
REVIEWS

Horizons of Heparin Therapy in COVID-19 and Pandemic-Related Diseases

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Abstract—The disease caused by the coronavirus SARS-CoV-2, named COVID-19, has been spread around the world at a high transmission rate. It was initially considered to be an acute respiratory distress syndrome. Recent clinical data has highlighted that COVID-19 is characterized by a vascular dysfunction and thrombosis, which are not typical for many other acute respiratory diseases. Thrombotic complications are markers of severe COVID-19 and are associated with multiple organ failure and increased mortality. The application of unfractionated and/or low-molecular-weight heparins as anticoagulant medications, significantly reduced the severity of the disease and COVID-19-induced mortality, since heparin is a multifunctional agent. The goal of this review is to summarize the literature data on the pathogenic mechanisms of SARS-CoV-2 and to characterize the properties of heparin, which allow inhibiting these mechanisms at any stage of pathogenesis. We proposed a vicious circle hypothesis of SARS-CoV-2 pathogenesis, as well as an original approach to low-dose heparin therapy beyond its anticoagulant properties. The analysis of a wide range of effects and mechanisms of action of heparin will help create an idea of current possibilities and future potential of applying this drug.

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INTRODUCTION

Members of the vast family *Coronaviridae* are the largest known, single-stranded respiratory RNA viruses. They are anthroozoonotic infectious pathogens that have natural reservoirs of infection and form unified dynamic gene pools. The name “*Coronaviridae*” (coronavirus) was given to the family of these viruses due to large (up to 20 nm) corona-like peplomers (the spikes on the viral surface) integrated into the envelope.

The causative agent of the modern pandemic is the SARS-CoV-2 (Severe Acute Respiratory Syndrome-Related Coronavirus 2). Coronavirus disease 2019 named COVID-19 (Coronavirus Disease 2019, COVID-19) manifests itself in a wide range of signs and symptoms, from a low-symptom, flu-like syndrome to catastrophic multiple organ failure.

Initially, COVID-19 was considered to be an acute respiratory distress syndrome (ARDS), therefore antiviral and anti-inflammatory drugs

have begun to be used to treat the disease. However, it soon became clear that the effectiveness of the medications used was insufficient, since a high incidence of thrombotic events in patients hospitalized with COVID-19 was identified during the pandemic. It was found that these complications determine the catastrophic consequences of the disease [1]. According to the data reported by the researchers from Wuhan (China), the main marker associated with the development of a severe clinical course of the disease and its possible mortal outcome is a high and continuously increasing level of D-dimer [2].

Hypercoagulation is quite unusual for the symptoms associated with respiratory viral diseases. Due to the appearance of a large number of publications on COVID-19-associated thrombosis, many clinicians and researchers now consider this disease as prothrombotic. However, to date, there is no specific unified strategy and effective targeted treatment for COVID-19. In fact, there is an empirical selection of national and international treatment protocols. Currently, according to the World Health Organization (WHO), the use of heparins for the treatment of critical patients with COVID-19 is preferable to other anticoagulants [3, 4].

Heparin is the oldest natural anticoagulant, which is still being widely used in various clinical cases, such as thromboembolism, acute myocardial infarction, transfusion medicine, cardiac surgery, hematology, etc. Despite a long history of study and use in medicine, many of the properties of heparin are little known and insufficiently applied in clinical practice. The therapeutic utility of heparin has sparked debates in the medical community because of the fact that most physicians are well aware of the side effects of heparins but little aware of the whole spectrum of their therapeutic properties, as well as doses and routes of administration. Nevertheless, clinicians of different countries had to use heparin, which reduced D-dimer values, improved patient survival, and caused the transition from pathological inflammation to an effective immune response.

This review article aims to acquaint readers with the wide spectrum of heparin's properties and to demonstrate its advantages and clinical situations when the scope of its use would be worth

expanding, especially in the context of current COVID-19 pandemic. The article emphasizes the role of Russian researchers in studying the molecular structure of heparin and the unique effects of this biologically active compound.

PROPERTIES OF ENDOGENOUS HEPARIN USED TO CREATE COMMERCIAL DRUGS

The era of using heparin for venous thromboembolism prevention has begun in 1916 with the discovery of a substance isolated from hepatic cells with anticoagulant activity. The discovery was made by medical student Jay McLean, who worked under the guidance of the famous scientist—Professor William Howell at the Department of Physiology at Johns Hopkins University in Baltimore [5]. Subsequently, the anticoagulant substance was named “heparin”. Active research and use of commercial drugs in the clinic began after the development of sodium and calcium salts of heparin [6]. Currently, commercial preparations of heparin are obtained from lung tissues of cattle or intestines of pigs.

Heparin, which is a glycosaminoglycan, an active polyanion, is one of the mediators of mast cells. Mast cells are present in all tissues and organs, but the lungs and intestines of mammals are especially rich in them. Heparin is secreted into the extracellular space, and does not enter the bloodstream under physiological conditions. It is used locally, performing the functions of a non-specific adaptogen, protecting the body from toxins, various parasites (including viruses and bacteria), as well as regulator of intercellular interactions [7]. The anticoagulant properties of heparin become significant under the influence of any external or internal factors leading to the threat of microcirculation disorders, stasis, thrombosis, etc. Heparin enters the bloodstream already in the early stages of pathological processes, where it prevents damage of the vascular endothelium by binding (complexation) and inactivation of biologically active substances. It also reduces the endothelial adhesiveness, restoring the altered membranes electronegative potential, and inhibits the activation of cellular and plasma coagulation factors [7, 8]. Thus, endoge-

nous heparin is a polyfunctional biologically active mast cell mediator, while the anticoagulant effect is only one of its effects. By preventing thrombosis, heparin promotes the restoration of the habitat of surrounding cells, providing them with a full-fledged delivery of trophic and energetic substances [7, 8].

The molecular weight of commercial unfractionated heparin (UFH) molecules released from tissues ranges from 3000 to 60000 Da. As in mast cells, the UFH molecule is a natural polysaccharide biopolymer. It is a linear unbranched chain consisting largely of repeated disaccharide units 2-O-sulphated IdoA, and 6-O-disulphated GlcN glycosidic bonds. A high degree of molecule sulfation provides a high negative charge and a high degree of binding with other biologically active substances, thus changing their properties. Due to the great similarity with endogenous heparin, UFH reveals multifunctional qualities [7, 8].

Low-molecular-weight heparins (LMWHs) represent a class of variously depolymerized UFH derivatives designed to reduce their side effects. Each type of LMWHs has a pronounced cumulative effect and pharmacological profile, therefore, the information about the properties of one LMWH cannot be extrapolated to others [7, 8, 9].

The UFH and LMWH anticoagulant properties are different. UFH is able to bind (form a complex) with antithrombin III and, at the same time, with thrombin (ATIII-UFH-thrombin), inhibiting the thrombin activity [10]. Thrombin catalyzes the conversion of fibrinogen to fibrin, which is transformed first into fibrin monomer, then fibrin polymer, and after stabilization, together with platelets, it turns into a thrombus. The ATIII-UFH-thrombin complex deactivates coagulation factors such as IXa, Xa, XIa, XIIa [10].

At the same time, UFH is able to bind to the heparin cofactor II, which also neutralizes thrombin. However, the effect of UFH is weakened (bioavailability decreases) due to its high ability to bind to biologically active substances, such as enzymes, hormones, nucleic acids, alkaloids, etc. In addition, UFH has a number of side effects, which are partially neutralized by the shortening of the molecule [8, 9]. According to a number of data, the advantages of LMWH include a more

pronounced direction of anti-Xa effect, greater bioavailability, and fewer complications [9]. At the same time, the advantages of UFH are a relatively low cost of UFH-based drugs, the absence of teratogenic and embryotoxic effects, as well as the presence of an antidote (protamine sulfate). Protamine sulfate (PS) is a base and, through binding to heparin acid residues, forms a stable complex with UFH. At the same time, PS induces a destruction of the ATIII-UFH-thrombin complex, which leads to a decrease in the heparin anticoagulant activity. Neutralization of UFH occurs within a few minutes. The duration of PS action is about 2 h (depending on the body temperature). PS itself has insignificant anticoagulant activity [9].

LMWH and UFH are most often injected intramuscularly and subcutaneously, however, the effectiveness of heparin action has also been proven with intranasal, intrarectal, inhalational and external (as ointments) administration. Heparin is also used in medical devices, for example, for extracorporeal blood purification [7–9, 11].

HEPARIN INHIBITS THE MECHANISMS OF SARS-COV-2 INTERNALIZATION INTO HOST CELLS

The ongoing COVID-19 pandemic caused by the SARS-CoV-2 has brought the angiotensin-converting enzyme 2 (ACE2) to the focus of attention. This coronavirus, as many other viruses, uses the host cell ACE2 protein to enter and infect epithelial cells. Human carboxypeptidase ACE2 is encoded by the *ACE2* gene located on chromosome 22 [12]. ACE2 is a type I transmembrane protein with an extracellular N-glycosylated N-terminal region containing a carboxypeptidase site and a short intracellular C-terminal cytoplasmic tail. The N-terminal peptidase domain is the site of ACE2 binding to SARS-CoV. The cellular (membrane-bound) and circulating (soluble) forms of the ACE2 protein are also distinguished. The cellular form is a complete protein synthesized in large quantities by pneumocytes, enterocytes of the small intestine and the other cells. The circulating form (it retains the N-terminal peptidase site) results from a cleavage of the cellular ACE2 form by ADAM17

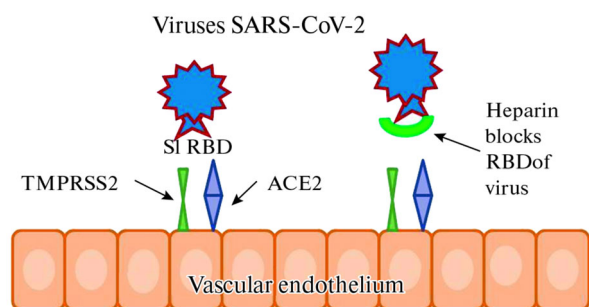


Fig. 1. SARS-CoV-2 binds to the surface of endothelial cells via the host receptors. Heparin blocks the receptor-binding domain of the virus.

metalloprotease, and enters the intercellular space thereafter [12].

The receptor-mediated virus penetration depends on the membrane-bound serine protease, a product of the *TMPRSS2* gene. It was established that, for successful entry into host cells, SARS-CoV-2 viruses require both ACE2 and TMPRSS2 [13, 14]. It has been shown that the virus uses a surface spike glycoprotein (S) with two subunits (S1 and S2) to bind to ACE2. The S1 subunit has N-terminal (NTD) and C-terminal domains (CTD1, CTD2 and CTD3). The SARS-CoV-2 virus has a receptor-binding domain (RBD) on CTD1, which interacts with ACE2 on the cell surface. S2 subunit triggers the fusion of the virus with the cell membrane, which leads to the penetration of the virus inside (Fig. 1). Cleavage of S protein at the junction of S1 and S2 is carried out by host proteases such as TMPRSS2 [13, 14].

This internalization pathway is typical for many viruses. It has long been known that heparin, having the ability to form complex compounds, exploits these universal mechanisms in its antiviral effects against herpes viruses (HSV-1), Zika viruses (ZIKV), and other viruses [9, 15, 16]. Quite recently, Partridge et al. (2021) found that UFH is able to inhibit SARS-CoV-2 penetration into host cells by 80%, forming a competitive binding, namely, complex compounds with RBD domains, and can block the virus internalization (Fig. 1). As in other cases, the antiviral effect is more clearly expressed in UFH than in LMWH [17].

SARS-CoV-2 penetrates into host cells by disrupting the endothelial glycocalyx, which rep-

resents a highly hydrated fibrous meshwork of carbohydrates covering the endothelial cell membrane. The endothelial glycocalyx is mainly composed of a complex of membrane-bound proteoglycans, glycosaminoglycan chains, glycoproteins and plasma adhesive proteins that perform protective functions toward the cell membrane. It ensures transport selectivity of substances, participates in the formation of intercellular contacts, and performs receptor and marker functions [7, 8]. Disruption of the glycocalyx layer in patients with COVID-19 causes a destruction of cell membranes, which leads to an increase in the number of phospholipoprotein particles in the bloodstream, which have significant thrombogenic activity (Fig. 2). It was reported in preclinical studies that glycocalyx disruption in the pulmonary microvessels is induced by TNF- α -dependent heparanase activation, which destroys heparan sulfate. The use of UFH or LMWH protects the glycocalyx from degradation by inhibiting heparanase activity [18]. Since heparanase activation can increase the metalloproteinase expression level, heparin is able to simultaneously attenuate an increase in the concentration of these endopeptidases (specifically MMP-2 and MMP-9) in COVID-19 [19].

COVID-19-ASSOCIATED COAGULOPATHY AND MECHANISMS OF HEPARIN ACTION

Penetration of SARS-CoV-2 causes gross damage to the blood vessel endothelium and other host cells (Fig. 2) [19]. It is common knowledge that the endothelial lipid-bilayer membrane plays an important role in the retention of blood anticoagulant properties, maintaining the concentration gradient of substances between the cell cytoplasm and environment. In all cases of endothelial membrane damage, including in COVID-19, purinergic transmission of thrombogenic signals is of great importance, starting with the ATP and ADP release from damaged, activated cells (Fig. 2). In the extracellular space, membrane ATP and ADP receptors (such as P2X7) are activated, which induces signaling mechanisms for the entry of calcium ions (Ca^{2+}) into the cytoplasm of vascular cells (Fig. 2) [20]. The resulting significant increment in the intracellular Ca^{2+} concen-

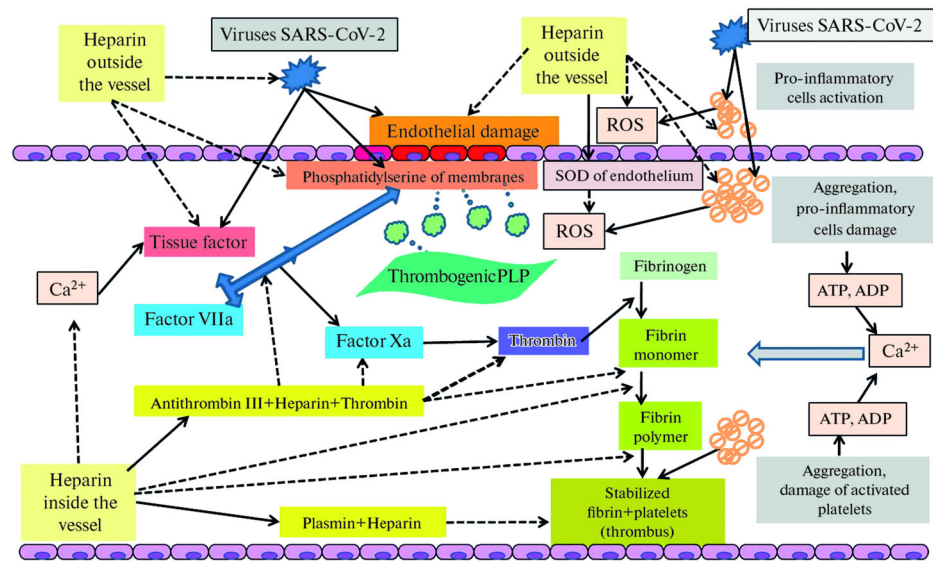


Fig. 2. SARS-CoV-2 thrombogenic action and antithrombogenic heparin effects. ROS—reactive oxygen species, SOD—superoxide dismutase, dotted lines—inhibition, solid lines—activation, Ø—proinflammatory cells.

tration in endothelial cells blocks translocases, the enzyme systems of transmembrane carrier proteins involved in the transfer of phosphatidylserine and phosphatidylethanolamine from the outer side of the membrane to the inner. As a result, a chain of events occurs, leading to membrane loosening and changes in the structure of the cytoskeletal protein framework. In this case, phospholipoprotein particles with thrombogenic activity can be rejected into the bloodstream (Fig. 2). On the transformed cell surface, negatively charged phospholipid acidic residues, with the involvement of ATP, ADP and Ca^{2+} , activate and form a bond with vitamin K-dependent factors. The key phase of these events is an increase in the expression of the tissue factor (TF), an almost ubiquitous protein component of the mammalian cell surface that exhibits high thrombogenic activity when exposed to pathogenic factors (Fig. 2) [20, 21].

It is not widely known that UFH regulates the ATP effects, forming complexes with ATP that have anticoagulant properties and prevent thrombogenesis in the bloodstream [22]. At the same time, heparin is a selective inhibitor of inositol-1,4,5-triphosphate receptors involved in the process of ATP-dependent Ca^{2+} flow into the cell; it is able to inhibit coagulation factors at the initial stage of activation, reducing the level of intracellular Ca^{2+} [23]. Consequently, heparin normal-

izes the permeability and function of cell membranes. The possibility of heparin influences on the Ca^{2+} concentration is also an important mechanism of its action on the immune processes [7–9].

The most well-known UFH property is its anticoagulant function as an inhibitor of blood coagulation factors, which is carried out through natural anticoagulants present in the body of animals and humans. An extremely important and well-known anticoagulant is serpin (antithrombin III), an essential physiological inhibitor of thrombin. It has long been called the main anticoagulant, since antithrombin III is able to inhibit almost all blood coagulation proteases, plasmin, trypsin, and the C1s component of complement. Antithrombin III has a predominant anticoagulant activity toward thrombin, as well as factors Xa and XIa. Antithrombin III-heparin-thrombin complex formation significantly increases the anticoagulant effect of antithrombin III (1000–100000-fold, Fig. 2). This is partly due to the fact that after complex formation, heparin dissociates therefrom and binds to another antithrombin III molecule, generating multiple cycles of thrombin enzyme inactivation [10]. This interaction is implemented only if the heparin molecule contains at least 18 saccharide residues. It is important to note that the property of UFH and LMWH to form complexes with many biologically active substances

was studied and characterized in detail in the 1950s–1970s by Russian scientists under the guidance of Professor B.A. Kudryashov [10, 26], while abroad, this complex was learned to isolate and study later [24, 25].

Other anticoagulants, such as heparin cofactor II, protein z-dependent protease inhibitor, protein C inhibitor, protease nexin-1, inhibitor of plasminogen-1 activator, tissue factor pathway inhibitor (TFPI), inhibitor of the external pathway of prothrombinase formation (annexin V), as well as antithrombin III, form complexes with UFH, which greatly enhances their action [9, 25].

It is noteworthy that, in addition to fibrin formation, thrombin acts beyond the mechanisms of blood coagulation. In the norm, when thrombin reaches the threshold concentration in the circulating blood, it interacts with thrombomodulin (CD141 or BDCA-3), a membrane-bound glycoprotein that functions as a thrombin receptor on the intact endothelial surface; the thrombin-thrombomodulin complex activates the reflex arc of the anticoagulation system [26]. As a result, thrombin induces the release of the tissue plasminogen activator (t-PA) from the endothelium, which stimulates fibrinolysis and thus prevents the formation of stabilized fibrin in the vascular bed. The fibrinolytic system contains both enzymatic and non-enzymatic components. The main component of the non-enzymatic fibrinolytic system is heparin, which was discovered and studied by B.A. Kudryashov and his collaborators [10, 26].

In contrast to healthy people, COVID-19 patients develop a profound depression of the fibrinolytic system against the background of hypercoagulation activation. Interestingly, the idea of using heparin to normalize the fibrinolytic system is not commonly accepted among researchers and clinicians, despite the fact that heparin is able to stimulate plasmin generation through heparin (UFH and LMWH) binding with the sites of plasminogen activators, both of urokinase (u-PA) and tissue (t-PA) types. These effects of heparin contribute to balancing the coagulation, anticoagulation, and fibrinolytic blood systems [9, 27, 28].

In addition to activating enzymatic fibrinolysis, heparin, being the main component of the non-enzymatic fibrinolytic system, has pronounced

antipolymerization and fibrinolytic activities toward fibrin monomers and unstabilized fibrin polymers (UFH to a greater extent than LMWH) (Fig. 2) [9, 10, 26].

INFLAMMATORY IMMUNE RESPONSE IN COVID-19 AND ANTI-INFLAMMATORY EFFECTS OF HEPARIN

It is well known that coagulation, anticoagulation and fibrinolytic blood systems, together with the immune system, constitute the unified protective functional system of human organism. A disturbance of one of them immediately affects the others. For example, the interaction between tumor tissue, hemostatic and immune systems occurs as a cascade of mutual activation, leading thereby to the formation of a vicious circle, which results in endothelial damage, pro-inflammatory reactions, and thrombosis in the bloodstream, i.e. the development of thrombotic microangiopathy. It has been shown that cytokines act as mediators in this interaction [29].

Apparently, similar mechanisms form in COVID-19 and, by inducing an inflammatory response or cytokine storm (in severest cases), affect the whole organism, as well as have a direct and indirect impact on the central nervous system (CNS) [30]. Cytokine storm may be associated with the atrophy of lymphoid organs, which also contributes to a decrease in the number of circulating lymphocytes (lymphopenia [31]).

Normally, initiation of the inflammatory response leads to a nonspecific activation of such pro-inflammatory cells as leukocytes and platelets, increasing their ability to migrate, adhere, and infiltrate tissues. In humans, most of the leukocytes are neutrophils (40–70%). In addition to degranulation and phagocytosis, activated neutrophils release extracellular traps (networks) consisting of extracellular DNA, histones, biologically active proteins, and reactive oxygen species (ROS). There is growing body of evidence that neutrophilic extracellular networks, which form in large numbers, play a decisive role in the pathogenesis of intravascular thrombosis and multiple organ failure in COVID-19 (Fig. 3) [32].

Oxidative stress is an important aspect of the inflammatory process in COVID-19, character-

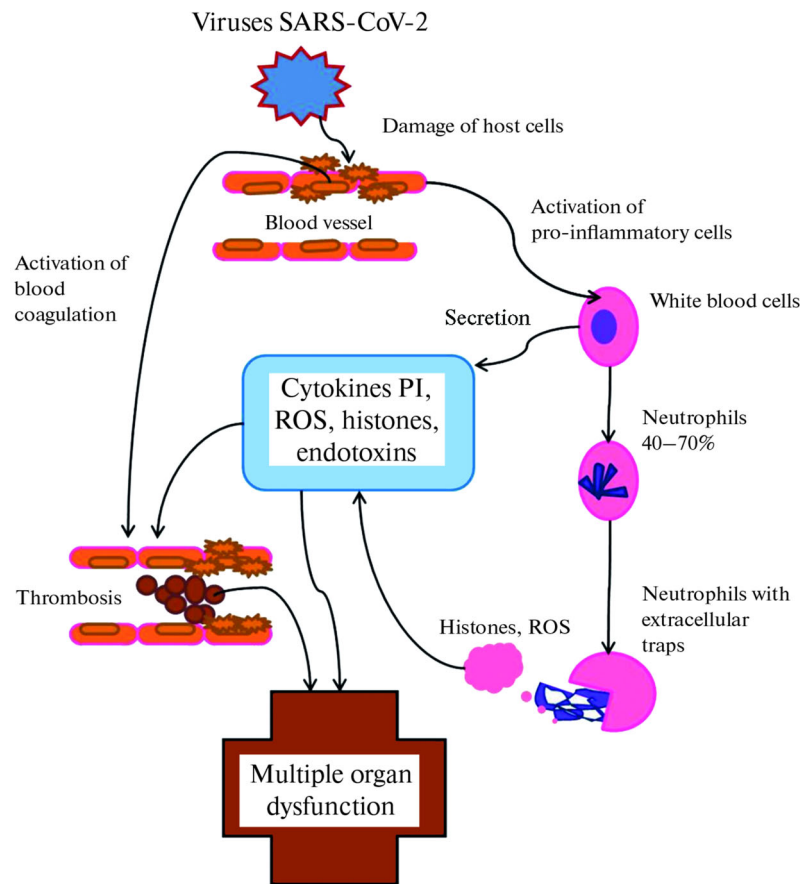


Fig. 3. Changes in the blood coagulation system in COVID-19. ROS—Reactive oxygen species.

ized by an imbalance in ROS production and feedback responses of the antioxidant systems [33]. It is manifested in a significant increase in the ROS level, which impairs the permeability of blood-tissue barriers. Thus, oxidative stress leads to cell destruction, DNA, lipid and protein damage, and dysfunction of various growth factors (Fig. 3). All these pathogenic processes can stimulate massive secretion of pro-inflammatory cytokines, up to a cytokine storm.

Just as with sepsis, in COVID-19, the intestine, along with the lungs, is the target of viral infection. As a result, the intestinal wall permeability becomes impaired, and the pro-inflammatory endotoxin produced by resident gram-negative bacteria enters the systemic circulation. Bacterial DNA and endotoxins have been found in virtually all critically ill COVID-19 patients [34, 35]. These inflammatory response triggers further activate the coagulation cascade mechanisms through the TF pathway (Fig. 3). As shown in experiments

on mice, using this pathway, endotoxin and tumor necrosis factor (TNF- α) induce the production of interleukin (IL-6) and other pro-inflammatory cytokines, which is accompanied by an increase in the thrombin and fibrin synthesis (Fig. 3). Notably, LMWH administration normalizes the state of the intestinal barrier and anticoagulation blood system [36].

Based on the above data, we can briefly describe how heparin can help with the inflammatory response associated with COVID-19. There are at least five possibilities:

(1) commercial heparin UFH and selectively desulfated heparin (UFH with reduced anticoagulant activity) are able to inhibit the expression of main pro-inflammatory cytokine IL-6, IL-8, IFN γ , tissue factor and complement component C3A [7–9];

(2) UFH and LMWH reduce the concentration of toxic histones that appear in the extracellular space due to the release of neutrophilic extracel-

lular networks (Fig. 3). For the manifestation of these properties, heparin requires the presence of sulfated groups, at least in a small amount [7–9, 32];

(3) UFH and LMWH administration inhibits the activation of pro-inflammatory cells, reduce their ability to migrate, aggregate and adhere, as well as suppresses tissue infiltration with leukocytes (Figs. 2, 3) [7–9, 15];

(4) UFH exhibits antioxidant properties, as it stimulates the expression of superoxide dismutase (SOD) in various cells. SOD plays a major role in antioxidant protection against ROS (Figs. 2, 3) [7–9];

(5) UFH and LMWH cause a decrease in endotoxin-stimulated gene expression that contributes to the restoration of the intestinal endothelial barrier [34, 35].

STRESS-RELATED DISEASES IN COVID-19 PANDEMIC, ANTI-STRESS EFFECTS OF HEPARIN

Epidemics like COVID-19 always entail multiple negative consequences. Psychological effects of social isolation, impact of constant emotional stress concerned with the need to maintain continuous heightened vigilance toward a compliance with the requirements of preventive medicine, and many other external factors, are associated with adverse effects on the population mental health. All these factors led to the emergence of numerous data in 2020, indicating a significantly increased incidence of severe stress symptoms (anxiety and depression) in the population of many countries during COVID-19 pandemic even in people who have not had COVID-19 [37]. Therefore, the population of many countries has revealed a high percentage of post-traumatic stress disorder (PTSD) symptoms. Thus, there is a need for psychological and medical countermeasures against short- and long-term psychopathological consequences of the COVID-19 pandemic.

PTSD is regarded as a serious multisystem disease characterized by impaired psychological adaptation and concomitant somatic diseases. A PTSD-induced decrease in the level of circulating corticosterone, dystrophic changes in the liver

and adrenal glands, impaired hematological homeostasis (hypercoagulation) were recorded in our experimental works. It was found that the post-PTSD intramuscular UFH administration course at very small (below the therapeutic) doses (64 IU/kg) led to successful adaptation, behavior normalization, and improvement of the adrenal and hepatic morphofunctional parameters [38]. The latter plays an important role, since the regeneration of the liver, where most of the blood system's factors are synthesized, correlated with the normalization of the blood coagulation and anticoagulant systems. Morphofunctional restoration of the adrenal glands contributed to the normalization of the corticosterone level. The optimization of the behavioral and psychoemotional state after heparin administration is most likely due to its ability to cross the blood-brain barrier, improve blood flow, and participate in the regulation of neurotransmitter receptors. As established previously, UFH and LMWH form complexes with neurotransmitters (ACTH) and stress hormones (adrenaline, cortisol in humans, corticosterone in laboratory rodents), altering thereby their blood levels and contributing to adaptive processes [38, 39]. These results may provide a rationale for expanding the clinical use of low-dose heparin to prevent and treat psychosomatic pathology in PTSD of various etiologies, including COVID-19.

SIDE EFFECTS OF HEPARIN THERAPY

Heparin (UFH and LMWH), like many other drugs, has side effects. At the same time, many clinicians find no difference in the incidence of complications between UFH and LMWH. Since clinical benefits and safety concerns exist side-by-side, efforts should be focused on maximizing the therapeutic effect while minimizing side effects of heparin therapy.

The most common and evident potential complication of heparin (especially UFH) administration is bleeding. Heparin-induced thrombocytopenia ranks second in terms of the frequency of potential complications. Other potential complications, such as osteoporosis, skin reactions, eosinophilia, alopecia, liver dysfunction, acute heparin “anaphylaxis” and hypoaldostero-

nism, occur quite occasionally. The incidence of heparin therapy complications is the same in men and women; age is not a risk factor [9].

The major reasons of heparin therapy complications are as follows: (1) a high dose of heparin (more than 500 IU/day); (2) a significant duration of the administration course (more than 2 weeks); (3) a combination of drugs and comorbidities; (4) individual features. Bleeding is most often observed in patients suffering from chronic alcoholism, as well as in heparin and aspirin co-administration [7–9].

DEVELOPMENT OF NOVEL HEPARIN-LIKE DRUGS

Commercial UFH preparations for clinical application are currently derived from biological raw materials. This method does not exclude the possibility of viral and prion contamination, etc. For this reason, and to minimize heparin side effects, a promising direction is the development of methods for obtaining heparin on an industrial scale from plant sources. Preliminary results obtained by Russian scientists, B.A. Kudryashov's followers, indicate a high efficacy of plant-derived heparin-like anticoagulants. An anticoagulant, which has a UFH-like mechanism of action but lacks its side effects, was isolated from the roots of the peony, *Paeonia anomala*. When administered into the bloodstream of laboratory rodents, this heparinoid affected all the phases of blood coagulation, evoked a release of the tissue activator plasminogen from the vascular endothelium, and had a fibrin-depolymerization effect. It was found that the plant-derived heparinoid, in a similar way as UFH, is able to form complexes with biologically active substances. The data obtained substantiate the expediency and necessity of a follow-up study of plant-derived heparinoids [40].

CONCLUSION

Both unfractionated and low-molecular-weight heparins (UFH and LMWH, respectively) are applied in clinic as anticoagulants. The most commonly used routes of heparin administration are intramuscular and subcutaneous. The smallest number of adverse side effects was found with

low-dose and inhalational heparin administration. UFH and LMWH treatment should be carried out under the control of hemostasis indicators. Like all drugs, heparin has a number of negative side effects, the number of which decreases with a lowering of the administered dose, treatment duration, length and sulfation degree of the heparin molecule.

In the context of the COVID-19 pandemic, heparin attracts particular attention of clinicians, pharmacologists, physiologists and biologists as a multifunctional agent that regulates many biochemical and physiological processes in the human organism via complexing with many biologically active substances. Both endogenous and exogenous heparin can dissociate from one complexes and form the others, altering the properties and levels of most growth factors, cytokines, chemokines, ATP, ADP, calcium ions, etc. The degree of heparin-induced modification of different substances depends on its affinity, the properties of the heparin molecule, concentration of both components, and environmental conditions. Eventually, the heparin effects create prerequisites for the functional normalization of tissues and organs, provide the anti-stress effects under acute stress conditions and post-traumatic stress disorders.

According to current guidelines, the prescription of UFH or LMWH is indicated for all hospitalized patients with COVID-19. There were found no proven advantages of any one LMWH over the others. Heparin application in many clinics all over the world contributes to an increase in the survival rate and improvement of patients, in which heparin therapy transforms pathological inflammation into an effective immune response.

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CONFLICT OF INTEREST

The authors declare that they have neither evi-

dent nor potential conflict of interest related to the publication of this article.

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