Role of P-Selectin in the Development of Hemostasis Disorders in COVID-19

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Abstract—This is a review of data on the impact of COVID-19 on blood clotting. An important feature of the pathogenesis of severe acute respiratory syndrome caused by the SARS-Co-2 coronavirus is the risk of thrombotic complications including microvascular thrombosis, venous thromboembolism, and stroke. These thrombotic complications, like thrombocytopenia, are markers of the severe form of COVID-19 and are associated with multiple organ failure and increased mortality. One of the central mechanisms of this pathology is dysregulation of the adhesive protein P-selectin. The study of the mechanisms of changes in hemostasis and vascular pathology, and the role in these processes of biomarkers of thrombogenesis, and primarily of P-selectin of various origins (platelets, endothelial cells, and plasma), can bring some clarity to the understanding of the pathogenesis and therapy of COVID-19.

Keywords: COVID-19, hemostasis, P-selectin, fibrinolysis, coagulopathy
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INTRODUCTION

The huge number of publications related to the COVID-19 pandemic testifies to the desire of researchers to find effective methods for the treatment of this severe disease. Many patients infected with coronavirus-2 (SARS-CoV-2) develop a syndrome that fits the Berlin definition of acute respiratory distress syndrome (ARDS), characterized by very high mortality (Zhou et al., 2020). The influx of polymorphonuclear cells into the extravascular regions of the lungs is considered as a defining characteristic of this disease, the pathogenesis of which is still under investigation. Particular attention is paid to changes in the hemostasis parameters: blood coagulation and fibrinolysis (Coccheri, 2021). At the moment, it is believed that changes in the hemostatic system are decisive, especially in severe cases. With COVID-19, massive microthrombosis is observed, combined with an increase in both inflammation and an immune response similar to a cytokine storm, a state of the immune system in which it damages its own tissues instead of protecting itself. Thrombotic microangiopathy leads to destruction of the lung alveoli and obstructive neoangiogenesis. This is facilitated by changes in the fibrinolysis system, which can lead to both activation and inhibition of fibrinolytic mechanisms. With a decrease in fibrinolytic activity, there is an increase in the stability of microthrombi. It is thrombotic complications that are most dangerous in this disease. In 2002–2004 during the epidemic of SARS-CoV-1 coronavirus infection, the frequency of thrombotic complications was 11–20%, however in COVID-19 this frequency is up 79% (Kichloo et al., 2020). These figures are alarming and indicate that it is necessary to study the causes and mechanisms of such massive thrombotic complications in more detail, and improve the methods of treatment.

Coronaviruses comprise an extensive family of 40 viruses, 7 of which cause disease in humans (Belyakov et al., 2020). The human coronavirus strains that caused the SARS-CoV-1 epidemic and the COVID-19 pandemic belong to the betacoronavirus genus. Four proteins are involved in the structure of coronaviruses—the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. When inhaled into the human respiratory tract, the S protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in pulmonary type 2 pneumocytes, cardiac myocytes, and vascular endothelial cells. First, a fragment of the S-protein of the virus binds tightly to the ACE2 host cell receptor and then the bound fragment is cleaved off by the TMPRSS2 transmembrane protease, and the virus, together with the remaining part of the S protein, enters the host cell for replication (Hoffman et al., 2020). Entry of SARS-CoV-2 into the cell triggers apoptosis, which ultimately leads to phagocytosis of the apoptotic cell, especially by macrophages. All this leads to activation of the immune response and increased release of inflammatory mediators, including IL-6, IL-10, G-CSF.
and TNF-α (Smirnov and Totolyan, 2020; Kichloo et al., 2020). The complete SARS-CoV-2 genome has already been sufficiently studied, the first publication on which was made by the Chinese health authorities shortly after the discovery of the virus and facilitated the process of diagnosing and identifying the infectious agent. SARS-CoV-2, a single-stranded RNA-containing virus belongs to the Coronaviridae family, is a group 2b betacoronavirus and has at least 70% similarity in genetic sequence with SARS-CoV-1, its size is about 100 nm (Belyakov et al., 2020).

The probability of infection in humans depends on the expression of ACE2 receptors, which is not the same in different tissues and correlates with indicators of age, sex and race. It has been established that men get sick more often than women, which may be due to both the location of the ACE2 gene on the X chromosome and the activating effect of testosterone on ACE2 expression (Khirmanov, 2021). It is also noted that chronic diseases of the heart, lungs, diabetes mellitus, oncological diseases lead to an increase in the expression of ACE2, an increase in the risk of disease, and an aggravation of the severity of its course.

Clinicians and pathophysiologists pay particular attention of autopsies of patients who have died of this disease. Studies show that venous thromboembolism (VTE) occurs in approximately 30% of patients with COVID. Among cases of VTE, pulmonary embolism (PE) is observed in 26% and leads to a high probability of death (Coccheri, 2020). The extensive microthrombosis observed is predominant in the lungs and associated with severe, often fatal, respiratory failure. Microthromboses are also observed in other organs— in the kidneys, brain, etc. But it is microthrombosis of the lungs that seems to be most associated with exacerbation of severe respiratory failure, leading to death. PE and microthrombosis may occur as concomitant, separate, or sequential events in the same patient. Lung biopsy shows damage to blood cells (erythrocytes, leukocytes, monocytes, platelets) and fibrin filaments and intra alveolar hemorrhages. In the lungs of patients with COVID-19, severe endothelial damage is observed associated with the presence of intracellular virus and damaged cell membranes. Histological analysis of pulmonary vessels in patients with this disease shows widespread thrombosis with microangiopathy. Alveolar capillary microthrombi are observed 9 times more often in patients with COVID-19 than in patients with influenza \( p < 0.001 \). In the lungs of patients with COVID-19, angiogenesis is enhanced, with growth of new vessels 2.7 times more intense than in the lungs of patients with influenza \( p < 0.001 \), mainly due to the mechanism of invagination rather than external growth, which leads to rapid occlusion of the alveoli from the inside (Ackermann et al., 2020).

It is worrying that in the series described, this complication occurred in patients despite routine heparin prophylaxis. With the more aggressive variant of thrombotic complications observed in lethal cases, extensive microthrombosis of both lungs is noted, extending to the entire respiratory area (Raj et al., 2021). A more detailed follow-up revealed diffuse and severe endothelial and alveolar damage with disruption of alveolar membranes, perialveolar microangiopathy, and widespread microthrombosis with intra alveolar hemorrhages.

**THE FIBRINOLYSIS SYSTEM AND ITS ROLE IN HEMOSTASIS DISTURBANCES IN COVID-19**

It is clear that in disorders of hemostasis and in the enhancement of blood coagulation potential, the fibrinolytic system plays an important role, which is associated not only with blood coagulation, but also with the renin-angiotensin system (RAS). In fact, the main component of the RAS, ACE2, acts as a natural receptor for SARS-CoV-2 and other similar viruses. After binding of the virus to ACE2, angiotensin II remains in excess, acting as a powerful stimulator of PAI-1 (plasminogen activator inhibitor 1), the main inhibitor of fibrinolysis. At the same time, elevated levels of bradykinin stimulate the main natural fibrinolytic agent, tissue plasminogen activator (TPA) (Kwaan, 2020). Thus, fibrinolysis can undergo simultaneous or increased activation of TPA or inhibition of PAI-1, causing a prothrombotic or prohemorrhagic state, depending on the sites and phases of the biological process. It is the increase in locally increased activity of TPA that explains intra alveolar bleeding, while phases or areas with increased inhibitory activity of PAI-1 contribute to the preservation or stimulation of microthrombosis and lead to pulmonary fibrosis. Some authors have demonstrated complete disabling of fibrinolysis in the blood in severe COVID-19 (Wright et al., 2020). Thus, the unstable balance between activation and inhibition of fibrinolysis may explain the coexistence of thrombotic and hemorrhagic features in the lungs and other organs, and the term “pulmonary thrombosis” can now be attributed to COVID-19-induced pulmonary microthrombosis (Thachil and Srivastava, 2020).

**P-SELECTIN AND ITS ROLE IN HEMOSTASIS**

Selectins form the family of Ca\(^{2+}\)-dependent carbohydrate-binding proteins that mediate the initial stage of leukocyte involvement in the inflammatory process. Therefore, blocking selectins is considered a promising therapeutic approach for the treatment of acute and chronic inflammatory diseases. The selectin family includes E-, L- and P-selectins (Larsen et al., 1992; Setiadi and McEver, 2008).

E-selectin, a glycoprotein located on the cell surface, which belongs to the class of adhesive proteins, is produced by endothelial cells and, in tissue damage, for example, during inflammation or infection, pro-
An internal reserve of this protein, which is rapidly expressed on the cell surface immediately after the onset of inflammation. At an early stage of inflammation, P-selectin ensures rapid adhesion of neutrophils and monocytes to activated vascular endothelium, as well as leukocytes to activated platelets (Honn and Tang, 1992).

To determine the level of expression of P-selectin on the cell surface as a marker of platelet activation, flow cytometry is used with antibodies labeled with various fluorescent dyes (Frenette et al., 2000; Advukhina et al., 2012). This method makes it possible to judge the functional activity of blood cells and individual components, in particular, P-selectin.

It is now generally accepted that inflammation directly affects thrombosis and that thrombosis is also a pro-inflammatory event. This strong bond is partly due to P-selectin, which functions not only when expressed on the surface of activated platelets and endothelial cells, but also when cleaved to form its soluble form, called sP-selectin. sP-selectin is a glycoprotein of dense platelet granules with a molecular weight of 190 kDa. This form of P-selectin, found in serum and plasma, is a product of proteolysis and is most likely a soluble fragment that lacks a transmembrane region. However, clinical evidence linking sP-selectin to athrogenesis is sparse and inconsistent. However, since sP-selectin is found in plasma and serum, and modulates the interaction between blood cells and endothelium, it can also be considered as a valuable biomarker for both diagnosing and predicting the need for intensive treatment for COVID-19.

In the 1990s it was shown that when bound to its ligand on leukocytes, P-selectin mediates the initial movement of leukocytes to sites of inflammation (Celi et al., 1997). The main P-selectin ligand, PSGL-1, is a homodimeric mucin, a 240 kDa homodimer consisting of two 120 kDa polypeptide chains (Patrik, 2004).

Thus, it can be said that the membrane form (on activated endothelial cells, and activated platelets), and the soluble form of P-selectin are agonists of thrombotic and inflammatory processes. At the same time, P-selectin activates monocytes for the synthesis of tissue factor (Celi et al., 1994).

Given these data, it was necessary to explore the possible role of P-selectin in attracting leukocytes to the lungs during ARDS (Neri et al., 2020). Infusion of monoclonal antibodies to P-selectin dramatically reduced lung injury in a rat model of ARDS. It has been shown that the sP-selectin level is elevated in ARDS patients compared to controls and in non-survivors compared to survivors. More recently, in a genome-wide association study of SELPLG (selectin P ligand gene) the authors reported a significant reduction in lung injury in mice exposed to monoclonal antibodies to P-selectin ligand. SELPLG has been recognized as a new gene for susceptibility to ARDS (Bime et al., 2018; Frenette et al., 2000).
An important aspect of the clinical management of ARDS is early recognition to prevent further lung injury during mechanical ventilation, but there are currently no specific genetic or non-genetic biomarkers to identify those who are more likely to develop ARDS or to explain observed differences in health status. Therefore, there is a need to identify markers of increased susceptibility to ARDS. The SELPLG gene and PSGL-1 which it encodes, is a potential new therapeutic target for reducing the pathogenicity of ARDS (Bime et al., 2018).

The expression of P-selectin is not limited to platelets and endothelial cells, P-selectin expression on pneumocytes should also be considered. This expression was observed in autopsy specimens from a patient who died from SARS-CoV in 2002 (Yen et al., 2006). These data are consistent with the assumptions about the pathogenetic role of P-selectin and deserve further study, given the high incidence of thrombotic complications in patients with COVID-19. This, in turn, is consistent with P-selectin-mediated activation of intravascular coagulation.

The COVID-19 pandemic has prompted numerous studies aimed at exploring potential therapeutic approaches. It should be taken into account that increased expression of P-selectin by endothelial cells was observed earlier and is one of the reasons for the increased adhesion of platelets and leukocytes to endothelial cells. This was shown in studies conducted on transgenic mice with sickle cell anemia (Wood et al., 2004), in which there is an increase in adhesion of platelets and leukocytes to endothelial cells. Currently, the possibilities of using monoclonal antibodies to P-selectin as medicines are being considered. With the blockade of this protein by monoclonal antibodies, the adhesion of blood cells is significantly reduced. This is also observed in isolated vessels of patients with this disease. Thus, sickle cell anemia is a pathological condition in which there is an increased proinflammatory and procoagulant state in the microcirculation, and P-selectin is a key factor, as in COVID-19 (Matsu et al., 2001; Fallerini et al., 2021).

P-SELECTIN IS AN EARLY BIOMARKER OF THROMBOTIC COMPLICATIONS IN COVID-19

Among hospitalized patients with COVID-19, high rates of changes in inflammatory and coagulation biomarkers correlate with a poor prognosis (Lopez Castaneda et al., 2021). Physicians at a public hospital in Mexico assessed inflammatory and procoagulant biomarkers in patients with COVID-19. In the blood plasma of patients of varying severity, and healthy volunteers, they analyzed inflammatory and coagulation biomarkers, including D-dimer, IL-6 and -8, PAI-1, P-selectin and VWF (von Willebrand factor). Standard laboratory and clinical biomarkers were also included in the group comparison. Analysis of the results showed that the plasma concentrations of all prothrombotic and proinflammatory biomarkers were significantly higher in patients with a fatal outcome. A significant difference was found in the levels of IL-6, PAI-1 and P-selectin in non-severely ill and healthy volunteers compared with patients with severe COVID-19 who died ($p < 0.001$). VWF levels were also significant ($p < 0.0001$) and differed between the severe (153.5 ± 24.3 UI/dL) and non-severe (133.9 ± 20.2 UI/dL) patient groups. White blood cell and glucose levels were also significantly elevated in patients with severe COVID-19. Similar results have been reported in other clinical trials (Agrati et al., 2021a). The authors believe that the concentration of P-selectin in plasma can be considered as a biomarker of this disease.

Thus, the central element of the pathology of COVID-19 is the dysregulation of P-selectin, which is a biomarker of inflammatory coagulation involved in blood clotting, and which modulates the interaction between blood cells and endothelial cells. It is found inside platelets and endothelial cells, on cell membranes, and is present in plasma in a soluble form. It acts as an adhesion receptor, its soluble form (sP-selectin) plays an important role in modulating the interaction between blood cells and endothelial cells (Venter et al., 2020). In a special study, the relationship between sP-selectin levels and the clinical severity of COVID-19 infections was assessed. It was shown (Karsli et al., 2021) that serum levels of sP-selectin in both the mild and moderate pneumonia groups and the severe pneumonia group were higher than in the control group ($p = 0.0001$ and $p = 0.0001$, respectively). The authors conclude that sP-selectin can be used as a valuable biomarker for both diagnosing and predicting the need for intensive treatment of COVID-19 infection.

Systemic vascular damage with micro/macrophlebitis is a typical sign of the severe form of COVID-19. When investigating the association of plasma concentrations of blood clotting proteins with the occurrence of VTE in COVID-19, it was shown that nine clotting proteins were differentially expressed in patients with thromboembolism. At the same time, P-selectin showed the highest expression among the studied blood coagulation proteins, regardless of the severity of the disease. The authors believe that this confirms the importance of endothelial activation in the VTE mechanism in this disease (Fenyves et al., 2021). However, other authors believe (Gelzo et al., 2021) that endothelial damage is less relevant, since the level of E-selectin did not change, in contrast to platelet P-selectin. However, as the experience of many researchers shows, in most patients, along with coagulopathy, endotheliopathy is observed, and there is a need to strictly monitor the blood coagulation parameters of patients with varying degrees of COVID-19. Thus, when measuring inflammation, coagulation factors, and the state of the endothelium.
in mild to moderate disease, it was shown (Cacciola et al., 2021) that IL-6, TNF-α, VWF, tissue factor (TF), and tissue factor inhibitor (TFPI) are significantly increased in moderate disease, as are D-dimer, thrombin—antithrombin complex, platelet factor P4, thromboglobulin, P-selectin, and platelet adhesion. All patients with moderate COVID-19, compared with patients with mild COVID-19, had shorter clotting time and clot formation time, high clot density and a low percentage of lysis after 30 minutes. The authors conclude that even with moderate severity, patients have deep inflammation associated with severe endotheliopathy and clotting pathology. Such monitoring will allow the timely use of appropriate anticoagulants, improve the prognosis of moderate COVID-19, and prevent the development of the severe form of the disease.

P-selectin undoubtedly contributes to the adhesion of pathological and possibly healthy erythrocytes to the damaged endothelium, as well as to neighboring erythrocytes and to hyperactivated platelets. Clear changes in gene expression profiles of circulating platelets in patients with COVID-19 were found (Manne et al., 2020). They also showed that platelets from COVID-19 patients aggregate faster and increase the spread of fibrinogen and collagen. In addition, the authors hypothesized that the increase in platelet activation and aggregation may be partly due to thromboxane generation.

Based on the studied literature, it can be assumed that there is a causal relationship between elevated serum ferritin and P-selectin concentrations, and platelet hyperactivation and their interaction with erythrocytes (Grobler et al., 2020; Venter et al., 2020). Much has been written on the participation of iron in the development of pathologies arising from COVID-19, so we will only note here that serum ferritin levels are elevated in blood samples from COVID-19, as it is known as a marker of damaged cells (Venter et al., 2020). Its presence in the bloodstream can cause pathology of red blood cells, platelets, and plasma fibrinogen. Thus, P-selectin, serum ferritin, and blood cell abnormalities, in addition to thrombotic complications, may contribute to the reduction in oxygen saturation commonly seen in COVID-19.

When studying the expression of some transmembrane proteins in platelets, it was shown that during infection with SARS-CoV-2, a significant increase in the expression of these proteins was found, compared to control. The presence of such platelets (hyperactive phenotype) contributed to hypercoagulability (Bon-giovanni et al., 2021).

Analyzing a huge body of literature, we have come to the conclusion that platelet hyperactivity plays a leading role in the pathology of COVID-19. Progressive respiratory failure is regarded as the main cause of death in patients with COVID-19, and may be largely associated with microthrombi in the circulatory system and, in particular, in the lungs. P-selectin may be an important early risk marker for severe vascular disease. Observations of structural changes in plasma showing microclots and large platelet aggregates may help clinicians plan anticoagulant therapy early in care (Venter et al., 2020).

New evidence suggests that SARS-CoV-2 can infect endothelial cells with an associated immune response and subsequent activation of inflammatory pathways, leading to endothelial dysregulation, leukocyte activation, complement deposition, and platelet consumption.

The challenge is to quickly find therapeutic approaches for urgent care of patients with COVID-19. The key clinical sign of the severe form of the disease seems to be a strong prothrombotic state, which is associated with an increased incidence of arterial, venous and microvascular thrombosis, as well as lethal outcomes. These pathways can provoke a prothrombotic state (immunothrombosis), which can lead to serious thrombotic complications. Platelet/leukocyte aggregates may be markers of the anti-inflammatory efficacy of antiplatelet drugs (McFadyen et al., 2020). It is important to note that the transition to early introduction of antithrombotic therapy for the prevention and treatment of thrombosis associated with COVID-19 will lead to improved outcomes for patients with COVID-19. An example is the antiplatelet agent clopidogrel or Plavix, which differs from other antiplatelet agents because it appears to be more effective at blocking platelet surface P-selectin expression and more effective at reducing platelet/leukocyte aggregation than aspirin or GPIIb/IIIa receptor inhibitors (Klinkhardt et al., 2002, 2003). The success of the next generation of antiplatelet agents is likely to depend on their ability to prevent platelet activation.

In addition to antiplatelet agents, anticoagulants that are now successfully in use in clinical practice, in particular, anticoagulants directly inhibiting factor Xa, - Xarelto or rivaroxaban, have also shown high efficiency. It is known that the activation of factor X with the formation of factor Xa (FXa) through the internal and external pathways plays a central role in the blood coagulation cascade. FXa directly converts prothrombin to thrombin via the prothrombinase complex, which ultimately leads to fibrin clot formation and platelet activation via thrombin. One FXa molecule is capable of producing more than 1000 thrombin molecules. In addition, the reaction rate of prothrombinase-bound FXa is 300000 times faster than that of free FXa, which causes an explosive increase in thrombin formation—it is this “explosion” that selective FXa inhibitors are able to stop, which, therefore, reduces activation platelets (https://www.vidal.ru).
CONCLUSIONS

An analysis of the extensive literature on the significance of P-selectin in the development of severe, often lethal, disorders in the blood coagulation system and the functional activity of endothelial cells suggests a central role of the interaction of the endothelium and platelets as part of the complex pathogenic mechanism of COVID-19, leading to local activation of the hemostasis system and forming pulmonary blood clots. It is believed (Agrati et al., 2021b) that larger-scale studies are needed to investigate the significance of P-selectin as a marker of platelet and endothelial activation, to determine the degree of risk and adverse prognostic outcomes. This type of study offers the opportunity to unravel the mechanisms governing platelet activation and endothelial injury, as well as to identify specific therapies aimed at minimizing endothelial activation and reducing the risk of thrombosis. However, the existing literature on the role of P-selectin in patients with COVID-19 suggests that it may be a valuable biomarker for predicting clinical outcomes. Based on the experience of numerous clinics and understanding the difficulty of standardizing methods and research results, it can be seen that an increase in the expression of P-selectin on damaged endothelial cells and activated platelets contributes to a prothrombotic state that leads to immune thrombosis and thromboinflammation (Agrati et al., 2021b).

Clinical experience suggests that the use of drugs (anticoagulants, antiplatelet agents) may be useful in the treatment of patients with COVID-19 and they can be included in treatment protocols. These drugs include aspirin and curantyl, or dipyridamole.

Dipyridamole (DIP) is an antiplatelet drug that acts by inhibiting phosphodiesterase and increasing intracellular levels of cAMP/cGMP (Golubeva, 2020). DIP supplementation has been associated with significantly lower D-dimer concentrations, and higher lymphocyte and platelet counts in the circulation. This markedly improved clinical outcomes in a study involving 31 patients with COVID-19 compared to controls (Liu et al., 2020). However, the effectiveness of DIP in hospitalized patients with COVID-19 requires further study.

Aspirin, well-known since 1890, is an inexpensive, widely available drug that, at low doses, irreversibly inhibits the cyclooxygenase-1 (COX-1) enzyme, which is necessary for the formation of thromboxane A2 and pro-inflammatory prostaglandins (Golubeva, 2020). Aspirin has been shown to prevent both arterial and venous thrombotic events in people infected with SARS-CoV-2 and reverse platelet hyperactivity in vitro (Baigent et al., 2009; Manne et al., 2020). Although the effect of aspirin on clinical outcomes in patients with community-acquired pneumonia has been studied, and preliminary results have been obtained on its potential usefulness in reducing mortality, data on the effectiveness of antiplatelet drugs in COVID-19 are clearly lacking (Chow et al., 2021). In addition, any potential benefit of antithrombotic treatment in patients with COVID-19 may depend on the timing of treatment initiation, especially if clots have already formed by the time of hospitalization. Work is being carried out in several directions. Some pharmaceutical companies and research centers are trying to develop new drugs to fight COVID-19, while others are trying to determine whether any existing drugs can be effectively repurposed.

The main difficulties that clinicians face in treating patients with this new disease are primarily related to the presence of coronavirus mutations. The emergence of new strains requires a rapid change in treatment tactics, increased control to reduce contacts between infected people, the search for new drugs to help patients, and the combined efforts of doctors from different countries to fight the pandemic.

COMPLIANCE WITH ETHICAL STANDARDS

The author declares no conflicts of interest.

All experiments were carried out in accordance with the ethical principles and regulations recommended by the European Science Foundation (ESF) and with a declaration of humane treatment of animals.

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