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Review

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Endothelial Dysfunction in Trauma: Pathogenesis, Clinical Significance, Diagnosis and Treatment

V.V. Matyukhin[1, 2] ✉, S.S. Maskin[1], V.V. Aleksandrov[1], G.P. Dudchenko[1], O.V. Ostrovsky[1], M.N. Alimov[2], O.V. Werle[1]

Department of Hospital Surgery
[1] Volgograd State Medical University
Pavshikh Bortsov Sq. 1, Volgograd, Russian Federation 400131
[2] Municipal Clinical Emergency Hospital No. 25
Zemlyachki Str. 74, Volgograd, Russian Federation 400138

✉ **Contacts:** Viktor V. Matyukhin, Candidate of Medical Sciences, Associate Professor, Department of Hospital Surgery, Volgograd State Medical University.
Email: victor.matyukhin@gmail.com

ABSTRACT Severe trauma is a major medical and social problem. Severe injures is the leading cause of death in people under the age of 44. Many trauma survivors become disabled. Apart from immediate death of victims at the prehospital stage, in-hospital mortality is usually due to hemorrhagic shock, coagulopathy, systemic inflammation, both infectious and non-infectious nature, and multiple organ failure. In the last decade, a significant role of endothelial dysfunction in the development of these pathological processes has been recognized. Endothelial dysfunction refers to excessive activation of the endothelium, accompanied by multisystem manifestations. This literature review presents current data on the physiology of normal endothelium, the pathogenesis of endothelial dysfunction in trauma, its role in the development of systemic inflammation, increased vascular permeability and coagulopathy, and methods for its diagnosis and correction.

Keywords: endothelium, endothelial dysfunction, endothelial glycocalyx, coagulopathy, syndecan-1, thrombomodullin, von Willebrand factor, plasma, tranexamic acid

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Affiliations

Viktor V. Matyukhin	Candidate of Medical Sciences, Associate Professor, Department of Hospital Surgery, Volgograd State Medical University; https://orcid.org/0000-0002-8195-6172, victor.matyukhin@gmail.com; 40%, article concept development, data collection, text writing
Sergey S. Maskin	Doctor of Medical Sciences, Full Professor, Head, Department of Hospital Surgery, Volgograd State Medical University; https://orcid.org/0000-0002-5275-4213, maskins@bk.ru; 20%, article concept development, text editing
Vasily V. Aleksandrov	Candidate of Medical Sciences, Associate Professor, Department of Hospital Surgery, Volgograd State Medical University; https://orcid.org/0000-0001-8364-8934, 79178304989@yandex.ru; 10%, data collection, text writing
Galina P. Dudchenko	Doctor of Biological Sciences, Associate Professor, Professor, Department of Theoretical Biochemistry with a Course of Clinical Biochemistry, Volgograd State Medical University; https://orcid.org/0000-0002-3027-3355, dgalina@mail.ru; 10%, text editing
Oleg V. Ostrovsky	Doctor of Medical Sciences, Full Professor, Head, Department of Theoretical Biochemistry with a Course of Clinical Biochemistry, Volgograd State Medical University; https://orcid.org/0000-0001-9827-9545, ol.ostr@gmail.com; 10%, text editing
Maxim N. Alimov	Surgeon, Surgical Department, Municipal Clinical Emergency Hospital No. 25; https://orcid.org/0000-0002-6313-0908, qwmajlo@gmail.com; 5%, data collection

Olga V. Werle — Assistant, Department of Theoretical Biochemistry with a Course of Clinical Biochemistry, Volgograd State Medical University;
https://orcid.org/0000-0003-0853-0148, verle_olga@mail.ru;
5%, data collection

ALI — acute lung injury
cfDNA — cell-free DNA
DAMP — danger-associated molecular patterns
ED — endothelial dysfunction
EG — endothelial glycocalyx
EV — extracellular vesicles
FFP — fresh frozen plasma
HS — hemorrhagic shock
ISS — Injury Severity Score
MA — maximum amplitude
MAP — mean arterial pressure
MOF — multiple organ failure
mtDNA — mitochondrial DNA
SDC1 — syndecan-1
TEG — thromboelastography
TM — thrombomodulin
tPA — tissue plasminogen activator
TXA — tranexamic acid
VWF — von Willebrand factor
WHO — World Health Organization

INTRODUCTION

Trauma is the leading cause of death and disability. Every year, more than 5 million people die worldwide as a result of injuries. These fatal outcomes account for 9% of all deaths, more than HIV/AIDS, malaria and tuberculosis combined. Trauma remains the leading cause of death for people aged 1 to 44 years. Another 20 to 50 million people suffer non-fatal injuries, which in many cases lead to disability. Road traffic injuries remain the main type of trauma, claiming the lives of 1.35 million people per year [1–4]. In recent years, there has been a tendency towards an increase in the percentage of deaths associated with transport and falls from height (catatrauma); and an increase in the average age of injured patients has also been noted [3, 5].

In the Russian Federation, according to the World Health Organization (WHO), 137,633 people died from injuries in 2019, which was 7.7% of all deaths. In road traffic accidents (according to WHO data for 2016), 259, 69 people died (18 per 100,000 population) [4, 6].

Bleeding accounts for 30–40% of trauma deaths, and 33 to 56% of these deaths occur at the prehospital stage (immediate death) [7]. Early mortality (within 48 hours after injury) was also associated with bleeding in 42–51% of cases [8]. Van Breugel J.M.M. et al. (2020) note that hospital mortality associated with bleeding has increased in recent years. The authors attribute this to the implementation of Advanced Trauma Life Support algorithms and rapid (within 60 minutes) delivery of victims to the hospital [1]. Late hospital mortality (7 days after injury) was 61–80% due to infectious complications or multiple organ failure (MOF), with the relative risk of late mortality increasing by 2.2% per patient per year [5, 8].

For the most severely injured patients requiring emergency surgical care, overall mortality has changed little, and remains close to 50%. The development of regional trauma systems, the use of damage control tactics, early initiation of blood transfusion, and the use of tranexamic acid have led to the fact that victims with more severe injuries and a deeper phase of shock are admitted to the clinic. Despite adequate surgical intervention and active intraoperative intensive care measures, 25% of victims with traumatic bleeding still die due to the development of pathological processes that are not fully understood [9, 10].

Over the years, many explanations were proposed for early and late death after severe trauma. Most of them include manifestations of sympathetic hyperactivity, endotheliopathy, trauma-induced coagulopathy, hyperinflammation, immune dysfunction, energy deficiency, and multiple organ failure [11].

Recently, one of the main roles in the pathogenesis of early and late complications after trauma was attributed to changes occurring in the vascular endothelium. The endothelium and endothelial glycocalyx (EG) are involved in circulation, hemostasis, vascular tone, and organ function in a complicated way. Endothelial damage during trauma contributes to the development of trauma-induced coagulopathy, shock-induced

endotheliopathy, and multiple organ dysfunction syndrome [12].

The aim of the review is to present modern data on endothelial dysfunction in trauma, the pathogenesis of its development, clinical significance, diagnostic principles, and correction methods.

STRUCTURE AND FUNCTIONS OF THE ENDOTHELIUM

The endothelium lining the blood vessels of the vascular bed is a continuous single-row cell layer weighing 1 kg, and with a total surface area of 4000–7000 m2 [13]. Endothelial cells have specific features in the vessels of various organs and surrounding tissues. The following morphological types of endothelium have been well studied: continuous (blood-brain barrier), fenestrated (exocrine and endocrine glands, gastric and intestinal mucosa, glomeruli and tubules of the kidneys), sinusoidal or discrete (liver, spleen and bone marrow) [14].

The endothelium is not an inert barrier, but rather a functionally highly active cell layer involved in a wide range of homeostatic processes, including control of vasomotor tone, transport of cells and nutrients, maintenance of blood rheology, and growth of new blood vessels.

The main functions of the endothelium can be identified as follows:

1. Regulation of vascular wall permeability. The endothelium is a specialized epithelium that acts as a semipermeable barrier between the two main internal environments: blood and interstitial tissue fluid. The endothelium with its basement membrane functions as a mediator and actively controls the bidirectional exchange of molecules through simple and active diffusion, receptor-mediated endocytosis, transcytosis, and other mechanisms [15];
2. Regulation of vasomotor tone (secretion of vasoconstrictors: angiotensin II, endothelin-1, etc., vasodilators: nitric oxide (NO), prostaglandin I2 (prostacyclin), etc.);
3. Regulation of vascular smooth muscle growth (platelet-derived growth factor, basic fibroblast growth factor, etc. are stimulated; NO, transforming growth factor β, etc. are inhibited);
4. Regulation of blood coagulation (plasminogen activator inhibitor, thromboxane A2, tissue factor, von Willebrand factor, etc. are procoagulants; prostacyclin, NO, thrombomodulin, heparin-like proteoglycans, tissue plasminogen activator, etc. are anticoagulants);
5. Regulation of oxidation-reduction reactions (NO, bradykinin, cyclooxygenase are prooxidants; angiotensin-II, endothelin-1, cytokines, etc. are antioxidants);
6. Regulation of inflammation (leukocyte adhesion molecules, selectins, intercellular adhesion molecules, platelet activating factor, etc. – proinflammatory activity; NO, bradykinin, prostacyclin, etc. – anti-inflammatory activity) [16].

Endothelial cell activation. Endothelial cell activation represents a spectrum of responses and occurs under both physiological and pathophysiological conditions. Endothelial cells receive signals from the extracellular environment (soluble mediators, intercellular interactions, oxygenation, hemodynamic forces, temperature, pH), and respond to them by changing vasomotor tone, permeability, hemostatic balance, cell lifespan, cell proliferation, and inflammation. Inactive endothelial cells typically exhibit anticoagulant, antiadhesive, and vasodilator properties, whereas activated endothelial cells exhibit procoagulant, proadhesive, and vasoconstrictor properties. Most types of endothelial responses probably evolved as adaptive mechanisms designed to serve and protect the host organism. When these reactions go beyond the point leading to maladaptation (or dysfunction), we can speak of endothelial cell dysfunction. Thus, the term of "endothelial dysfunction" (ED) should be understood as systemic manifestations of endothelial cell activation, characterized by disruption of critical homeostatic mechanisms [13, 16].

PATHOGENESIS OF ENDOTHELIAL DYSFUNCTION IN TRAUMA

Increased activity of the sympathoadrenal system, proportional to the severity of trauma and traumatic shock, leads to activation and damage of the endothelium. This process is realized by exocytosis of catecholamines (primarily norepinephrine) and enzymatically active tissue plasminogen activator (tPA) from the nervi vasorum, both into the vascular wall and directly into the microcirculatory bed [17, 18].

The release of catecholamines (in particular, the vasoconstrictor effect of norepinephrine) causes endothelial damage, glycocalyx cleavage, and de-

endothelialization of perfused vessels. Activated/damaged endothelium promotes thrombosis by causing microvascular occlusion. Together with increased capillary permeability, perivascular edema, and vasoconstriction, these vascular reactions provoke progressive tissue hypoperfusion, hypovolemia, hypoxic organ damage, and, – completing a vicious circle – increased sympathoadrenal activation. Increased tone of the hypothalamic-pituitary-adrenal system also elevates the level of circulating catecholamines in plasma [19].

tPA, in turn, exhibits profibrinolytic activity through enzymatic activation of plasminogen.

ED also leads to impaired synthesis of thromboxane A2 and leukotrienes. Decreased availability of thromboxane A2 and leukotrienes in the microcirculation impairs vasoconstrictor capacity and thus may contribute to the progression of shock in patients with ED [20].

A work by Krocker J.D. et al. (2022) showed a difference in the expression of 52 proteins, including danger-associated molecular patterns (DAMPs), proteins involved in endothelial activation, coagulation, inflammation, oxidative stress, etc., in victims with traumatic ED, as opposed to patients with non-ED trauma [21].

The corresponding endothelial and hemostatic changes depend on the severity of injury and traumatic shock: from physiological hemostasis to hypercoagulation in mild injury, to hypocoagulation in moderate injury, and finally to hyperfibrinolysis in severe injury [22, 23].

In recent years, much attention has been paid to the role of extracellular vesicles (EVs) in the pathogenesis of ED. EVs are a heterogeneous group of cell-derived membrane structures, including exosomes and microvesicles. EVs originate from many different cell types and intracellular structures, and perform different metabolic functions or roles depending on the parent cell. EVs are currently considered as an additional mechanism of intercellular communication, allowing cells to exchange proteins, lipids and genetic material. The presence of a metabolically active outer membrane is a distinctive feature of all EVs [24]. Administration of EVs from patients with severe trauma to mice resulted in more severe ED, histopathological lung damage, increased pulmonary vascular permeability, and intravascular fibrin deposition, in contrast to mice that were injected with EVs from victims with mild injuries [25].

EVs originating from different cells exert opposite effects on the development of ED. Leukocyte EVs enhance the manifestation of ED [26]. In contrast, mesenchymal stromal cell EVs promote restoration of local homeostasis, reduce inflammation and oxidative stress, have an antiapoptotic effect, and inhibit endotheliopathy [27]. Platelet EVs in an in vivo model attenuate vascular permeability induced by vascular endothelial growth factor, restore endothelial cell connections, reduce the manifestations of ED and, by enhancing whole blood aggregation, reduce the degree of blood loss [28].

Moreover, the development of ED is not accompanied by an increase in the content of endothelial EVs in the blood, which apparently indicates the leading role of EG destruction, but not damage or apoptosis of endothelial cells in the development of ED [29].

CLINICAL SIGNIFICANCE OF ENDOTHELIAL DYSFUNCTION IN TRAUMA

The most significant pathological manifestations of ED in trauma are as follows: increased vascular permeability, systemic inflammation, and traumatic coagulopathy.

Impaired permeability. By forming a barrier that retains plasma proteins, especially albumins, in the vascular bed, the endothelium plays a key role in controlling vascular permeability and regulating the colloid osmotic pressure necessary for adequate perfusion and oxygen supply to organs and tissues.

In normal conditions, endothelial barrier function is mainly supported by extracellular structures such as the glycocalyx, extracellular matrix, and intercellular junctions. The EG serves as a barrier protecting endothelial cells from spontaneous adhesion of leukocytes and platelets; and the negative charge of the glycocalyx repels red blood cells and macromolecules. In contrast, neutralization of the negative charge of the glycocalyx can induce vascular permeability. Adjacent endothelial cells are linked by junctional proteins such as gap junctions, tight junctions, and adherens junctions. Adherens junctions are of particular importance in controlling endothelial barrier function. Adherens junctions contain vascular endothelial cadherin (VE-cadherin), which

connects adjacent cells via its extracellular domain. Some inflammatory mediators, such as histamine, thrombin, or vascular endothelial growth factor, increase permeability by influencing VE-cadherin adhesion [30].

Tissue damage and shock lead to increased activity of RhoA GTPase (a family of cellular signaling proteins that regulate intracellular actin dynamics), promoting the generation of radial stress fibers and increased contractility of actomyosin, which leads to the destruction of tight and adherens junctions of the endothelium and increases its permeability [31].

Angiopoietin-1 (Agpt-1) and angiopoietin-2 (Agpt-2) are cytokine regulators of vascular endothelial integrity. In a study by Richter R.P. et al. (2019), elevated plasma Agpt-2 levels were observed in patients with tissue hypoperfusion 24 hours after injury. Elevated Agpt-2/Agpt-1 ratios in trauma were associated with adverse clinical outcomes [32].

Increased vascular permeability during trauma is in turn accompanied by the development of complications associated with tissue edema: acute lung injury and abdominal compartment syndrome [33].

Systemic inflammation. Cell damage during trauma is accompanied by the release of many endogenous factors that cause activation of the innate immune system - DAMP. Large amounts of circulating catecholamines damage the endothelium and lead to its breakdown with subsequent activation of DAMP-associated sterile inflammation [34, 35].

Cytokine release, phagocyte and granulocyte activation in the presence of NOXA (a mitochondrial protein that promotes apoptosis by disrupting the integrity of the mitochondrial outer membrane) lead to cytoskeletal changes and glycocalyx degradation. Two types of endothelial activation have been described. Activation of type I endothelial cells is typically mediated by transmembrane receptor signaling pathways such as Rho activation and elevated calcium ions. This results in the release of von Willebrand factor (VWF), which promotes platelet aggregation and the development of a procoagulant state. Activation of type II endothelial cells is mediated by stimuli that induce gene transcription and protein synthesis of cytokines, chemokines, and adhesion molecules. Consequently, type II endothelial cell activation persists longer than type I activation and induces a more robust inflammatory response. Type II activation also increases blood flow, promoting the release of plasma proteins beyond the capillaries with increased recruitment of leukocytes to the site of inflammation [36, 37].

A work by Yang Z. et al. (2022) showed a relationship between the degree of endothelial damage and activation of the complement system and coagulopathy in patients with polytrauma. The authors' logistic regression analysis, after adjusting for injury severity, showed that plasma Bb (a protein of the complement system) greater than 1.57 μg/mL, syndecan-1 greater than 66.6 ng/mL, or D-dimer greater than 6 mg/L upon admission to the hospital were associated with a 6-fold increase in the risk of MOF/death, and a 4-fold increase in the risk of infectious complications [38].

Traumatic coagulopathy. Traumatic coagulopathy is associated with significant mortality. In addition to the severity of the initial injury, the hemocoagulation response to trauma depends on the following factors: time from injury to treatment, age, gender, level of catecholamine secretion, platelet dysfunction, endotheliopathy, background anticoagulant therapy, activity of the coagulation systems (tissue factor), anticoagulation (activated protein C) and fibrinolysis [39]. Hemorrhagic shock (HS) and cellular ischemia affect the endothelium, activating to varying degrees both its procoagulant and anticoagulant responses [40, 41].

Immediately after injury, thrombin formation, as well as the release of vasoactive catecholamines (adrenaline), hormones (vasopressin) and inflammatory mediators (TNF-α, IL-1) lead to endothelial activation and the creation of a localized prothrombotic environment favorable for recovery in mild to moderate injuries. In severe and massive injuries, the human body is faced with the need to simultaneously control both excessive blood loss and microvascular thrombosis [42, 43]. Severe endotheliopathy, initiating microthrombogenesis, leads to the development of a syndrome similar to thrombotic thrombocytopenic purpura with consumption thrombocytopenia, microangiopathic hemolytic anemia, and multiple organ dysfunction syndrome [44].

Gradually, the increasingly procoagulant endothelium shifts the hemostasis system toward anticoagulation, associated with the development of

a kind of "autoheparinization" due to the release of endothelial glycocalyx components into the bloodstream: heparan sulfate and chondroitin sulfate, which in turn increase the activity of antithrombin and thrombomodulin. Endothelial damage also causes degranulation of Weibel-Palade bodies containing both procoagulant (VWF) and profibrinolytic (tPA, angiopoietin-2) agents. All this ultimately leads to an imbalance in the hemostasis system and the development of severe coagulation failure. These phenomena can explain the fluctuations in the thromboelastography (TEG) profile (normal, hypercoagulation, hypocoagulation, and hyperfibrinolysis) [42]. In this case, rapid depletion of fibrinogen reserves leads to the formation of a loose clot, abnormally long R time (reaction time is the distance from the start of the recording to the place where the TEG branches will be expanded by 1 mm) and a decrease in the MA/R ratio (MA is the maximum amplitude - the greatest distance over which the TEG branches diverge). The MA/R ratio ⩽11 was characterized by an increased risk of death, reduced levels of thrombin and fibrinogen [45]. In a study by Richter R.P. et al. (2022), it was found that victims with a clot lysis percentage 30 minutes after reaching maximum clot density (according to TEG) of less than 0.9%, and an increased content of D-dimers had a greater severity of injury (including severe head injuries), a significant increase in the content of endotheliopathy markers, a high risk of developing MOF and death [46].

It is believed, that hypocoagulation and hyperfibrinolysis that occur in severe trauma may be a compensatory counterbalance to the activated, coagulation-promoting endothelium in order to maintain microvascular patency. Since the physiological endothelium acts as an antithrombogenic surface that resists blood coagulation, in ED, roles may change to procoagulant endothelium with hypocoagulant/hyperfibrinolytic blood state in an attempt to balance hemostasis, reduce blood viscosity, and restore perfusion [47].

DIAGNOSTICS OF ENDOTHELIAL DYSFUNCTION

Syndecan-1. The most common method for assessing the severity of ED is the determination of the level of syndecan-1, a degradation product of EG [48].

The EG is a complex and important structure located on the inner surface of all blood vessels. EG plays an important role in normal vascular homeostasis, including the control of fluid exchange across the vascular barrier. Loss or degradation of EG affects vascular permeability and tone, inflammation and coagulation processes. Proteoglycans form the main framework of EG, and consist of a core protein and covalently attached glycosaminoglycan chains. EG contains 2 major proteoglycans: syndecan and glypican.

Syndecans are named based on the Greek word "syndein", meaning "to bind together". Syndecans, found on the surface of most cells in the body, are transmembrane proteins consisting of extracellular, transmembrane, and cytosolic domains. In vertebrates, four subtypes of syndecan are known, but EG mainly contains syndecan-1 (SDC1) [49].

Trauma always causes harm to the EG due to a combination of inflammation and vascular damage, with an increase in the concentration of EG components in plasma, such as hyaluronic acid, heparan sulfate, chondroitin sulfate and SDC1 [50]. Rahbar E. et al. (2015) observed an increase in the content of all four main components of EG in the plasma of patients with trauma compared to the control (healthy) group: chondroitin sulfate - 31.7 versus 21.2 U/L, heparan sulfate - 175.8 versus 121.9 ng/ml, hyaluronic acid - 946.7 versus 618.6 ng/ml, and SDC1 - 245.8 versus 31.6 ng/ml [51]. According to an experiment by Wallen T.E. et al. (2022), a significant increase in SDC1 was observed already 1 hour after combined injury accompanied by HS [52].

The concentration of SDC1 in the blood plasma of victims upon hospitalization, after adjustment for age and injury severity, is an independent predictor of mortality. Patients with SDC1 concentrations above average values also had elevated levels of inflammatory markers, signs of ED and fibrinolysis [53]. Thus, according to Wade C.E. et al. (2019), victims with signs of ED had an elevated SDC1 level of 230 ng/ml (158-293 ng/ml) compared to patients without endotheliopathy - 19 ng/ml (14-25 ng/ml) [54]. Patients with high circulating SDC1 levels had high levels of catecholamines, IL-6, IL-10, DNA fragments in complexes with histones, nuclear non-histone proteins, thrombomodulin, D-dimer, and plasminogen activators. A 3-fold increase in mortality (42% vs. 14%) was also noted, despite comparable injury severity according to ISS [55].

SDC1 levels were significantly elevated in patients with coagulopathy - 33.7 ng/ml (21.6–109.5 ng/ml) compared to patients without coagulopathy - 29.9 ng/ml (19.2–39.5 ng/ml). SDC1 concentration of at least 30.5 ng/ml in plasma of patients with traumatic brain injury positively correlated with the development of coagulopathy [56]. SDC1 concentration of at least 40 ng/ml in victims was associated with greater severity of injury, an increased need for blood transfusions – 71.7% versus 36.4% in patients with SDC1 levels less than 40 ng/ml, the incidence of complications and 30-day in-hospital mortality – 24.6% versus 12.1% with similar physiological parameters at the time of hospitalization [57]. SDC1 levels 4 hours after hospitalization in patients who subsequently developed sepsis averaged 165 ng/mL compared with 70 ng/mL in patients without sepsis [58].

However, patients with the same injury severity may show significant differences in the degree of ED measured by SDC1, since the endothelial response to injury is heterogeneous and most likely due to a genetic component. Henriksen H.H. et al. (2020, 2023) identified at least 4 phenotypes of shock-induced endotheliopathy that were independent of SDC1 levels (except for 1 phenotype) [59, 60].

Although SDC1 appears to be the most well-studied marker of EG degradation in trauma, elevated plasma levels of other EG components are also significantly associated with acute traumatic coagulopathy [50].

Thrombomodulin. Thrombomodulin (TM), a membrane protein, a thrombin receptor, expressed primarily on the endothelium, plays an important role in maintaining vascular homeostasis by regulating the blood coagulation system. In a state of hypercoagulation after endothelial injury, TM is released into the intravascular space by proteolytic cleavage of the endothelial component. TM, binding to thrombin, forms a complex that accelerates the protein C activation reaction a thousandfold. While bound thrombin is excluded from the hemocoagulation system. In addition, TM functions as an inflammation regulator through various mechanisms, TM neutralizes DAMP, suppresses excessive activation of the complement system, physiologically protects the endothelium, and affects both innate and acquired immunity [61]. Thrombomodulin dose-dependently reduces fibrinolysis activity determined by the TEG method [62]. The introduction of recombinant TM is accompanied by a decrease in in-hospital mortality by 17.7%, and 28-day mortality by 17.8% in patients with sepsis associated with severe organ dysfunction, severe coagulopathy with a high content of fibrin degradation products and D-dimers in the blood [63].

The level of soluble TM increases significantly 24 hours after combined injury accompanied by HS [52]. According to Kregel H.R. et al. (2022), the concentration of soluble TM increased in victims with latent hypoperfusion phenomena to 6.0 (4.5–7.8) ng/ml, in trauma accompanied by shock – to 5.7 (4.3–8.0) ng/ml (normal value 5.1 (3.8–7.0) ng/ml) [64]. An increase in the level of soluble TM above 6.5 ng/ml was associated with a higher risk of developing acute kidney injury in patients with trauma, and correlated with its severity and duration [65]. Multiple organ failure developed in 64% of victims with TM levels greater than 9.5 ng/ml [46].

Many authors have noted a positive correlation between the content of TM and SDC1 in victims with severe trauma and ED [64, 65].

Von Willebrand factor. Von Willebrand factor (VWF) is the largest multimeric glycoprotein in plasma. VWF is mainly synthesized in megakaryocytes and endothelial cells. After synthesis, VWF multimers are either released into the bloodstream or stored in Weibel–Palade bodies in endothelial cells and in α-granules of platelets, where multimerization continues to form ultra-large multimers [66].

Weibel-Palade bodies are specific endothelial organelles containing VWF, P-selectin, and angiopoietin-2, which are involved in platelet binding, leukocyte recruitment, and inflammation modulation, respectively [67].

When endothelial cells are activated, they release stored ultralarge VWF multimers, which are rapidly cleaved on the surface of endothelial cells into small multimers by the metalloprotease ADAMTS13, which is mainly synthesized by the liver. Ultra-large VWF multimers released in response to traumatic, ischemic, and inflammatory stimuli differ from circulating in plasma VWF by molecular weight and adhesive activity [66].

VWF is an important component of hemostasis, binding platelets at sites of endothelial injury. Plasma VWF levels are significantly elevated in trauma. 85 percent of trauma patients had elevated VWF levels on admission that persisted for the first 3

days. VWF levels correlate with injury severity indices and APACHE II scores. In patients with severe trauma complicated by acute lung injury (ALI), plasma VWF levels remained significantly elevated for the first 7 days compared with the control and less severely injured patient groups. Early elevation of VWF levels and their increase by more than 450% are a prognostic factor for a fatal outcome. The VWF content in deceased victims remained elevated for up to 7 days, indicating persistent ED [66].

Trauma victims also show an increase in the content of ultra-large VWF multimers, which is a consequence of an imbalance between the increase in VWF release by endothelial cells and the decrease in both the amount and activity of ADAMTS-13. Thus, in patients with an ISS (Injury Severity Score) greater than 15, ADAMTS13 activity 24 hours after injury was lower than in victims with an ISS less than 15 [66]. There are reports of a clinical association between VWF/ADAMTS-13 dysregulation and the development of hypercoagulability that rapidly evolves into consumptive coagulopathy in patients with severe trauma, which is associated with adverse clinical outcomes [68].

Other techniques for diagnosing ED include methods of visualizing microcirculation disorders, assessing the content of extracellular DNA and serum albumin.

Sidestream dark field imaging allows obtaining information on the degree of microcirculation impairment, and provides indirect data on the degree of damage to the EG. The sublingual videomicroscopy method allows us to detect deterioration of microcirculation and tissue perfusion associated with ED against the background of traumatic HS [69, 70].

Cell-free DNA (cfDNA) was proposed as a biomarker of endotheliopathy. A significant association was noted between the amount of cfDNA and the levels of SDC1 and TM. An increase in SDC1 by 50 ng/ml and TM by 1 ng/ml was accompanied by a 15% and 20% increase in cfDNA levels, respectively. In deceased victims, the amount of cfDNA was significantly increased at the pre-hospital and in-hospital stages [71].

Traumatic ED associated with glycocalyx breakdown is accompanied by increased capillary permeability, which leads to protein extravasation. At the same time, the determination of a decrease in the albumin level can be used for early screening of ED in patients with injuries. According to Gonzalez Rodriguez E. et al. (2018), in patients with ED (defined by SDC1 level of at least 40 ng/ml), the albumin content averaged 34 g/l, while in victims without ED it was 38 g/l, respectively. Patients with low albumin levels also required more frequent blood transfusions, had fewer hospital-free days and higher mortality rates [72].

TREATMENT OF ENDOTHELIAL DYSFUNCTION

While trauma itself leads to destruction of the EG, the choice of solution for infusion therapy is of great importance. A large number of studies examining the effects of various infusion media on the course of ED in trauma note the negative effect of crystalloid solutions and the positive effect of blood products.

The administration of physiological solution to healthy volunteers resulted in an increase in the level of SDC1, which indicated degradation of EG. In addition, hypernatremia associated with the infusion of saline solution contributes to EG deterioration and the release of its products (SDC1, hyaluronic acid) [50]. The introduction of crystalloids (saline), in contrast to the use of fresh frozen plasma (FFP), was accompanied by a loss of the endothelial barrier function, a decrease in tissue perfusion, and pronounced rolling and adhesion of leukocytes [73].

An experimental study conducted by Chi Y. et al. (2022) showed that the manifestations of ED in the restrictive infusion therapy group with Ringer's lactate solution (target mean arterial pressure (MAP) - 55-60 mmHg) were lower than in the traditional therapy group (target MAP - 70-75 mmHg) [74]. In an experiment by Barry M. et al. (2022), mice that were administered Ringer's lactate showed higher pulmonary and intestinal vascular permeability 3 hours after the modeling of HS compared to mice that received FFP [75].

Blood products. Because ED develops within minutes after injury, prehospital therapy with plasma products or whole blood may be necessary to prevent or mitigate EG injury and ED development. Prehospital plasma administration improved survival in patients whose transport time exceeded 20 minutes. Prehospital blood transfusion within 15 minutes of the start of medical evacuation was also associated with improved survival [76].

Whole blood transfusion after HS reduces SDC1 release and attenuates the manifestation of ALI. However, red blood cell mass stored for more than 14 days is not able to reduce ED [77].

Plasma reduces endothelial permeability, the intensity of inflammation and edema of internal organs after HS. Plasma and prothrombin complex concentrate also restore damaged tight and adherens junctions of endothelial cells, and reduce the production of proinflammatory cytokines. Platelets also reduce vascular permeability after injury. Transfusion of balanced ratios of red blood cells, plasma and platelets reduces the rate of early death from bleeding in trauma patients [76, 78]. Early use of FFP, in contrast to the use of Ringer's lactate solution, was accompanied by a decrease in the SDC1 level from 554±93 ng/ml to 187±36 ng/ml [79, 80].

The positive effect of plasma administration is due to the ability of fibrinogen to stabilize EG [81, 82]. Fibrinogen reduces the manifestations of ED after injury by inhibiting microRNA-19b, which reduces the translation of SDC1 components by binding to the corresponding mRNA and promoting its degradation [83].

The protective effect of early plasma administration may also be due to the sphingosine-1-phosphate (metabolite of sphingomyelin) it contains. The main carriers of plasma sphingosine-1-phosphate are apolipoprotein M and albumin. Sphingosine-1-phosphate maintains the barrier function of the endothelium and EG of the microcirculatory system under conditions of HS [84].

Cryoprecipitate provides endothelial protection due to its fibrinogen and other plasma proteins. Cryoprecipitate reduces pulmonary vascular permeability, manifestations of ALI, neutrophil infiltration and macrophage activation. Gene analysis of lung tissue from mice treated with cryoprecipitate demonstrates a decrease in the expression of proinflammatory genes [85].

Although intensive FFP-based HS therapy was shown to reduce ED in trauma, administration of FFP containing complement proenzymes may enhance the inflammatory cascade. Complement activation after injury promotes hemostasis, but is associated with complications and increased mortality. Complement C4 activation plays an important role in the development of inflammation after injury, and FFP may enhance this activation. FFP therapy within the first 6 hours was associated with increased complement C4 activation at 12 and 24 hours post-injury, which was associated with the development of MOF, longer need for mechanical ventilation, and increased mortality [86].

In this regard, new drugs based on blood products are of great interest. The use of modern blood products – solvent-detergent treated plasma, lyophilized plasma, cryopreserved or lyophilized platelet products – has demonstrated their effectiveness and safety for the treatment of traumatic HS and ED [87].

Solvent-detergent-treated plasma is a pharmaceutical product with a standardized content of blood coagulation factors, devoid of antibodies involved in the pathogenesis of hemotransfusion-associated ALI, and possessing a very high level of disinfection from transfusion-transmissible infectious agents. The use of solvent-detergent treated plasma demonstrated significantly less damage to the EG and endothelial contacts, a reduction in the need for blood transfusion, the use of hemostatic agents, and the time of mechanical ventilation compared to standard FFP [88]. Lyophilized platelets not only promote hemocoagulation similar to fresh human platelets, but also reduce vascular permeability both in vitro and in vivo [89].

Tranexamic acid (TXA). Administration of TXA to trauma patients, when started early after injury, is associated with improved survival and fewer complications. The mechanisms of this protective effect include antifibrinolytic and anti-inflammatory effects. A complete understanding of the cellular mechanisms of TXA action is currently lacking.

In vitro, administration of TXA for 60 minutes after ED modeling was accompanied by a decrease in the permeability of the endothelial cell monolayer, suppressed the expression of intracellular adhesion molecules, reduced the release of SDC1 and TM, and inhibited fibrinolysis (reduced the activity of tissue-type plasminogen activator and increased the activity of plasminogen activator inhibitor-1). Administration of TXA at later stages was not accompanied by a protective effect on the endothelium [90].

TXA inhibits the release of endogenous mitochondrial DNA (mtDNA) from granulocytes and endothelial cells. MtDNA is the major component of DAMPs that causes ED and the development of systemic inflammation. In addition, TXA attenuates

the loss of endothelial monolayer integrity induced by exogenous mtDNA. TXA also stimulates mitochondrial respiration, mitochondrial biogenesis, and inhibits mitophagy [91].

The results of the use of TXA in a clinical setting to suppress the development of ED are controversial. A multicenter study conducted by Anderson T.N. et al. (2020) showed a decrease in the release of SDC1 and angiopoietin-2 in response to the administration of 2 g of TXA during the first 2 hours after injury. Moreover, the content of angiopoietin-1, TM, thrombospondin-2, intercellular adhesion molecules 1 and vascular adhesion molecules 1 did not change significantly [92].

A study by Naumann D.N. et al. (2018) did not reveal any differences in the dynamics of ED markers (SDC1 and TM) in victims with ED and MOF who received TXA at the prehospital stage [93].

Also, experimental and clinical studies are currently being conducted to evaluate the effect of corticosteroids, heparin and heparinoids (sulodexide), TNF-α inhibitors on the protection and restoration of the EG against the background of ED development after trauma [50].

An experimental study by Diebel L.N. et al. (2021) showed that estrogen (estradiol) therapy, in contrast to testosterone, mitigated the adverse effects of HS on the barrier properties of the endothelium and EG, assessed by measuring the thickness of the EG layer and determining the content of SDC1, TM and hyaluronic acid [94].

Pilot studies show that low doses (1 ng/kg/min) of prostacyclin analogues (iloprost) improve endothelial function in critically ill patients with traumatic HS [95].

CONCLUSIONS

1. Endothelial dysfunction is a maladaptation reaction, "excessive" activation of endothelial cells, accompanied by the development of systemic pathological manifestations.
2. The main cause of endothelial dysfunction development in trauma is hemorrhagic shock and its accompanying hypovolemia, increased activity of the sympathoadrenal system, tissue hypoperfusion and hypoxia.
3. The main clinical manifestations of endothelial dysfunction are as follows: increased vascular permeability, leading to the development of acute lung injury syndrome and abdominal compartment syndrome, coagulopathy, which can be expressed as both hyper- and hypocoagulation states, and the development of systemic inflammation.
4. Currently, the most common methods for diagnosing endothelial dysfunction are the determination of syndecan-1 – a marker of endothelial glycocalyx destruction, – thrombomodulin, and von Willebrand factor, which reflect damage to membranes and internal structures of endothelial cells.
5. The leading method of correcting endothelial dysfunction in trauma is the early use of blood products (whole blood, fresh frozen plasma, cryoprecipitate, lyophilized plasma and platelet products, etc.). The effectiveness of tranexamic acid in relieving endothelial dysfunction in trauma, according to clinical studies, was assessed ambiguously.

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