Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.60.009423

Endothelial Dysfunction as a Pathogenetic Link for the Peritonitis Development

EV Husakouskaya*, NYe Maksimovich, P Omowasola Abayomi Akinduro, VA Kavaliova, YuM Belko and AA Golovnyova

Department of Pathological Physiology named after D.A. Maslakov Republic of Belarus, Grodno State Medical University, Belarus

***Corresponding author:** EV Husakouskaya, Department of Pathological Physiology named after D.A. Maslakov Republic of Belarus, Grodno State Medical University, Belarus

ARTICLE INFO

Received: December 17, 2024

Published: January 16, 2025

Citation: EV Husakouskaya, NYe Maksimovich, P Omowasola Abayomi Akinduro, VA Kavaliova, YuM Belko and AA Golovnyova. Endothelial Dysfunction as a Pathogenetic Link for the Peritonitis Development. Biomed J Sci & Tech Res 60(2)-2025. BJSTR. MS.ID.009423.

ABSTRACT

Objective of the Study: To collect and analyze literature data on the role of endothelial dysfunction in peritonitis development and identify problems associated with its incompletely understood mechanisms.

Materials and Methods: Search, study and analysis of literature data.

Results and Conclusion: Endothelial dysfunction in generalized peritonitis is caused by endotoxinemia and endotoxemia, excessive formation of endoperoxides, nitric oxide, peroxynitrite and superoxide anion, as well as accumulation of asymmetric dimethylarginine, which aggravates this condition. These substances contribute to the occurrence of hemodynamic disorders with subsequent development of multiple organ failure. At the same time, pathogenetic therapy of generalized peritonitis does not provide for correction of endothelial dysfunction, which necessitates research in this area.

Keywords: Peritonitis; Endothelial Dysfunction; Nitric Oxide; No Synthase; Nitrite Reductase; Peroxynitrite; Superoxide Radical; Asymmetric Dimethylarginine

Abbreviations: NO: Nitric Oxide; $ONOO^-$: Peroxynitrite; IL: Interleukin; TNF-α: Tumor Necrosis Factor-α; CD 14: Cluster of Differentiation 14; Bcl-2: B-Cell Leukemia/Lymphoma 2 Regulatory Protein

Background

Progression of inflammation in a closed and complex abdominal cavity is accompanied by the development of intoxication, pronounced hemodynamic and metabolic changes, which significantly affects the outcomes of peritonitis [1-7]. In 30-50% of cases, the outcome of generalized peritonitis is disability of patients [8-10]. It is important to note that the largest group of patients with peritonitis are people of working age [11,12]. Treatment of generalized peritonitis requires significant economic costs, which exceed the costs of treating non-infectious pathology. The above indicates the social and economic significance of the peritonitis problem [13-18]. In turn, the treatment of peritonitis, along with surgical intervention and antibacterial therapy, involves a pathogenetic approach, which includes anti-inflammatory, detoxification, anticoagulant therapy, and relief of intestinal paresis [2,4,13,14]. However, the existing pathogenetic therapy of peritonitis does not have a corrective effect on the development of endothelial dysfunction, while this mechanism can play one of the most important roles in the development of pathology, which determines the relevance of searching and analyzing literature on this scientific problem. Impact on this pathogenetic link can reduce the mortality of patients with peritonitis.

Materials and Methods

A search, study and analysis of literary data on modern views on the development of endothelial dysfunction in peritonitis were carried out.

Results

Endothelial dysfunction is understood as an imbalance between the production of vasodilatory, angioprotective, antiproliferative factors (nitric oxide, prostacyclin, tissue plasminogen activator, C-type

natriuretic peptide, endothelial hyperpolarizing factor), on the one hand, and vasoconstrictor, prothrombotic, proinflammatory, proliferative factors (endothelin-1, thromboxane A2, tissue plasminogen activator inhibitor, von Willebrand factor, tumor necrosis factor, superoxide radicals), on the other hand [19,20]. This process begins from the first hours after peritonitis induction and manifests itself in the form of microcirculation disorders in the intestinal wall, which leads to intestinal paresis, impaired absorption of fluid and gases, accumulation of products of incomplete metabolism and progression of hypoxia [21]. The resulting dysbacteriosis, bacterial translocation and colonization of the proximal intestine alter the barrier properties of the intestinal wall, which contributes to increased entry of bacterial endotoxins into the lymphatic system, portal and systemic blood flow, and abdominal cavity [22]. The microcirculation system of the visceral and peritoneum reacts to any impact by expanding its afferent links. Subsequently, due to the loss of water and changes in protein composition, erythrocytes aggregation and sludge occur inside the capillaries [23]. The resulting increase in hydrostatic pressure inside the afferent vessels leads to the hemorrhage formation.

As with any inflammatory process, peritonitis is characterized by the rolling of leukocytes along the endothelial surface, their attachment (adhesion) to the vascular wall, and transvascular transition to the site of inflammation [23]. These processes become possible due to the expression of intercellular adhesion molecules. In this case, under the influence of proinflammatory stimuli, endothelial cells are activated, release inflammatory mediators, and enhance the regulation of cellular adhesion molecules, facilitating the transmigration of leukocytes into the subendothelial space. According to new information, this occurs due to the epigenetic mechanisms, namely, methylation of nucleic acids, post-translational modification of histones, and non-coding Ribonucleic Acid [24]. In turn, a significant number of different biologically active substances, including prostaglandins and leukotrienes, contained in a large population of peritoneal macrophages, also have proinflammatory properties in relation to the vascular endothelium and increase vasodilation. Increased production of proinflammatory cytokines, reactive oxygen and nitrogen species (NO, $ONOO^-$) by leukocytes, especially those adherent to the endothelium, leads to increased secretion of proteinases that separate endothelial cells from the underlying basement membrane, leading to necrosis and desquamation of endothelial cells [24]. Nitric oxide (NO), which participates in this process, prevents damage to endothelial cells under physiological conditions due to implementation of antioxidant effects [25,26].

Acting on smooth myocytes of the vascular wall and released into the lumen of blood vessels, NO is captured by erythrocytes, affecting the oxygen-transport function of the blood [27]. Under conditions of ischemia, erythrocyte nitrite reductase restores NO, it is released from erythrocytes and has a vasodilating effect [28]. However, NO produced in large quantities by the inducible NO synthase isoform during inflammation leads to non-selective cell damage [29,30]. In addition, the increase in NO formation is associated with the «leakage» of the NO synthase substrate, L-arginine, from endothelial NO synthase to the inducible (macrophage) isoform of the enzyme. It is the decrease in endothelial NO synthase activity and/or activation of NO breakdown during oxidative stress that explain the development of endothelial dysfunction [31,32]. Under pathological conditions, the concentration of NO synthase inhibitors can increase significantly, which leads to suppression of enzyme activity and a decrease in NO levels to a greater extent. The so-called «L-arginine paradox» is due to the formation of high concentrations of an endogenous competitive inhibitor – asymmetric dimethylarginine, which is capable of modifying endothelial NO synthase bonds, as a result of which the enzyme generates superoxide anion instead of NO, increasing oxidative stress and leading to endothelial dysfunction [32,33].

Impaired blood flow under conditions of insufficient endothelial NO synthase expression leads to development of ischemia and hypoxia, which is a trigger for the implementation of nitrite reductase reactions with the NO release [34]. Thus, on the one hand, an increase in NO production during inflammation can lead to the formation of peroxynitrite (ONOO–), and a decrease in the content of L-arginine or its competitive displacement by asymmetric dimethylarginine leads to the production of O2– by endothelial NO synthase, which also potentiates the formation of ONOO– and can lead to damage to the vascular endothelium. At the same time, additional administration of L-arginine from the outside replaces some of the intracellular inhibitors [35], which leads to the activation of NO formation in the vascular endothelium [36,37]. It should be noted that endotoxinemia, hyperhomocysteinemia and hyperlactacidemia observed in systemic inflammatory response syndrome have an adverse effect on the vascular endothelium [38,39], leading to its damage and increased mortality of patients [40]. Excessive amounts of endotoxins formed in generalized peritonitis bind to serum proteins, which leads to the formation of endotoxin-protein complexes [39]. These complexes conjugate with all available CD14 cellular receptors – macrophage, neutrophil, endotheliocyte, stimulating the production of cytokines, active components of the complement system, vasoactive mediators, arachidonic acid metabolites, adhesins, kinins, platelet activating factors, histamine, endothelins, blood clotting factors, oxygen radicals, NO.

The septic response to acute endotoxin aggression in generalized peritonitis is characterized by excessive NO production [41], as a result of which the endothelium does not respond to vasopressor agents: endotoxin and the cytokinesis mediated by it initiate an uncontrolled release of NO, and TNF-α, aggravating these processes, contributes to vasoplegia [39,42]. The toxic effect of NO is enhanced by peroxynitrite, which has the ability to suppress the Krebs cycle, ribonucleotide reductase activity, and energy production in mitochondria. Limitation of the damaging effect of NO is achieved by its inac-

tivation with the superoxide radical, an increase in the production of which leads to angiospasm and contributes to the progression of endothelial dysfunction. It should be noted that the reduction of excess NO production during endotoxin aggression in the acute phase of generalized peritonitis is achieved by increasing the expression of Bcl-2 protein, heme oxygenase, heat shock proteins, superoxide dismutase, anti-inflammatory interleukins - IL-4, IL-10 [39]. The development of endothelial dysfunction in patients with peritonitis, otherwise known as «abdominal sepsis», leads to microcirculation disorders in various organs with changes in the functional activity of the liver and kidneys, respiratory and cardiovascular systems, impaired intestinal blood supply, the formation of portal congestion with liver hypoxia and a drop in its detoxification function, contributing to the formation of multiple organ failure [43-45].

Conclusion

Thus, endothelial dysfunction in generalized peritonitis is caused by endotoxinemia and endotoxemia, excessive formation of endoperoxides and other substances that contribute to the occurrence of hemodynamic disorders with the subsequent development of multiple organ failure. At the same time, pathogenetic therapy of generalized peritonitis does not provide for the correction of endothelial dysfunction, which necessitates research in this area.

References

1. Kerimov EYa, Kostyrnoy AV, Kerimov EE (2017) Postoperative peritonitis: a practical look at some issues. Sovrem probl Sciences and education 6: 116.
2. Sartelli M, Catena F, Ansaloni L (2013) Complicated intra-abdominal infections in a worldwide context: an observational prospective study (CIAOW Study). World J Emerg Surg 8(1): 1.
3. Sri sailaja rani M, Satya vani KS (2018) Study on factors effecting outcome of abdominal emergencies presenting with peritonitis. IOSR J Dent Med Sci 17(1): 1-14.
4. Brian JD (2019) Peritonitis and abdominal sepsis: guidelines, p. 1-37.
5. Lebedev NV, Agrba BS, Popov VS, Alexey E Klimov, Giorgy T Svanadze (2021) New system for predicting the outcome of secondary peritonitis. Russ Open Med J 10(3): 1-7.
6. Clements TW, Tolonen M, Ball CG, A W Kirkpatrick (2021) Secondary peritonitis and intra-abdominal sepsis: an increasingly global disease in search of better systemic therapies. Scand J Surg 110(2): 139-149.
7. Pathak AA, Agrawal V, Sharma N, Karan Kumar, Chinmay Bagla, et al. (2023) Prediction of mortality in secondary peritonitis: a prospective study comparing p-POSSUM, Mannheim Peritonitis Index, and Jabalpur Peritonitis Index. Perioper Med 12(1): 65.
8. Efimenko NA, Guchev IA, Sidorenko SV (2004) Infections in surgery. Pharmacotherapy and prevention. Smolensk Smol polygr. Combine, pp. 296.
9. Cattan P, Yin DD, Sarfati E, Zelicourt MD, Fagnani F (2002) Cost of care for inpatients with communityacquired intra-abdominal infections. Eur J Clin Microbiol Infect Dis 21(11): 787-793.
10. Tomskikh NN, Bogomolov NI (2007) Rehabilitation of patients with consequences of peritonitis. Bulletin of the SB RAMS 4: 179.
11. Zhidkov SA (2007) Features of diagnostics and treatment of emergency surgical diseases in elderly and senile patients: Abstract of Dr. of Medicine. Minsk, p. 45.
12. Zdzitovetsky DE, Borisov RN (2012) Analysis of the frequency of widespread peritonitis and the results of its treatment in a multidisciplinary hospital // Sovrem. problems of science and education 2: 7-11.
13. Kupchenko AM, Kosinets VA (2017) Pharmacoeconomic analysis of antibacterial therapy in patients with widespread peritonitis. Military Medicine 4: 31-36.
14. Khachatryan NN, Dyakov IN, Zyryanov SK (2019) Pharmacoeconomic evaluation of the use of ceftolozane + tazobactam in the treatment of complicated nosocomial intra-abdominal infections. Qualitative clinical practice 2: 55-68.
15. Chichom MA, Tchounzou R, Masso Misse P, C Pisoh, JJ Pagbe (2009) Analysis of operative indications and outcomes in 238re-operations after abdominal surgery in an economically disadvantaged setting. J Chir 146(4): 387-391.
16. Khachatryan NN, Fesenko TA, Vabishchevich NK (2013) Features of antibacterial therapy of patients with intra-abdominal infection. Clin microbiol antimicrob chemother 15(4): 301-308.
17. Dalfino L, Bruno F, Colizza S, Ercole Concia, Andrea Novelli, et al. (2014) Cost of care and antibiotic prescribing attitudes for community-acquired complicated intra-abdominal infections in Italy: a retrospective study. World J Emerg Surg 9: 39.
18. De Simone B, Coccolini F, Catena F, Massimo Sartelli, Salomone Di Saverio, et al. (2015) Benefits of WSES guidelines application for the management of intra-abdominal infections. World J Emerg Surg 10: 18.
19. Rebrov AP, Magdeeva NA (2008) Features of endothelial dysfunction in patients with gout and its changes against the background of therapy. Saratov scientific-medical journal 3: 59-62.
20. Verkholomova AV (2012) Influence of endothelial dysfunction on the nature of circulatory disorders in the vessels of the eye. Russ Allerg J 1(1): 75-76.
21. Kosinets VA, Samsonova IV, Ryzhkovskaya EL (2011) Structural changes in the small intestine in experimental widespread purulent peritonitis. News Surg 5: 9-16.
22. Dremina NN, Chepurnykh EE, Fadeeva TV (2018) Bacterial translocation in peritonitis. Modern Probl Sci Edu 6: 48.
23. Savelyev VS, Gelfand BR, Filimonov MI (2008) Peritonitis: Practical. Management, pp. 208.
24. Calabriso N, Massaro M, Scoditti E, Carluccio C, Verri T, et al. (2023) Epigenetic mechanisms in vascular inflammation: modulation of endothelial adhesion molecules and endothelium-leukocyte adhesion. Front Biosci (Landmark Ed) 28(9): 194.
25. Kozlovsky VI, Solodkov AP, Myadelets OD (2008) Methods for determining the number of endothelial cells circulating in the blood. Guidelines Vitebsk, p. 29.
26. Manukhina EB, Malyshev IYu (2003) The role of NO in the development and prevention of endothelial dysfunction. Vestn VSMU 2(2): 5-17.
27. Zincuk VV, Glebov AN (2015) Formation of NO-dependent mechanisms of oxygen-binding properties of blood under oxidative stress. J GrSMU 1: 139-142.
28. Atucha NM, Nadal FJ, Iyú D, Antonia Alcaraz, Alicia Rodríguez Barbero, et al. (2005) Role of vascular nitric oxide in experimental liver cirrhosis. Curr Vasc Pharmacol 3(1): 81-85.

29. Husakouskaya EV, Maksimovich NYe, Rathnamalala HY (2023) The activity of «L-Arginine-NO-system», severity of oxidative stress and state of endothelium and peritoneum in rodent peritonitis. Biomed J Sci Tech Res 51(1): 5802-5811.
30. Husakouskaya EV, Maksimovich N Ye (2022) Activity of oxidative stress and damage to vascular endothelium in rats with experimental peritonitis under administration of NO-syntase inhibitors. Am J Biomed Sci & Res 16(3): 341-344.
31. Kiellstein JT, Zoccali C (2005) Asymmetric dimethylarginine: a cardiovascular risk factor and a uremic toxin coming of age? Am J kidney Dis 46(2): 186-202.
32. Gilinsky MA (2007) Asymmetric dimethylarginine: metabolism, arginine paradox, pathophysiology. Advances in Physiol Sci 3: 21-39.
33. Brinkmann SJ, de Boer MC, Buijs N, Paul A M van Leeuwen (2014) Asymmetric dimethylarginine and critical illness. Curr Opin Clin Nutr Metab Care 17(1): 90-97.
34. Reutov VP, Sorokina EG Kositsyn NS (2005) Problems of NO and cyclicity in biology and medicine. Advances in Modern Biology 125(1): 41-65.
35. Teerlink T (2005) ADMA metabolism and clearance. Vascular Medicine 10: S73-S81.
36. Boger RH (2004) Asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, explains the L-arginine paradoxand acts as a novel cardiovascular risk factor. Nutrition 134: 2842S-2847S.
37. Boger RH, Eyal S Ron (2005) L-arginine improves vascular function by overcoming the deleterious effect of ADMA, a novel cardiovascular risk factor. Altern Med Rev 10(1): 14-23.
38. Savelyev VS, Petukhov VA (2012) Peritonitis and endotoxin aggression. Moscow, pp. 326.
39. Kozlovsky VI, Solodkov AP, Myadelets OD (2008) Methods for determining the number of endotheliocytes circulating in the blood. guidelines. Vitebsk, p. 29.
40. Husakouskaya EV, Rathnamalala HY, NYe Maksimovich (2023) Some indicators of intoxication and leukocyte response in rodent fecal peritonitis. Biomed J Sci Tech Res 50(5): 42055-42060.
41. Husakouskaya EV, Maksimovich NYe, Kavaliova VA (2024) Participation of NO-synthase in the mechanisms of oxidative stress and endothelial injury in rodent peritonitis. Biomed J Sci & Tech Res 54(5): 46306–46310.
42. El Awady MS, Nader MA, Sharawy MH (2017) The inhibition of inducible nitric oxide synthase and oxidative stress by agmatine attenuates vascular dysfunction in rat acute endotoxemic model. Environ Toxicol Pharmacol 55: 74-80.
43. Joffre J, Hellman J, Ince C (2020) Endothelial responses in sepsis. Am J Respir Crit Care Med 202(3): 361-370.
44. Schietroma M, Pessia B, Mattei A (2020) Temperature-neutrophils-multiple organ failure grading for complicated intra-abdominal infections. Surg Infect 21(1): 69-74.
45. Galkina S, Golenkina EA, Viryasova GM, Yulia M Romanova, Galina F Sud'ina (2019) Nitric oxide in life and death of neutrophils. Curr Med Chem 26(31): 5764-5780.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.60.009423

EV Husakouskaya. Biomed J Sci & Tech Res