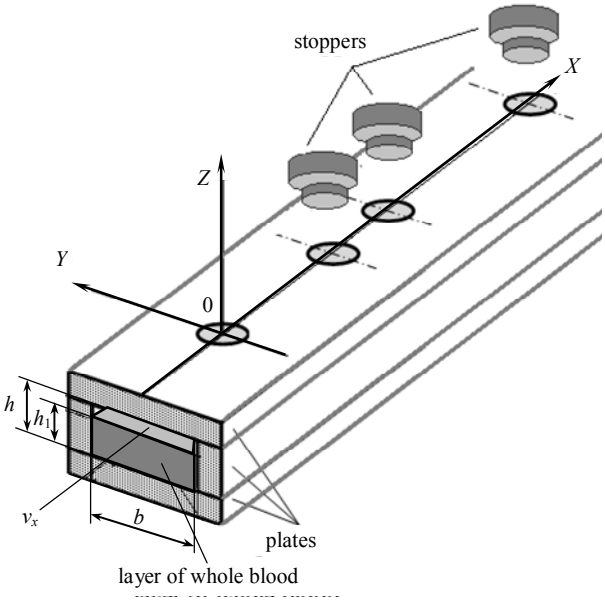

Fig. 1. The scheme of continuous-flow cell for studying the kinetics of ozone absorption by blood

The OOM feed rate into the cell was 40 ml/min and was chosen to provide a significant absorption of ozone by the surface layer of blood along the cell length. Knowing the flow rate of the OOM, the section of the channel in which the OOM moves, and the ozone concentration profile along the channel, it is possible to construct a time dependence of the ozone absorption by the surface layer of blood. Fig. 2 shows a plot of the change of ozone concentration in the OOM portion taken in each of the four cell openings. In this case, the point of intersection of the plot with the ordinate axis corresponds to the value of the ozone concentration in the OOM at the level of the first hole. As can be seen from the plot, ozone is effectively absorbed by the blood film, which creates fundamental prerequisites for the use of an updated blood film, which occurs when the glass tube rotates as a working medium of a heterophasic ozone-blood contactor.

The curve of the dynamics of the concentration change is rectified in semilogarithmic coordinates (Fig. 2, *b*), i.e. the reaction chemistry is described by the first order kinetics equation

$$C\ (t) = C_0 \cdot \exp(-kt)\,, \tag{1}$$

where $C(t)$ – ozone concentration at time point t;

C_0 – maximum ozone concentration;

k – constant of reaction rate, calculated from the experimental data (Fig. 2), $k = 0.63 \pm 0.04\ s^{-1}$.

Thus, the halftime drop in the ozone concentration according to (1) is equal to 1.07 ± 0.05 s.

As indicated above, the projected gas-liquid contactor is a rotating glass tube. Refining the geometric parameters of the contactor requires knowledge of how the ozone concentration is distributed along the axis of rotation.

Let us consider the transfer of particles in a tube of an arbitrary transverse profile with area S (Fig. 3).

Let I_1 – number of particles arriving per unit time in some small volume of the tube ΔV, i.e. $\Delta V = S \times \Delta x$; I_2 – number of particles leaving this volume; I_n – number of particles absorbed by the blood washing the walls of the tube.

Then the equation of continuity of the spatial variation of the ozone flow particles and the rate of density variation with time takes the form:

$$I_1 = I_2 + I_n, \tag{2}$$

where, taking into account the assumption of uniformity in the distribution of ozone concentration along the tube cross-section with area S, $I_1 = j_1 \times S$ and $I_2 = j_2 \times S$;

j_1 and j_2 – the density of the flows of particles entering and leaving a small volume of the tube for a unit of time ΔV, respectively.

Let us write down the expression for the number of ozone molecules absorbed by the blood washing the walls of the tube:

$$I_n = \int j_n dS_n = \Delta x \oint_p j_n dl, \tag{3}$$

where j_n – flow density of particles absorbed by blood;
p – length of tube cross-section.

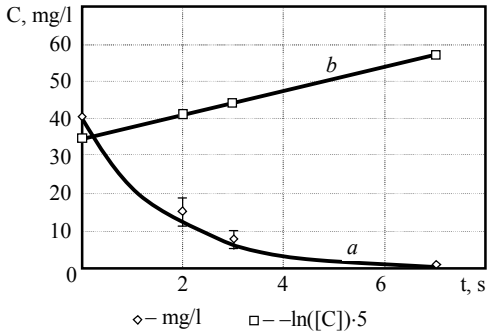

Fig. 2. The plot of ozone concentration change in the OOM portion: a – ozone concentration profile in the channel of the measuring cell, b – profile of the logarithm of the ozone concentration in the channel of the cell

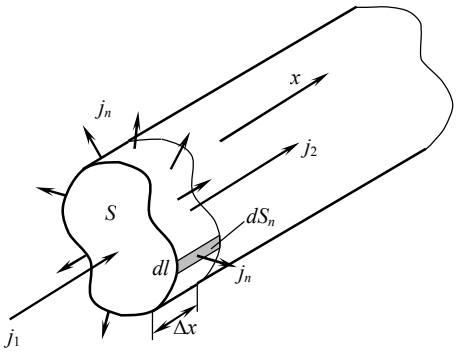

Fig. 3. The one-dimensional transport model

The flow density of the absorbed particles is proportional to the averaged particle concentration:

$$j_n = v_n c, \tag{4}$$

where v_n – the constant of the system whose physical meaning is the average velocity with which the particles move toward the absorbing surface.

Then the continuity equation (2) takes the following form [12]:

$$j_1 S = j_2 S + \Delta x \oint_p j_n dl,$$

whence it follows that

$$\frac{\Delta j}{\Delta x} + \frac{c}{S} \oint_p v_n dl = 0, \tag{5}$$

where $\Delta j = j_1 - j_2$.

After the transition (in Eq. 5) to the limit with $\Delta x \to 0$ we obtain the equation (2) in the form of a one-dimensional continuity equation:

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$$\frac{\Delta j_x}{\Delta x} + \frac{c}{S}\oint_p v_n dl = 0,$$

or

$$\frac{\Delta j_x}{\Delta x} + \frac{c}{\tau} = 0, \tag{6}$$

where $\tau = \left(\frac{1}{S}\oint_p v_n dl\right)^{-1}$ – lifetime of the particles (the average time from the moment of contact of ozone molecules in the tube to its absorption by the blood).

To write the problem of the distribution of the particle concentration in the final form, it remains to express the flow density j_x through the concentration of particles c. In the general case, accounting of the diffusion and drift of particles allows us to write expression

$$j_x = -D\frac{dc}{dx} + v_x c, \tag{7}$$

where D – particle diffusion coefficient;

v_x – particle flow velocity.

Then, when the formula (7) is substituted into expression (6), we obtain:

$$-D\frac{d^2c}{dx^2} + v_x\frac{dc}{dx} + \frac{c}{\tau} = 0$$

or

$$L^2\frac{d^2c}{dx^2} - 2\eta L\frac{dc}{dx} - c = 0, \tag{8}$$

where $L = \sqrt{D\tau}$ – average distance traveled by the particle during diffusion over the lifetime;

$\eta = \frac{v_x}{2}\sqrt{\frac{\tau}{D}}$ – coefficient characterizing the ratio of the particle flow velocity to particle diffusion.

The general solution of equation (8) is as follows:

$$c(x) = \exp\left(\frac{\eta x}{L}\right)\left(A\exp\left(-\frac{x\sqrt{\eta^2+1}}{L}\right) + B\exp\left(\frac{x\sqrt{\eta^2+1}}{L}\right)\right), \tag{9}$$

where A, B – constant of integration.

In the case of an infinitely extended configuration of the adopted model, we set $B = 0$, so

$$c(x) = c_0\exp\left(\frac{\eta x}{L}\right)\exp\left(-\frac{x\sqrt{\eta^2+1}}{L}\right) = c_0\exp\left(\frac{\eta-\sqrt{\eta^2+1}}{L}\right), \tag{10}$$

where $c_0 = c(0)$ – particles concentration at the initial time.

It is obvious that for practical use of the obtained results it is necessary to determine the value of the lifetime τ of particles. This, in turn, requires the definition of a parameter v_n – velocity with which the particles move to the absorbing surface, in our case, to the surface layer of blood.

A theoretical determination of the velocity v_n would require the solution of the continuity equation, taking into account the diffusion transport of particles, the transport of particles by the flow, and

the number of particles absorbed in the blood volume. Therefore, for practical purposes, we use the results of measurements in experiments with a continuous-flow cell (Fig. 1). As shown previously, knowing the flow velocity of OOM, the diffusion coefficient of ozone, the distance between the holes and the values of ozone concentration, it is possible to calculate the value of the velocity v_n based on equation (10).

In the very equation (10), the required quantity enters in a rather complicated manner, which makes it difficult to determine it. However, by entering new variables

$$\alpha = \frac{\eta}{L} = \frac{1}{2} v_x \frac{1}{\sqrt{D\tau}} \sqrt{\frac{\tau}{D}} = \frac{v_x}{2D} \tag{11}$$

and

$$\beta = \frac{1}{(\alpha L)^2} = \frac{4D}{v_x^2 \tau}, \tag{12}$$

we obtain:

$$c(x) = c_0 \exp(\alpha x(1 - \sqrt{1+\beta})), \tag{13}$$

where only one value β depends on velocity v_n (through the particle lifetime parameter τ). It follows

$$\beta = \left(1 + \frac{1}{\alpha x} \ln \frac{c_0}{c(x)}\right)^2 - 1, \tag{14}$$

that allows to determine the lifetime of the particles τ, and then – the desired value of the velocity v_n.

As already noted, in the experiment with a continuous-flow cell (see Fig. 1) at an OOM flow of 40 ml/min or $Q_{x0} = 0.67$ cm^3/s the half-time of ozone concentration fall is $t_2 = 1.07$ s. Since the absorption of ozone in the cell occurs only on a part of the surface with the length b, we have:

$$\oint_p v_n dl = \int_{-b/2}^{b/2} v_n dx = v_n b.$$

Then, taking the value of the diffusion coefficient to be $D = 0.204$ cm^2/s, with the cross-sectional area of the channel $S_0 = b\Delta h = 0.6$ cm^2 we obtain the OOM flow velocity $v_{x0} = Q_{x0}/S_0 = 1.11$ cm/s, the distance of half concentration fall of ozone $d_2 = v_{x0} t_2 = 1.19$ cm. Other parameters on the basis of formulas (11), (12) and (6) will take the following values: $\alpha = 2.72$ cm^{-1}, $\beta = 0.47$, $\tau_0 = 1.39$ s.

The velocity with which the particles move toward the absorbing surface can be calculated in turn by the formula:

$$v_n = \frac{S_0}{b\tau_0} = \frac{\Delta h}{\tau_0} = 0.22 \text{ cm/s}.$$

To create a rotary-film ozone-blood contactor, let us consider the use of an industrial-produced glass bottle for filling a physiological solution with a capacity of 500 ml, an inner diameter of 6 cm and a height between the bottom and the beginning of a constriction of 14 cm.

Let calculate the OOM flow rate, at which the ratio of the ozone concentration at the inlet and outlet of the rotating bottle is 0.01.

Having assumed a tube radius of 3 cm, a tube length of 14 cm, and an ozone concentration of 100 mg/l, the required OOM Q flow rate was determined, which was 10.43 cm^3/s, or 625 ml/min.

According to the developed theoretical model, the use of a rotating standard glass bottle equipped with a blood supply and bleeding system, as well as an OOM supply, allows the design of an efficient ozone-blood rotary-film contactor. A distinctive feature of the proposed method is the continuous pumping of blood from one section of the patient's circulatory system to another, while simultaneously treating the blood with ozone in a rotating glass rotor-film contactor (RFC).

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The essence of the new method is illustrated in Fig. 4, which shows the executive mechanisms of the hardware and software system BOZON-EOOK: RFC 1 with electric drive 2 for rotating the working volume, two peristaltic pumps 3 and 4, the OOM ozonizer 5 and the built-in source of medical oxygen 6 [13]. All RFC parts are made of ozone-resistant materials – glass and polypropylene. The developed design of the RFS allows to regulate the interaction rate of the blood surface and OOM in the range from 0.2 to 2 m^2/min due to a change in the rotational frequency of the working container. Connection of the patient's blood system to the "BOZON-EOOB" complex is carried out with the help of a special set of sterile trunks: blood sampling – 7 and blood return – 8. The blood return tube 8 includes a special buffer bypass with a filter 9. During the procedure of the highway 7, 8 and RFCs are in thermostat 10 at a stable temperature. The line 11 serves to feed the OOM from the OOM 5 ozonizer to the RFC.

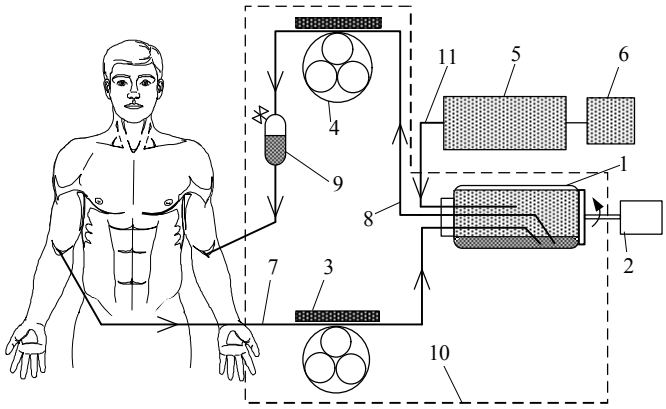

Fig. 4. Scheme of the software and hardware system "BOZON-EOOK"

The hardware-software system "BOZON-EOOK" allows:

– regulate the concentration of ozone in the OOM in the range of 0.1 to 0.5 mg/l;

– to regulate the flowrate of OOM in the range from 0.2 to 0.3 l/min;

– to regulate the rotational speed of the RFC working volume in the range from 35 to 45 rpm;

– regulate the volumetric rate of blood sampling and return in the range from 25 to 45 ml/min using two independently regulated peristaltic pumps;

– to monitor the amount of blood processed;

– to monitor the presence of blood in the sampling and return lines;

– to thermostate the blood in the contactor and supply lines at the level of 37.5 °C with a deviation of not more than ± 0.5 °C.

In preliminary experiments it was shown that the rotation of the contactor with a frequency exceeding 100 rpm leads in some cases to blood coagulation in places of contact of moving blood and the blood sampling tube in the contactor. In connection with this, the rotational speed of the contactor volume was chosen to be a half smaller. A simple calculation shows that the area of the renewed blood surface at such a rotational speed in a container of specified sizes exceeds 1 m^2/min, which is comparable with the area of standard hemodialysis filters. The installation was tested in the following order:

1. The rotor-film contactor was filled with 200 ml of heparinized normal saline (1000 units of heparin) through the "arterial" line of the standard system for hemodialysis;

2. The drive of rotation of the rotor-film contactor was turned on at a rotational speed of 60 rpm and heparinization of the glass surface of the contactor capacitor was carried out. After heparinization, 150 ml of the solution from the bottle was pumped out by the second peristaltic pump through the "venous" part of the main line. The remainder of the heparinized normal saline in the contactor vessel was designed to prevent blood coagulation;

3. The venipuncture of a cubital vein of a volunteer was performed by an intravenous catheter connected to the "arterial" main line of the system. The first peristaltic pump was switched on, and the contactor was filled with blood with a volume of 200 ml; the catheter was detached from the circulatory system and the rest of the blood from the main was pumped into the bottle;

4. With continued rotation of the contactor, the OOM contactor was purged with an ozone concentration of 1 mg/l and a flow rate of 100, 200, 300, 400, 500, 600, 700, 800 and 900 ml/min.

It has been established that ozone "slip" at the bottle outlet at 1% of the initial concentration is observed at a flow of 500 ml / min and above. Thus, the experimental results show good agreement with the theoretical model.

Conclusions. In this paper, as a result of theoretical analysis and practical experiments, a new EOOB method was developed and the possibilities of implementing extracorporeal treatment of large volumes of blood using a new type of ozone-blood contactor were explored. A mathematical model of the heterophase ozone-blood reaction in a rotor-film contactor is developed. A prototype of the installation for extracorporeal treatment of large volumes of blood with ozone was developed based on the model.

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