Modern Treatment of Inflammatory Pulmonary Pathology: Theoretical Justification and Implementation of the Extracorporeal Blood Hyperthermia Apparatus into Medical Practice

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Abstract. For the first time in Ukraine, our team successfully applied extracorporeal blood hyperthermia (EBH) within a closed-loop circuit to manage inflammatory conditions of the lungs and pleura. Controlled warming of autologous blood to 38°C and its subsequent reinfusion produced rapid, clinically significant reductions in exudative pleurisy, pleural empyema, and paracancerous inflammatory lesions. Earlier, EBH had been incorporated into U.S. military field protocols between 2003 and 2007, and it is now formally included in therapeutic guidelines across the United States, Canada, New Zealand, multiple European nations, and several African healthcare systems. Our findings corroborate international data showing that mild systemic hyperthermia enhances phagocytic activity, improves microcirculation within the pleural cavity, and accelerates resorption of inflammatory exudate while maintaining a favorable safety profile. No severe adverse events or hemodynamic instabilities were observed during or after the procedures in our cohort. Beyond its direct anti-inflammatory impact, EBH may potentiate antibiotic penetration into pleural tissues, offering a valuable adjunct in the era of rising antimicrobial resistance. Future multicenter trials with larger patient populations and comparative cost-effectiveness analyses are warranted to refine treatment parameters and confirm long-term benefits of this promising modality.

Keywords: inflammatory pulmonary pathology, treatment, extracorporeal blood hyperthermia.

Introduction. The history of human development shows that hyperthermia methods have long been used to treat inflammatory processes in patients [1-3]:

- ✓ Parmenides in the 6th century BC said: "Give me the power to cause fever – and I will cure all diseases";
- ✓ Hippocrates, in turn, used hyperthermia to treat malignant neoplasms in the lungs [1];
- ✓ in ancient Egypt [2] and India [3], hyperthermia was used as a method of treatment.

From ancient history, for colds, fever, flu, it is known about the use of hot drinks (milk, tea, raspberries, blueberries, mint, lemon balm), warming the feet in hot water with mustard, various thermal procedures (steam baths, saunas, hot potato wraps of the chest to warm the lungs), local application (chest, back) of various hyperthermic agents (mustard pastes, thermal applicators). It is important to note that fever is so closely related to the inflammatory reaction that heat is one of the 4 cardinal signs of inflammation, along with pain, redness and swelling, as described by Celsus around 30 BC [4]. As Evans S.S., Repasky E.A., Fisher D.T. note:

- induction of fever in endothermic (warm-blooded) animals occurs at a high metabolic cost, so that an increase in body temperature by +10°C requires an increase in metabolic rate by 10-12.5%;
- it has been established that an increase in body temperature by +10–+4°C, which occurs during fever, is associated with improved survival and recovery from many infectious diseases;
- uncontrolled use of antipyretic drugs to reduce fever correlates with an increase in mortality among patients infected with the influenza virus (by +5%) and negatively affects the results of treatment of patients in the intensive care unit (intensive care unit);

- preclinical studies in rabbits infected with rinderpest virus also found increased mortality when fever was suppressed with the antipyretic drug acetylsalicylic acid (70% of animals treated with acetylsalicylic acid died of infection compared with only 16% of animals with normal fever);
- fever is not useful in cases of extreme inflammation, where a decrease rather than an increase in body temperature has evolved as a protective mechanism;
- the difficulty in determining the exact meaning of fever in endothermic animals is that antipyretics used to suppress fever target several aspects of the inflammatory response in addition to temperature regulation;
- thermal regulation of heat shock proteins (HSPs) and induction of fever occur during infection of the patient's brain (Fig. 1) [4].

Heat shock proteins are cytoprotective proteins that are constitutively expressed and rapidly induced under conditions of proteotoxic stress, such as heat, hypoxia, oxidative stress, exposure to toxins, nutrient deprivation, and infection.

Although heat shock proteins were originally discovered in the context of heat shock (42.0-45.0°C), they are also induced by febrile temperatures in mammalian cells (38.0-41.0°C).

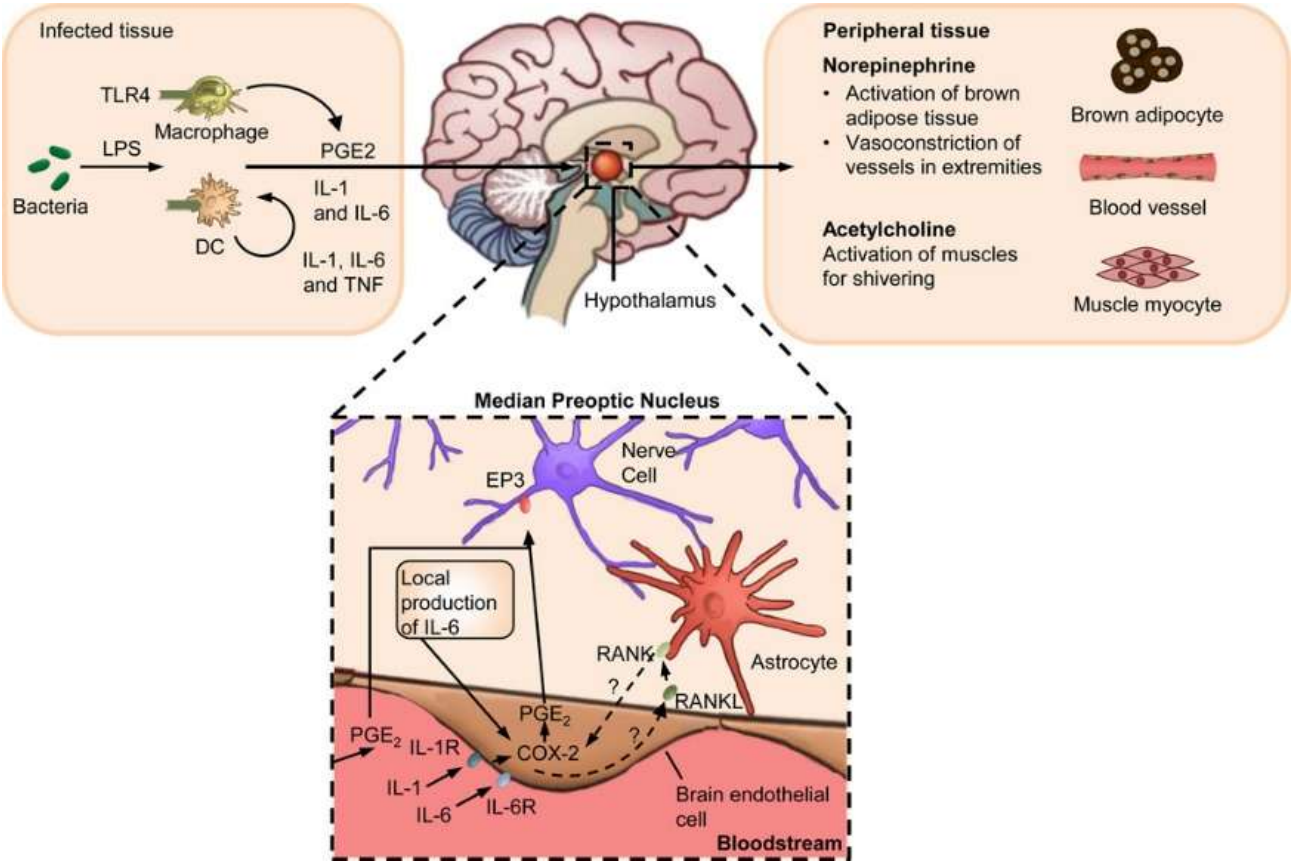

Fig. 1. Thermal regulation of heat shock proteins and induction of fever during brain infection [4].

On the background of covid, post-covid, long-covid, comorbid disorders in accordance with ICD-11 [5-9], citizens are faced with road traffic accidents, domestic injuries, injuries at work, during the elimination of the consequences of natural disasters, in conditions of combat operations in hospitals [10-33], with the use of artificial intelligence [34], innovative medical technologies of quantum medicine [35, 36]. This is confirmed by clinical experience gained because of participation in combat operations in Afghanistan and Iraq, when US military doctors switched attention to the benefits and risks of using warmed fresh whole blood to treat life-threatening injuries in wounded soldiers [37, 38].

As noted by Deb P.K., Odetallah H.M.A., Al-Jaidi B., Habash R.W., Bansal R., Krewski D., Alhafid H.T., hyperthermia, thermotherapy is a new therapeutic technique that includes several

methods superficial, whole-body hyperthermia, intracavitary, deep and partial body hyperthermia [39, 40]:

- is considered one of the promising options not only for the treatment of cancer, but also for the treatment of arthritis, wounds, and pain of various genesis;
- is based on heating target cells or tissues to a temperature sufficient for their destruction, without affecting neighboring normal cells.

The purpose of the study was to introduce modern, high-quality, and safe treatment of inflammatory pulmonary pathology by developing and implementing into medical practice an apparatus for extracorporeal blood hyperthermia under a closed circuit. At the same time, a whole complex of positive effects is launched, namely:

- which develop during hyperthermia of the patient's body and there are no negative effects and complications that are recorded when the entire human body is overheated;
- extracorporeal blood hyperthermia is provided according to clearly defined temperature parameters;
- the device allows for a continuous, controlled, high-quality and safe cycle of extracorporeal blood hyperthermia.

Materials and methods.

92 patients participated in the studies, of whom:

- 14 patients with paracancerous inflammatory changes in the lungs, who received extracorporeal blood hyperthermia in complex treatment;
- 24 patients with pleural empyema, who received extracorporeal blood hyperthermia in complex treatment;
- 54 patients with exudative pleurisy, who received extracorporeal blood hyperthermia in complex treatment.

During the study, the following methods were used [41, 42]:

- X-ray examination methods;
- for the diagnosis of exudative pleurisy, pleural punctures, thoracoscopic and videothoracoscopic examination methods were performed;
- ultrasound diagnostics for exudative pleurisy;
- ultrasound diagnostics for limited exudative pleurisy, as well as for the diagnosis of the presence of a small amount of exudate in the pleural cavity.

The method of extracorporeal blood hyperthermia, i.e., when heated, the following reaction occurs in blood macrophages, namely:

- interleukin-1 is released, which is one of the active pro-inflammatory cytokines (Fig. 2) [43];
- induces the synthesis of interleukin-3, interleukin-4, interleukin-5, interleukin-6, interleukin-8, gamma interferon, as well as the expression of receptors for interleukin-2;
- causes chemotaxis of macrophages and neutrophils, promotes their migration through the endothelium of blood vessels to the focus of inflammation;
- activates the synthesis of cytokines, prostaglandins, collagen and fibronectin, acute phase proteins (C-reactive protein, etc.) in inflammation;
- is a factor in the activation, growth, and maturation of T- and B-lymphocytes, NK-cells, fibroblasts, endothelial cells (Fig. 3) [44];
- interferon is released upon heating, which contributes (Fig. 4) [45]:
- increased secretion of antibodies by B-lymphocytes;
- stimulation of hematopoiesis, which exhibits radioprotective properties;
- antitumor activity in some forms of cancer;
- stimulation of the synthesis of hormones of the hypothalamus, pituitary gland, thymus.

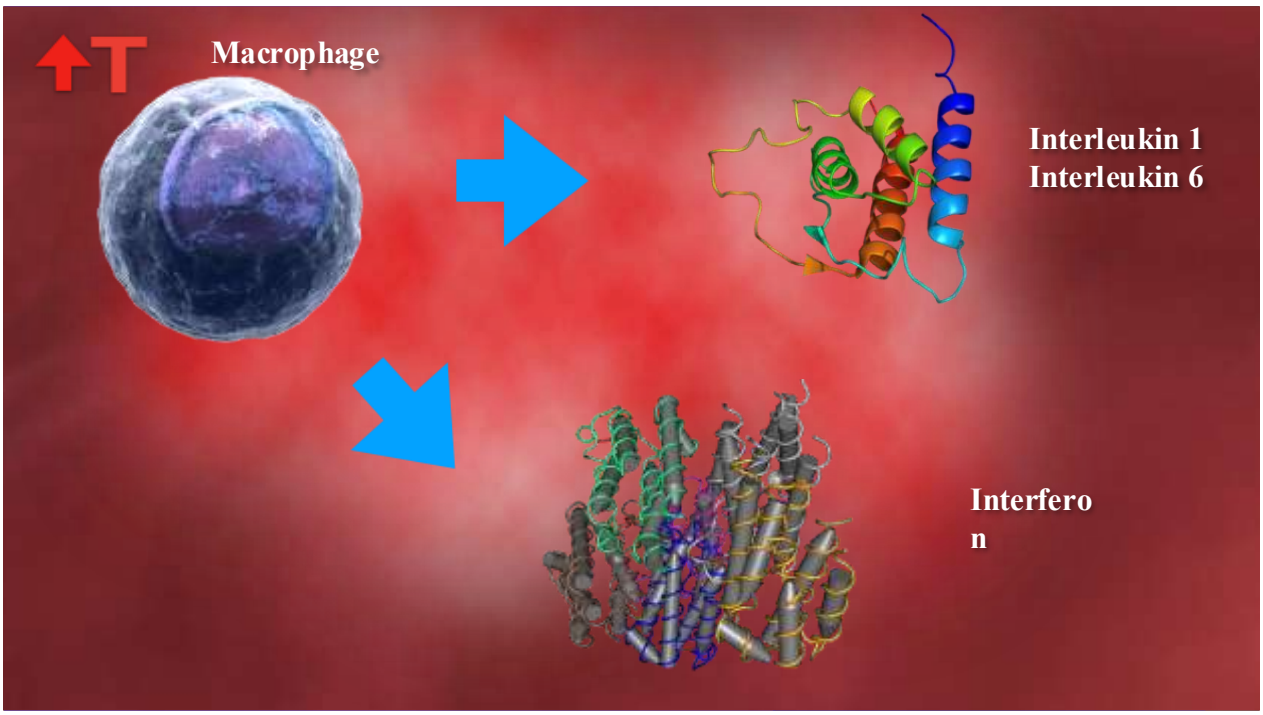

Fig. 2. Release of interleukin-1, interleukin-6, and gamma-interferon by macrophages upon heating [43].

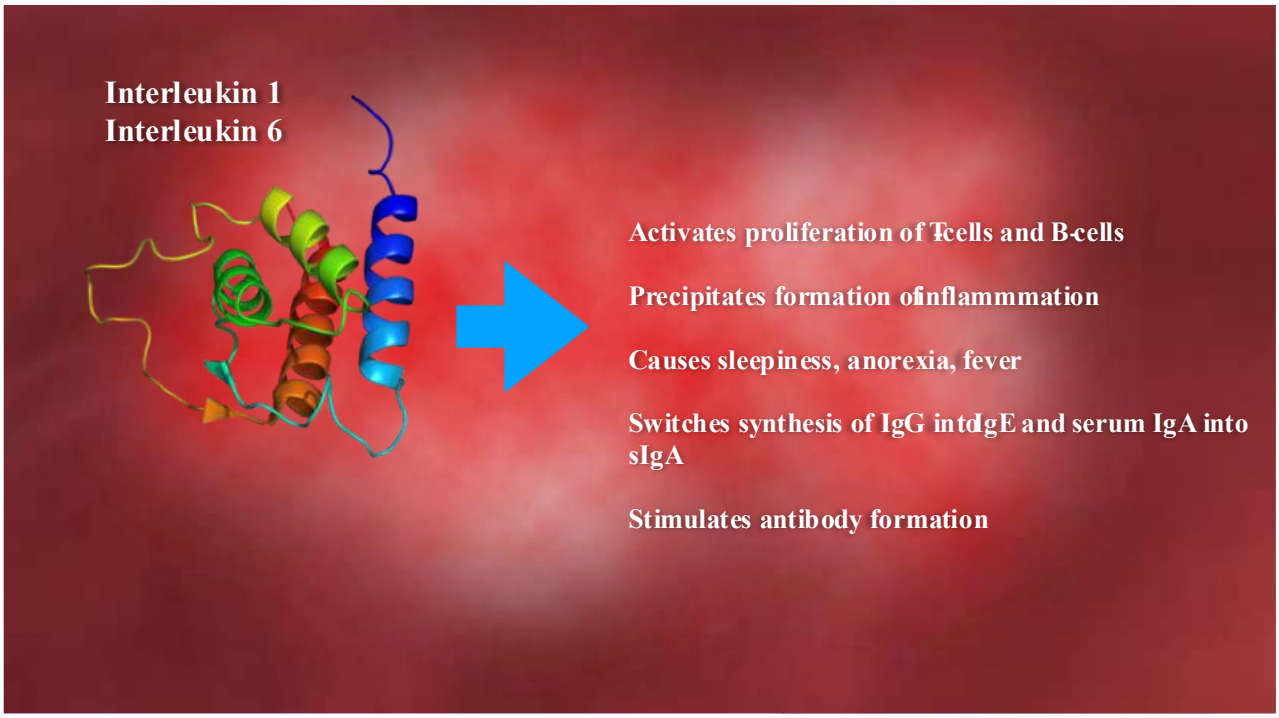

Fig. 3. Factors of activation, growth, and maturation of T- and B-lymphocytes, NK-cells, fibroblasts, endothelial cells [44].

Interferon, which is released during heating:

- increases the secretion of antibodies by B-lymphocytes,
- stimulates hematopoiesis, exhibits radioprotective properties,
- has antitumor activity in some forms of cancer,
- stimulates the synthesis of hormones of the hypothalamus, pituitary gland, thymus (Fig. 4) [45].

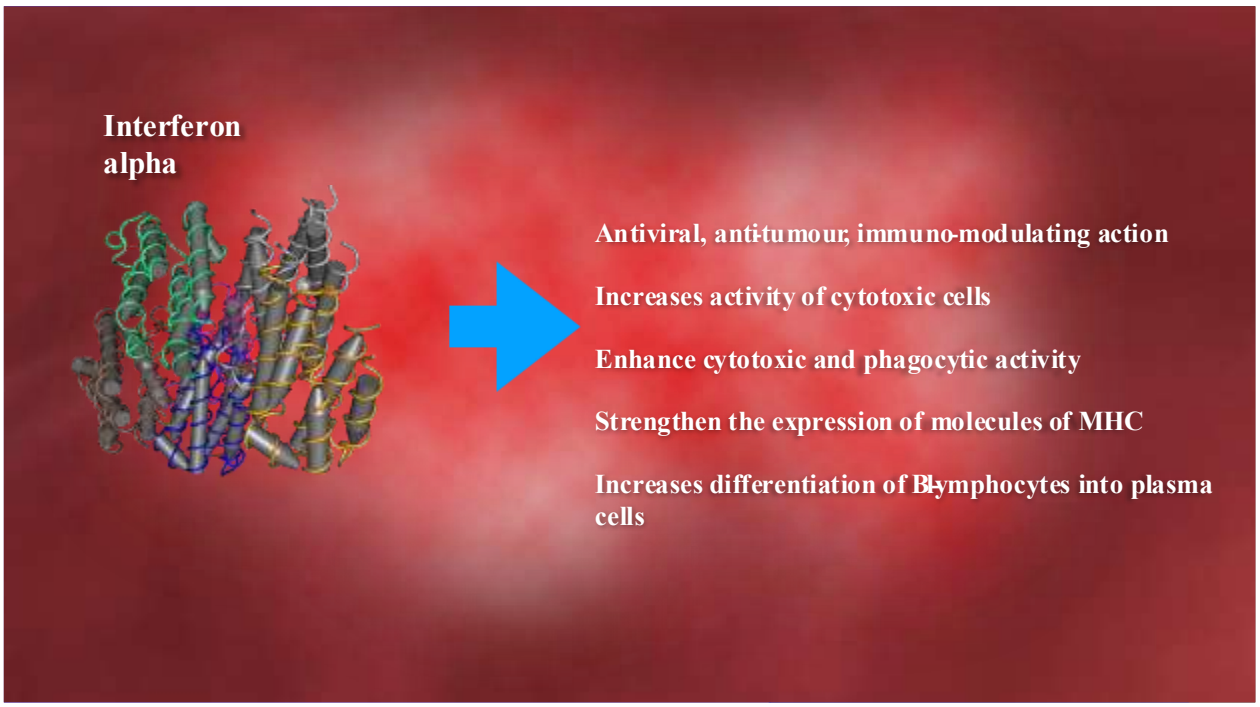

Fig. 4. The action of interferon, which is released upon heating [45].

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Results and discussion. Working in healthcare institutions (Lviv), we drew attention to the experience of substantiating the official use of blood heating using an apparatus for extracorporeal blood hyperthermia. The apparatus was manufactured by the Biofizprilad plant (Lviv). It was introduced into industrial production and medical practice for heating blood during plasmapheresis.

The current experience described in the publications of Leon L.P., Helwig B.G., Markota A., Kalamar Ž., Fluher J., Pirkmajer S. was studied. It indicates the use of [46, 47]:

- hyperthermia, the degree of increase in body temperature itself can determine whether protective or harmful effects prevail. On the other hand, temperature-dependent activation of the immune system in fever and heat stroke can be fundamentally different;
- elevated body temperature of the patient in the context of fever, which apparently promotes various aspects of immune function, thereby enhancing its protective effect against infectious agents and contributing to the overcoming of infection;

- heat stroke, which demonstrates that the same or similar mechanisms, such as cytokine secretion, can become counterproductive and cause additional complications, thereby reducing the chances of survival.

However, current studies indicate that the effect of elevated temperature on antibiotic susceptibility during the treatment of SARS-CoV-2 in a wide range of patients has:

- ✓ the virulence of various rhinovirus isolates from a sick person is attenuated by increasing temperature, and the replication rate in the temperature range usually observed in the nasal cavity (33.0-35.0°C) is higher compared to body temperature (about 37.0°C) [48];
- ✓ temperature regime, which also affects the virulence of SARS-CoV-2, which attaches to respiratory cells with angiotensin-converting enzyme-2. This interaction is enhanced at a temperature of about 37.0°C and limited at a temperature of about 40.0°C (Fig. 5) [49, 50];
- ✓ similar, the virulence of influenza B virus, which is higher at a temperature of about 33.0°C compared to higher temperatures. The mechanism is the increased expression of viral hemagglutinin at 33.0°C, which promotes membrane fusion and infection (Fig. 5) [49, 50];
- ✓ consequences after infection, as evidenced by intracellular viral replication, which is also inhibited by higher temperatures due to a decrease in the messenger RNA process [51].

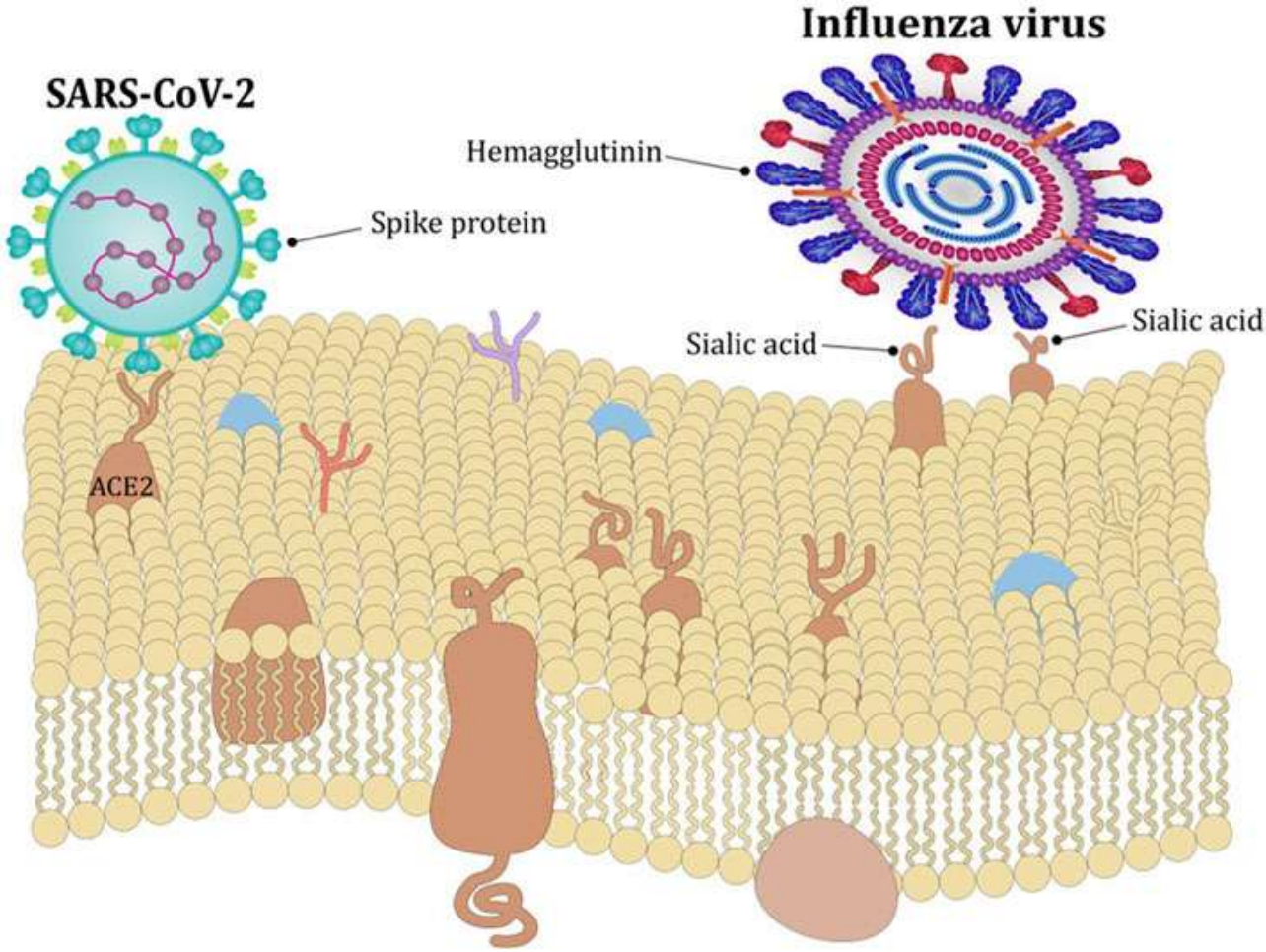

Fig. 5. Effect of temperature on the penetration of influenza virus, SARS-CoV-2 into the patient's body [49, 50].

In combat operations between March 2003 and July 2007, US medical personnel transfused more than 6000 units of warm, machine-warmed, fresh whole blood in Afghanistan and Iraq to military patients with life-threatening traumatic injuries and more than 6000 cases of bleeding. Preliminary results obtained in approximately 500 patients with massive transfusion indicate that [37, 52]:

- for military patients with life-threatening bleeding who require massive transfusion, if full component therapy is not available or does not adequately correct coagulopathy, the risk-benefit ratio of warm fresh whole blood transfusion favors its use;
- the amount of fresh warm whole blood transfused is independently associated with improved 48-hour and 30-day survival;
- the amount of stored red blood cells is independently associated with reduced 48-hour and 30-day survival in patients with traumatic injuries requiring massive transfusion;
- hyperthermia with warm fresh whole blood may be more effective than therapy with stored components, which includes stored red blood cells, in critically ill patients in the intensive care unit requiring massive transfusion.

In addition, according to the recommendations of the Tactical combat casualty care course [53], module-infusion therapy is used for hemorrhagic shock in tactical medical care on the battlefield. Apparatus hyperthermia of whole blood in massive hemotransfusions associated with hemorrhagic shock should be performed according to the following parameters: heating of blood to 38 degrees with a transfusion rate of up to 150 ml/min. The priority in transfusion is cold-stored whole blood of low titer O, and pre-tested fresh whole blood of low titer O. Whole blood is heated using an apparatus, the introduction of heated blood into the human body is intravenous. The temperature indicated is 38.0°C, to which whole blood should be heated before introduction into the human body.

Clinical indications for transfusion of heated blood at present are [53]:

- large volume of blood transfused rapidly (for example, >50 ml/kg/h in adults and >15 ml/kg/h in children).
- exchange transfusions in newborns.
- traumatic situations where general body warming measures are required.
- warming phase of cardiopulmonary bypass surgery.
- transfusions in patients with clinically significant cold-reactive antibodies (“cold agglutinins”), such as in symptomatic cold hemagglutinin disease.

The Association for the Advancement of Blood and Biotherapy protocol includes blood warming technologies, advantages of blood warming devices, indications, contraindications, warnings, and administrative aspects, and indications for blood warming [54]:

- exchange transfusion in newborns;
- therapeutic plasmapheresis or red cell replacement procedures;
- warming phase of cardiopulmonary bypass;
- potent, high-titer cold autoantibodies that are reactive at body temperature and can bind complement, causing hemolytic anemia;
- Raynaud’s phenomenon or other cold-induced vasoactive phenomena;
- infusion rates greater than 50 mL/min for 30 minutes or more (for adults) and greater than 15 mL/kg/h (for children);
- in the United States, collection, testing, preparation, storage, and transportation of blood and blood components must comply with FDA regulations and guidelines.

Devices that warm blood are required to have a heating range of 35.0°C to 41.0°C. This is what is meant by temperature. Guidelines for the use of blood warming devices [54]. Blood warming is a method included in several protocols and standards of care [54], Manitoba Transfusion Best Practice Resource Manual 2024, African Blood Transfusion Protocols.

During the research of the authors of the article, an apparatus for extracorporeal blood hyperthermia was used to heat blood [55]. It consists of a cylindrical heating device with spiral grooves, into which a polyvinyl chloride tube is inserted, in which the patient's blood flows, according to the following algorithm:

- in a closed circuit, the patient's blood from the cubital vein is supplied to the apparatus for extracorporeal blood hyperthermia from the lead line with a catheter, where it is heated to a set temperature of 38.0 -39.5°C;

- to prevent heat loss, the cylindrical heating device is covered with an external heat-resistant cylinder;
- after heating on the cylindrical heating device, the blood is supplied to another cubital vein of the patient through a lead line with a catheter;
- on the side surface of the cylindrical heating device there is a regulator for setting the set temperature and an electronic temperature indicator. The set temperature parameters can be adjusted within the range from 36.0°C to 41.0°C with a step of 0.1°C. for conducting non-primary extracorporeal hyperthermia of blood, a closed sterile cycle is used.

In this case, blood from the right cubital vein through a sterile closed system of polyvinyl chloride trunks is supplied to the apparatus for extracorporeal hyperthermia of blood by means of a pump. After that, blood through a closed system of trunks is supplied to the left cubital vein. To prevent blood clotting at the beginning of the sterile closed system, a heparin solution is constantly controlled at a dose of 50-75 units/min through a separate polyvinyl chloride tube from a dropper. The rate of blood sampling from the right cubital vein is regulated by means of a pump.

Blood sampling is carried out from one cubital vein of the patient through a system of trunks. Blood stabilizer and heparin are added through a separate system at a dose of 50-75 units/min. Next, the system with blood and heparin passes through a pump-rotor. The authors of the article used a pump-rotor. The blood supply rate is 15 ml per minute. Then, the blood line is fed to the extracorporeal blood hyperthermia apparatus. The required temperature of 38.0°C-39.0°C is set on the apparatus sensor. The blood line is spirally wound repeatedly on the cylindrical heating element of the apparatus for extracorporeal blood hyperthermia and is in the grooves of the cylindrical heating element. It is closed from above with an external plastic cylinder for thermal insulation. Then, the blood line is fed into the patient's second vein through a catheter. To prevent air bubbles from entering the distal part of the blood line, a conventional air filter from a drip intravenous system is placed in the middle of the line.

Thus, blood is drawn from one vein, the first is heated using an apparatus for extracorporeal blood hyperthermia, and extracorporeally heated blood is supplied to the second vein of the patient. All this occurs in a closed sterile circuit with a continuous cycle of operation.

The proposed model for extracorporeal blood hyperthermia is illustrated by the following diagram:

- 1st, cylindrical heating element with a heat exchanger and thermostat;
- 2nd, temperature regulator;
- 3rd, electronic temperature indicator on a cylindrical heating device, - an external plastic heat-resistant cylinder;
- 4th, blood system, spirally wound in the grooves of the heat exchanger;
- 5th, rotary pump;
- 6th, blood line from the patient's cubital vein;
- 7th, heparin solution line;
- 8th, heparin solution bottle;
- 9th, heated blood line;
- 10th, air filter from the drip system;
- 11th, inlet catheter, through which heated blood is introduced into the cubital vein;
- 12th, outlet catheter, through which blood is collected from the cubital vein;
- 13th, silicone insert in the pump system;
- 14th, external plastic heat-resistant cylinder.

The device for performing extracorporeal blood hyperthermia is used exclusively by trained medical personnel and functions according to the following algorithm - as follows, namely:

- ✓ patient is in a supine position on the operating table; the right and left arms are on flat armrests;
- ✓ before the procedure, for anticoagulant purposes, the patient is intravenously administered heparin at a dose of 200 units/kg;
- ✓ blood is taken from the patient from the cubital vein using the output catheter 12;

- ✓ in the immediate vicinity of the catheter 12 to the main line with the patient's blood, a heparin solution is supplied through the tee along the main line 7 at a dosage of 50-75 units/min from the vial 8;
- ✓ vial 8 is placed on a tripod in a higher position compared to the patient's body;
- ✓ main line 7 is a conventional intravenous dropper. Further, the main line 7 with the patient's heparinized blood passes through the pump-rotor 5;
- ✓ in this case, a silicone insert 13 is used for pumping blood in the main line system;
- ✓ further, the main line with the patient's blood 6 is fed to the heating cylindrical device with spiral grooves!
- ✓ the main line 6 with the patient's blood 4 is spirally wound in the grooves of the heat exchanger;
- ✓ the required temperature in the grooves of the cylindrical heating device is set using the temperature regulator 2 and is displayed on the electronic temperature indicator 3;
- ✓ for better heating of the blood in the grooves of the cylindrical heating element, to prevent heat loss, the cylindrical heating device 1 with the main line with the patient's blood 4, which is spirally wound in the grooves of the heat exchanger, is covered with an external plastic heat-resistant cylinder 14;
- ✓ subsequently, the heated blood flows in the main line 9, passes through the air filter 10;
- ✓ the air filter 10 is mounted on a tripod;
- ✓ subsequently, the main line 9 is connected to the input cubital catheter 11, through which the heated blood is supplied to the patient's left cubital vein;
- ✓ the procedure is carried out from 40 to 90 minutes;
- ✓ the temperature on the heating cylindrical device is set from 38°C to 39°C.

To diagnose exudative pleurisy, pleural punctures, thoracoscopic and videothoracoscopic research methods were performed [56-60].

At the same time, the authors of the article used [61] to control the quality and safety of the process:

- X-ray examination methods for this pathology;
- ultrasound diagnostics for exudative pleurisy;
- ultrasound diagnostics in limited exudative pleurisy, as well as for diagnosing the presence of a small amount of exudate in the pleural cavity (with ultrasound diagnostics, it is detected from 25 ml of liquid content).

In patients with pleural empyema, an apparatus for extracorporeal blood hyperthermia was used in the treatment. The diagnosis of this pathology is currently based on data from X-ray, ultrasound examination, pleural punctures, laboratory, and bacteriological studies. Treatment tactics have remained practically unchanged for many decades [62].

The use of new treatment methods is a promising and clinical direction. The authors of the article selected three main groups of patients (Fig. 6).

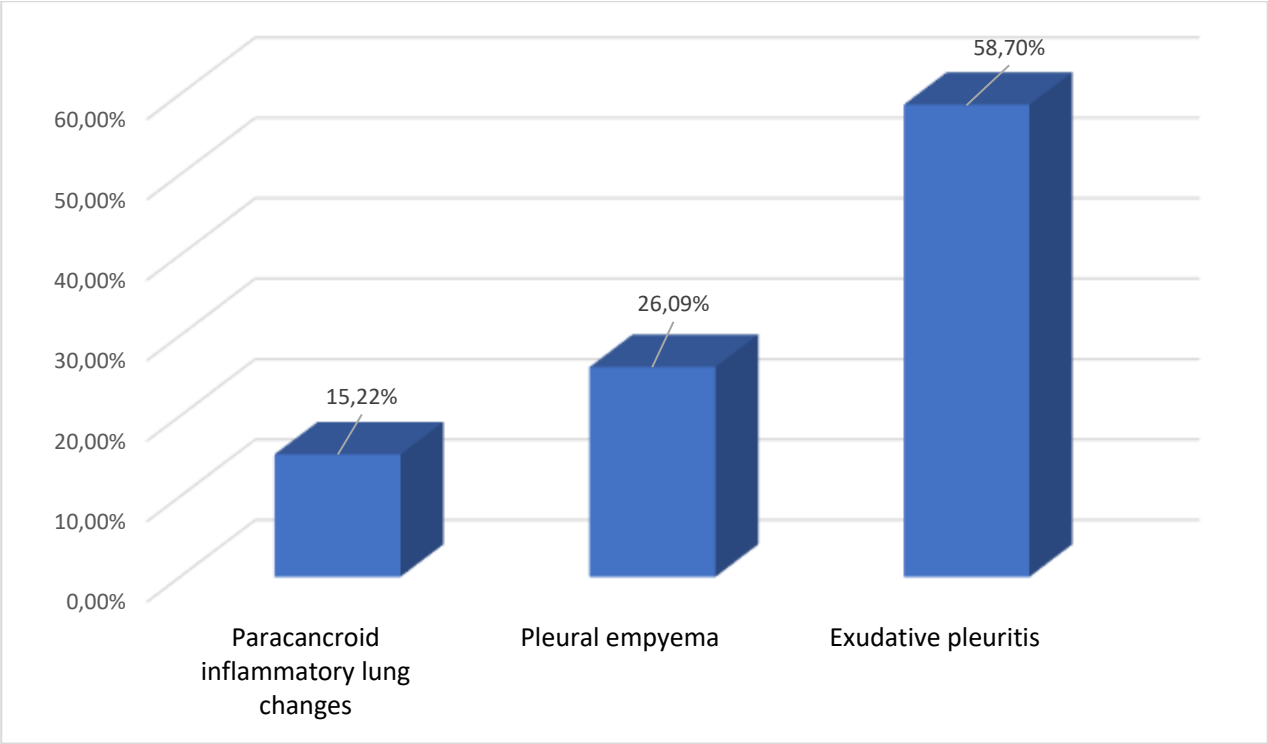

Fig. 6. Three groups of patients.

- 14 patients with paracancerous inflammatory changes in the lungs, who received extracorporeal blood hyperthermia in the complex treatment;
- 24 patients with pleural empyema, who received extracorporeal blood hyperthermia in the complex treatment;
- 54 patients with exudative pleurisy, who received extracorporeal blood hyperthermia in the complex treatment.

Need to note that the authors of the article used the apparatus for extracorporeal blood hyperthermia in the treatment of inflammatory paracancerous pulmonary processes. 14 patients with paracancerous inflammatory changes in the lungs, who received extracorporeal blood hyperthermia in the complex treatment, participated in the studies.

Thus, the first group included nine patients. The control group consisted of five patients suffering from paracancerous inflammatory changes in the lungs. Extracorporeal blood hyperthermia was not used for them. In this case:

- all patients complained of general weakness, shortness of breath, productive cough;
- three patients had pain in the left hemithorax;
- an increase in body temperature was noted in all patients from 37.8 to 39.6°C;
- nine patients of the first group and 3 patients of the control group were diagnosed with lung adenocarcinoma;
- five patients of the first group and 2 patients of the control group were diagnosed with squamous cell carcinoma;
- X-rays showed tumor-like formations in the lungs of different sizes and shapes;
- diagnosis was confirmed histologically during fibrobronchoscopy by biopsy of exophytically located tumors;
- 3 patients of the first group and two patients of the control group had metastases to the liver; confirmed by ultrasound examination;
- during laboratory examination, leukocytosis was noted in patients of the first and control groups (respectively: 12.6+/-0.7 and 12.1+/-0.8), a shift of the leukocyte formula to the left;
- nitroblue tetrazolium recovery test indicated the functional activity of leukocytes;

- in patients of the first group and the control group, the nitroblue tetrazolium test was reduced (respectively 4.25+/-0.33% and 4.01+/-0.27% with a norm of 7-9%).

After comprehensive treatment using extracorporeal blood hyperthermia, the following data were established, which are given during comparison in Table 1.

Table 1. Results of the study after comprehensive treatment using extracorporeal blood hyperthermia in patients of the first group compared with patients of the control group.

Patients of the first group	Patients of the control group
already on the 4th day, a significant improvement in the general condition was subjectively noted	on the 4th day, no improvement in the general condition was observed
the intensity of cough and shortness of breath significantly decreased, the body temperature decreased to subfebrile values, the feeling of general weakness decreased	the intensity of cough and shortness of breath practically did not change, the increase in body temperature was practically unchanged
the level of blood leukocytosis in patients significantly decreased to 9.1+/-0.6; $p<0.05$	the level of blood leukocytosis in patients practically unchanged (11.6+/-0.7; $p<0.05$)
a significant increase in the nitroblue tetrazolium test was noted in patients (6.31+/-0.28%; $p<0.05$)	insignificant changes in the nitroblue tetrazolium test in patients (4.11+/-0.35; $p<0.05$)
in 3 patients after extracorporeal blood hyperthermia	in patients the disappearance of metastases in the liver was not observed

Evaluating the results of the apparatus for extracorporeal blood hyperthermia in patients of the first group, the following were recorded according to ICD-11 [63, 64]:

- decrease in leukocytosis 9.1+/-0.6; $p<0.05$;
- increase in nitroblue tetrazolium test (6.31+/- 0.28%; $p<0.05$);
- significant improvement in general condition;
- decrease in elevated body temperature;
- decrease in the intensity of cough and shortness of breath.

The study also included 24 patients with pleural empyema, who received extracorporeal blood hyperthermia in complex treatment. The control group consisted of 7 patients with pleural empyema, who did not receive extracorporeal blood hyperthermia.

All patients complained of general weakness, shortness of breath, and productive cough. Five patients had pain in the left hemithorax. An increase in body temperature was noted in all patients from 37.8°C to 39.6°C. During laboratory examination, leukocytosis was noted in patients of the first and control groups (respectively: 18.6+/-2.7 and 17.1+/-3.8), a shift of the leukocyte formula to the left. A nitroblue tetrazolium recovery test was also performed, which indicates the functional activity of leukocytes. In patients of the first group and the control group, the nitroblue tetrazolium test was reduced – 3.37+/-0.65% and 3.41+/-0.58%, respectively, with a norm of 7-9%.

In the first group of 17 patients, after comprehensive treatment using extracorporeal blood hyperthermia, on the 6th day, a significant improvement in the general condition was subjectively noted: the intensity of cough and shortness of breath significantly decreased, the body temperature decreased to subfebrile values, and the feeling of general weakness decreased. In the patients of the control group, subjectively, on the 6th day, no improvement in the general condition was observed, the intensity of cough and shortness of breath practically did not change, the increase in body temperature was practically unchanged. The level of blood leukocytosis in the patients of the first group significantly decreased to 12.1+/-1.6; $p<0.05$; in the patients of the control group - practically unchanged 14.8+/-2.7; $p<0.05$. A significant increase in the nitroblue tetrazolium test was noted in the patients of the first group (6.31+/-0.28%; $p<0.05$); insignificant changes in the nitroblue tetrazolium test in patients of the control group (3.75+/-0.27; $p<0.05$). Evaluating the results of extracorporeal blood hyperthermia in patients of the first group, a significant decrease in leukocytosis

was noted, a significant increase in the nitroblue tetrazolium test was noted (6.31+0.28%; $p<0.05$), a significant improvement in the general condition, a decrease in elevated body temperature, a decrease in the intensity of cough and shortness of breath. The above was not observed in patients of the control group.

A patent was obtained for the treatment of pleural empyema with an apparatus for extracorporeal blood hyperthermia [65].

The study included 26 patients with exudative pleurisy, who received extracorporeal blood hyperthermia in complex treatment. The control group consisted of 15 people with exudative pleurisy, who did not receive extracorporeal blood hyperthermia.

Patients complained of general weakness, shortness of breath. 6 patients had total exudative pleurisy, which was accompanied by significant shortness of breath and signs of respiratory failure. Also, patients had an increase in body temperature to 37.3°C-38.5°C.

Laboratory examination revealed leukocytosis in patients of the first group and the control group (respectively: 10.5+/-2.3 and 10.3+/-2.9), a shift of the leukocyte formula to the left. A nitroblue tetrazolium recovery test was also performed, which indicates the functional activity of leukocytes. In patients of the first and control groups, the nitroblue tetrazolium test was reduced (respectively 4.02+/-0.71% and 3.98+/-0.67% with a norm of 7-9%).

In patients of the first group, after comprehensive treatment using extracorporeal blood hyperthermia, a significant improvement in the general condition was subjectively noted on the 7th day: the intensity of shortness of breath significantly decreased, body temperature normalized, and the feeling of general weakness disappeared.

In patients of the control group, subjectively on the 7th day, no improvement in the general condition was observed, the intensity of shortness of breath decreased slightly, the increase in body temperature decreased slightly. The level of blood leukocytosis in patients of the first group significantly decreased to the norm 6.2+/-1.7; $p<0.05$; in patients of the control group – practically unchanged 9.4+/-1.8; $p<0.05$.

A significant increase in the nitroblue tetrazolium test was noted in patients:

- the first group (6.42+/- 0.32%; $p<0.05$);
- insignificant changes in the nitroblue tetrazolium test in patients of the control group (4.45+/-0.81; $p<0.05$);
- the average bed day of patients of the first group was – 18+/-4 days;
- the second group – the average bed day of patients was – 27+/-5 days.

Evaluating the results of the apparatus for extracorporeal blood hyperthermia in patients of the first group, a significant decrease in leukocytosis was noted. A significant increase in the nitroblue tetrazolium test was noted (6.42+/-0.32%; $p<0.05$), a significant improvement in the general condition, normalization of elevated body temperature, disappearance of shortness of breath, a significant reduction in the duration of treatment in the hospital compared to patients of the second group. The above was not observed in patients of the control group.

The authors of the article received patents regarding the treatment of exudative pleurisy of nonspecific genesis with an apparatus for extracorporeal blood hyperthermia [55, 64-67].

In favor of the research of the authors of the article on this topic, the analysis of sources of foreign scientists Van der Zee J. indicates the advantages and reasons for the limited implementation of hyperthermia (Fig. 7) [68].

Hyperthermia:

- ✓ an additional treatment method to radiotherapy and many cytotoxic drugs;
- ✓ has not yet received wide recognition as a treatment method due to insufficient susceptibility;
- ✓ most positive randomized studies on hyperthermia were relatively small and were conducted in some Asian countries;
- ✓ in the USA, hyperthermia is used by specialized institutes for oncological patients;
- ✓ requires investment in equipment and training of personnel;
- ✓ has insufficient public awareness;

- ✓ adding hyperthermia to radiotherapy or chemotherapy leads to a doubling of the complete response rate, which is confirmed in the treatment of certain groups of patients;
- ✓ there are problems with procedural clinical application.

Advantages:
• Enhances the effect of radiotherapy and cytostatics • Works as a sensitizer of anticancer drugs • Clinical studies confirm efficacy (increased complete response, overall survival)
Reasons for limited implementation:
• Limited availability of technology • Small-scale clinical trials (mostly Asia) • High cost of equipment and staff training • Lack of awareness among doctors and patients • Equipment production limited to a few small companies • Method still needs improvement and standardization • As a monotherapy – effectiveness only ~13%, in combination – doubling of results
Prospects:
• Expanding access → large-scale research → integration into the healthcare system

Fig. 7. Hyperthermia: possibilities and limitations [68].

Thus, the current level of theoretical justification for the development and implementation in medical practice of the apparatus for extracorporeal blood hyperthermia (the use of warm fresh whole blood) for the high-quality and safe treatment of inflammatory pulmonary pathology in healthcare institutions was studied.

Conclusions. For the first time, the authors of the article used extracorporeal blood hyperthermia. It was proven that hyperthermia is highly effective in the treatment of inflammatory processes in exudative pleurisy, paracancerous pulmonary inflammatory pathologies and empyema diseases of the pleural cavity. It was studied that the infusion of heated blood was used in US military medicine in 2003–2007. It was analyzed that the introduction of blood heated to 38.0°C into the body of patients is approved by treatment protocols in the USA, Canada, New Zealand, European countries, and Africa. The authors of the article were the first in Ukraine to apply extracorporeal blood hyperthermia in a closed circuit for the treatment of inflammatory processes of the lungs and pleura with a therapeutic anti-inflammatory purpose. It was proven that the method of extracorporeal blood hyperthermia is effective in the treatment of exudative pleurisy, pleural empyema, and paracancerous inflammatory processes.

Declaration of conflict interest. The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. The authors confirm that they are the authors of this work and have approved it for publication. The authors also certify that the obtained clinical data and research were conducted in compliance with the requirements of moral and ethical principles based on medical and pharmaceutical law, and in the absence of any commercial or financial relationships that could be interpreted as conflict and/or potential conflict of interest.

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Ethical approval. Ethical clearance was obtained from the administration of the Danylo Halytsky Lviv National Medical University. Permission statement for conducting the experiments was received from the administration of the Danylo Halytsky Lviv National Medical University. Before any data collection, the main purpose of the study was clearly explained to each department (concerned personnel) in accordance with the Law of Ukraine "On the Protection of Personal Data", which regulates legal relations related to the protection and processing of personal data, and is aimed

at protecting the fundamental rights and freedoms of a person and a citizen, in particular the right to non-interference in personal life, in connection with processing of personal data. This Law applies to the processing of personal data, which is carried out in whole or in part using automated means, as well as to the processing of personal data contained in the card file or intended to be entered in the card file, using non-automated means.

Data availability statement. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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