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SCIENTIFIC REVIEWS

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ACUTE ENDOTHELIAL CELL INJURY IN CARDIAC SURGERY PATIENTS UNDER ARTIFICIAL BLOOD CIRCULATION: THE CURRENT STATE OF THE PROBLEM

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This study summarizes the existing literature data on endothelial damage and its etiology, pathophysiology, and diagnosis in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). Data on endothelial dysfunction and the history of its study were obtained from various medical databases, including PubMed, Cochrane, Elibrary, and Cyberleninka. We suggest that endothelial injury that occurs during and after the surgery predicts poor clinical outcomes, and should therefore be considered by anesthesiologists, intensivists, cardiac surgeons, and transfusion medicine specialists.

Keywords: endothelium, endothelial dysfunction, cardiopulmonary bypass (CPB), endothelial glycocalyx (eGCX).

Introduction. Numerous studies conducted in recent decades have demonstrated the crucial role of endothelium in physiological and pathological processes in the body. The endothelium constantly counteracts the effects of damaging factors and produces multiple biologically active substances thus preventing negative impacts of these factors on the vascular wall and regulating its functions.

However, in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), acute endothelial cell injury occurs, which significantly impairs vascular function and serves as a predictor of postoperative complications.

Over the past seven decades, there have been significant changes in the CPB technologies. CPB is a crucial component of open-heart surgery. New equipment and circuits made from biocompatible materials with minimal priming volumes have been developed, and techniques such as hemodilution, hypothermia, and myocardial protection have been implemented [1]. However, despite undeniable advances, CPB remains a non-physiological procedure that disrupts the homeostasis. This increases the risk of postoperative complications associated not only with blood coagulation disorders but also with damage to the functional vascular layer, i.e. the endothelium. Numerous experiments aimed at improving and enhancing the quality of perfusion involve modifications to available devices as well as the timely diagnosis of disorders that develop during and after perfusion.

General functions of endothelial cells, such as the regulation of vascular tone, hemostasis, adhesion, and angiogenesis, depend on the location of the blood vessels and the specific characteristics of their cells [3]. The morphological and physiological diversity of endothelial cells throughout the vascular tree is driven by their heterogeneity. Another factor contributing to the variation in structure and function of the endothelium is the endothelial glycocalyx (eGCX).

Our current understanding of the pathophysiology of certain disorders (including cardiovascular diseases, atherosclerosis, systemic autoimmune diseases, chronic kidney disease, diabetes mellitus, and multiple other conditions) recognizes endothelial dysfunction as a critical factor in the pathological process [4,5].

Patients undergoing heart surgery usually have pre-existing chronic vascular damage as a result of cardiovascular diseases, putting them at particularly high risk. Moreover, cardiovascular surgery itself results in acute endothelial injury, which contributes to the development of perioperative or postoperative multiple organ dysfunction syndrome (MODS). Mortality rates in patients with MODS exceed 50-80%, and this parameter does not tend to decrease over time [9].

The effects of acute endothelial cell injury associated with the use of cardiopulmonary bypass on the functions of organs and systems. Many researchers believe that markers of endothelial dysfunction in patients undergoing heart surgery are predictors of postoperative complications and poor clinical outcomes as a result of damage to various systems and organs [8, 12]. The endothelium has been shown to affect the vascular tone directly via the release of vasodilators and vasoconstrictors such as endothelin-1, which is the most potent vasoconstrictor. Ilker Mercan et al. (2020) showed that endothelin-1 levels were elevated in all patients who had undergone cardiac surgery with the use of CPB, which, in the authors' opinion, was a factor contributing to the development of endothelial cell injury [17]. Similar results were obtained in another study (Dorman et al., 2004) that demonstrated significantly elevated endothelin levels in a comparable patient cohort. Thus, plasma endothelin levels in patients recovering after coronary artery bypass grafting (CABG) with CPB increased to 200%. Meanwhile, in patients who underwent surgery without the use of CPB, the concentration of endothelin increased by no more than 50%. The authors believe that the significant elevation of endothelin as one of the markers of endothelial injury occurs for a number of reasons, such as platelet activation, myocardial reperfusion injury, endothelial injury associated with *pulsatile flow during CPB, as well as atrial and aortic cannulation. Moreover, a multiple-fold increase in the endothelin concentrations results in vasoconstriction of the pulmonary and graft vessels and is associated with a higher risk of complications during the postoperative period* [15]. These conclusions are supported by the study conducted by Mikheev et al. (2017) evaluating the endothelin-1 levels in patients who underwent CABG with CPB before and after surgical procedures. The authors revealed a direct correlation between plasma endothelin-1 levels and the severity of postoperative complications. It should be noted that patients who developed MODS after the surgery had a high level of endothelin before the surgery and maintained this high level in the postoperative period. According to the researchers, this correlation could indicate that high concentrations of endothelin-1 was a predictor for postoperative complications [7,8].

Another technique used to assess acute endothelial injury is the evaluation of endothelial vasomotor function after exposure to various vasoactive substances, most commonly acetylcholine and adenosine that cause NO-mediated vasodilation. Reduced vasodilation indicates the presence of endothelial dysfunction. Similar findings were observed in a study by Krispinsky et al. (2019), which included infants who had undergone surgical procedures with the use of CPB for their congenital heart defects. The authors applied acetylcholine and sodium nitroprusside delivered via iontophoresis. Immediately after surgery with CPB, vasodilation in response to acetylcholine administration was significantly decreased. Interestingly, no changes were observed in response to sodium nitroprusside administration in the postoperative period. The authors suggested that acetylcholine affected the endothelium, while nitric oxide (NO) acted on the vascular smooth muscle cells, whose function remained unchanged after the surgery. The researchers also measured blood creatinine levels in the postoperative period: they were elevated in all patients indicating the development of acute kidney injury (AKI), which was thought to be related to impaired renal vascular endothelial barrier [20].

Fouquet et al. (2020) obtained contrasting results, finding that endothelium-dependent vasodilation in response to intra-arterial administration of acetylcholine was maintained. Vasodilation was assessed using myography: a tungstyen introducer was placed intraoperatively inside the internal thoracic artery. The authors also investigated whether the pump type (roller or centrifugal) affected the acetylcholine-dependent vasodilation; however, the analysis showed no differences between two groups. The researchers also suggested that these results are related to the absence of a local inflammatory response despite the development of systemic inflammatory response during surgery with CPB [16].

Scientific literature described different methods for studying endothelial dysfunction by examining histological specimens and cell cultures. For example, a study by Marc Ruel et al. (2005) investigated patients who underwent CABG with or without CPB. For this purpose, endothelial progenitor cells were isolated and cultured from peripheral blood before and 24 hours after the surgery. The cells were then identified using double fluorescent lectin and lipoprotein staining and examined under a microscope. The researchers concluded that CABG with or without CBP resulted in an increased number of endothelial progenitor cells with equivalent proliferative activity. However, both the migratory activity of endothelial progenitor cells and the postoperative viability of endothelial

progenitor cells (adjusted for the baseline preoperative level) were higher in patients who underwent CABG without CPB compared to those who underwent CABG with CPB. Endothelial progenitor cells in patients who underwent CABG with CPB were less viable after the surgery compared to baseline, whereas the patients who underwent CABG without CPB demonstrated the opposite results. The authors concluded that CABG without CPB resulted in fewer cardiovascular complications compared to CABG with CPB [19]. N. Dekker et al. also conducted a cell culture study. Renal and pulmonary microvascular cells were incubated with patient plasma, and the endothelial barrier function was assessed in vitro using electric cell-substrate impedance sensing. The researchers demonstrated that the decrease in the renal and pulmonary endothelial barrier function (i.e. hyperpermeability) was significantly more pronounced in patients who underwent surgical procedures with CPB and was maintained for at least 72 hours after the surgery. According to the authors, this abnormal endothelial hyperpermeability was associated with increased levels of circulating angiopoietin-2 in this patient cohort. The study proved that the angiopoietin/tyrosine kinase-2 system was involved in the development of endothelial dysfunction in patients who had undergone surgical procedures with CBP, which represents a new step of scientific research in this field [22,23].

The function and state and endothelial glycocalyx in patients undergoing surgery with CPB. On the surface of the endothelium, there is a complex multicomponent system called the glycocalyx. In healthy subjects, the blood contains low concentrations of endothelial glycocalyx (eGCX) molecules; however, under pathological conditions, this structure can be partially or completely lost, causing its components to be released into the bloodstream in large quantities. Such molecules include syndecan-1, hyaluronan, heparan sulfate, VE-cadherin, and endocan [13]. Wu Qiaolin et al. (2019) assessed plasma concentrations of syndecan-1, heparan sulfate, and hyaluronan as markers of glycocalyx damage before and after surgery using CPB. The researchers came to an unambiguous conclusion regarding a significant increase in these biochemical markers as a sign of endothelial glycocalyx degradation [18]. A study conducted by Florian Brettnera (2017) also evaluated the markers of eGCX damage in patients undergoing surgery with and without CPB. The results showed that in both groups, the concentration of these markers increased regardless of the type of surgical procedures and the use of CPB. However, the patients in the CPB group had higher plasma levels of these markers. The researchers attributed this increase not only to the negative impact of CPB on eGCX but also to the presence of chronic comorbidities in this cohort, which is an important factor influencing the postoperative recovery [28]. Robich M. et al. obtained similar data when investigating the impact of CPB time on the endothelial glycocalyx degradation. The study revealed a significant correlation between the duration of CPB exposure and blood levels of syndecan-1 using correlation analysis. The scientists also pointed out that patients undergoing surgical procedures with CPB could benefit from the development of therapy aimed at removing endothelial glycocalyx degradation products from the blood [25]. Moreover, the measurement of blood levels of syndecan-1 will help predict the development of early postoperative complications, which was demonstrated by Hye-Bin Kim et al. who investigated the connection between blood syndecan-1 concentrations and the development of acute kidney injury (AKI) during the early postoperative period in patients undergoing valve replacement surgery using CPB. The study showed that the syndecan-1 levels over 90 ng/mL could reliably predict the development of AKI in this patient cohort [21].

There have been studies of eGCX using dark-field microscopy, is one of the main non-invasive techniques used for *in vivo* studies of glycocalyx in humans. In a study by Claudia Nussbaum et al., 2015, this method was used in children who underwent heart surgery with and without CPB. The glycocalyx thickness was assessed by measuring the perfused boundary region of the sublingual microvessels before and after the surgery. Additionally, the microcirculatory flow index and the vessel density were assessed. After the surgery using CPB, the thickness of the glycocalyx significantly decreased, gradually returning to baseline values in the postoperative period. The authors also reported a transient decrease in microcirculatory parameters [24]. Similarly, Dekker [29] used this method to assess eGCX in a study of adult patients who underwent CABG with CPB. Perfusion of the sublingual micro-vessels was measured before, during, and after CPB, followed by an analysis of the perfused vessel density and the perfused boundary region (the parameter inversely related to the glycocalyx thickness). This study revealed that the use of *phosphorylcholine* coating of extracorporeal *circuits was associated with better* preservation of the endothelial glycocalyx compared to heparin-coated circuits, while the microcirculatory perfusion was impaired to an equal extent in both groups. Therefore, microcirculatory perfusion disorders caused by CPB do not seem to depend on the coating type.

Our literature review suggests that endothelial dysfunction, as well as eGCX degradation, may predispose patients undergoing cardiac surgery to postoperative complications, and also serve as markers of progressive organ damage associated with the use of CPB.

Conclusion: The analysis of scientific publications indicate that endothelial injury is a primary abnormality associated with the use of CPB is endothelial injury. Factors affecting the endothelial function include hemodynamic factors (such as blood pressure and shear rate), along with blood gas composition, hormones, and mediators (such as catecholamines, vasopressin, acetylcholine, endothelin, bradykinin, angiotensin II, thrombin, cytokines, lipoproteins, endotoxins, and other molecules).

Thus, despite the essential role of CPB in heart surgery practice, this method produces certain negative effects on the body. These effects include contact activation of white blood cells and the blood coagulation system, blood cell damage, hyperoxia, hypothermia, and hemodilution. The non-pulsatile blood flow is also one of the additional damaging factors associated with CPB. Pulsatile blood flow is of constant interest in clinical perfusion science because, according to current concepts, it contributes to the normalization of total peripheral vascular resistance, improves tissue perfusion, increases oxygen extraction, and reduces the level of stress hormones, and produces a beneficial effect on renal and cerebral blood flow [10,26]. However, it is not always possible to choose a blood flow mode in surgical practice or to rule out the influence of other adverse factors on the patient's body. Therefore, researchers are evaluating possible ways to improve clinical outcomes by studying important pathophysiological patterns and methods to influence them. This explains the numerous studies of endothelial dysfunction in patients undergoing heart surgery with or without CPB [6; 11].

Despite the growing number of clinical studies evaluating the number of circulating markers of endothelial cell injury, evidence of a causal relationship between endothelial barrier dysfunction and the development of postoperative compli-

cations is scarce and mainly limited to experimental models [27,23]. However, patients with evident endothelial injury must receive pharmaceutical therapy in the postoperative period. Thus, a study by Yakubtsevich et al. [14] demonstrated the positive effects of therapy with angiotensin-converting enzyme inhibitors, calcium sensitizers, phosphodiesterase-3 inhibitors, and beta-blockers on the endothelial function in patients underdoing heart surgery.

Patients undergoing off-pump CABG are also prone to the development of endothelial dysfunction, as was shown in a study by Shlyk I.F. However, CABG with CPB is a risk factor for more severe intra- and postoperative complications compared to off-pump CABG [2, 11]. Endothelial dysfunction developing during heart surgery requires more thorough evaluation and treatment. Thus, Kornev et al. reported that minimally invasive CPB was associated with less pronounced endothelial dysfunction compared to that occurring when using the conventional extracorporeal circuit. Therefore, the use of minimally invasive CPB systems or the choice of off-pump surgical techniques significantly reduces the risk of developing ED in the postoperative period.

Endothelial dysfunction is closely linked to the development of complications during and after heart surgery. Such diagnostic methods as assessment of endothelial vasomotor function using Doppler color flow imaging, evaluation of endothelial glycocalyx using *dark-field* imaging, laboratory tests and histological examination can be used since they help reliably evaluate the condition of the vascular wall. These tests expand our understanding of microcirculatory dysfunction that occurs in patients receiving surgical care with and without CPB. Early diagnosis of this disorder can contribute to a more thorough approach to choosing the surgical technique. Raising awareness among healthcare providers (especially anesthesiologists and critical care specialists) about the importance and the diagnostic methods to evaluate endothelial dysfunction is necessary since even mild endothelial injury may have serious consequences (i.e. multiple organ failure). The implementation of methods for evaluation of the endothelial structure and function (including those of the eGCX) will aid in the search for markers and predictors of poor clinical outcomes in patients undergoing cardiac surgery with CPB. This will help assess the patient's condition during the perioperative period and predict the development of postoperative complications.

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POINT OF VIEW

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RESULTS OF PRIMARY DRAINAGE OF THE ABDOMINAL CAVITY IN PREMATURE INFANTS WITH NECROTIZING ENTEROCOLITIS

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For newborns with severe stages of necrotizing enterocolitis, peritoneal drainage should be used as initial treatment, as peritoneal drainage can provide initial stabilization; most of these infants will require subsequent laparotomy. In premature infants with necrotic enterocolitis, peritoneal drainage, reducing intra-abdominal pressure, improves lung and liver function and stabilizes the position, performs a kind of detoxification by reducing the level of toxic fluid accumulated in the abdominal cavity; determines the nature of the effusion, that is, the presence of odorous, fibrous secretions indicating necrobiosis of the intestinal wall, thereby definitively diagnoses the perforation. The overall survival rate when using peritoneal drainage appears to be higher, and it should be assumed that it is preferable to use peritoneal drainage in severe stages of necrotizing enterocolitis before laparotomy to reduce intra-abdominal pressure and sanitize the abdominal cavity, thus avoiding complications associated with direct laparotomies.

Keywords: premature newborns, necrotic enterocolitis, primary peritoneal drainage, intra-abdominal pressure.

Introduction. Percutaneous injection of Penrose drainage into the abdominal cavity of newborns with intestinal perforation was first described by Ein SH et al. [7].

Initially, this procedure was recommended as a temporary measure for premature infants (PI) in critical condition with perforation of the intestinal wall caused by necrotizing enterocolitis. It was hoped that the drainage of air and feces collected in the abdominal cavity as a result of perforation would alleviate the symptoms of abdominal syndrome and sepsis and allow the child to better tolerate subsequent laparotomy [5]. Back in 2000, Cass DL and co-authors reported the use of peritoneal drainage (PD) for 15 years in PI with very light weight as an initial treatment measure for isolated or complicated intestinal perforation caused by necrotic enterocolitis (NEC) [6]. The results of NEC treatment using PD turned out to be unexpected - they were the same, and possibly more effective than when treated with immediate laparotomy [3.19]. Some researchers recommend PD primarily at the stages of NEC, when perforation is noted with extremely low weight of PI. In general, clinicians attach great importance to PD in severe forms of NEC. PD, even in the severe stage of NEC at an early stage, can help in the resuscitation and recovery of a seriously ill child, and in some cases can become a decisive surgical intervention [8,9].

In the UK, surgeons use PD to stabilize the general condition in 95% of patients and as a radical treatment in 58%. Most surgeons use PD in newborns of any weight, while others do not recommend it in newborns with a body weight of less than 1000 g [14].

Other recent studies in the literature have not found significant benefits or harms of PD compared to laparotomy [16].

Thus, there is no consensus in the literature on whether laparotomy should be performed after PD or without it.

The aim of the study was to use a randomized clinical trial to determine how primary peritoneal drainage affects the dynamics of intra-abdominal pressure and the outcome of treatment of premature newborns with severe necrotizing enterocolitis with very low birth weight.

Materials and methods. The prospective study included 87 premature newborns (PN) who were examined and treated with a diagnosis of necrotic enterocolitis in the intensive care unit of the Farajeva Research Institute of Pediatrics (Baku, Azerbaijan Republic) in the period from 2010 to 2021. Among them, 13 (14.95%) had extremely low body weight, 22 (25.29%) had very low body weight and 44 (50.57%) had low body weight (the minimum body weight averaged 650 g). Only 8 (9.19%) PN had a maximum body weight of 4,200 g.

Of the total number of newborn boys, there were 68 (78.16%), girls – 19 (21.84%). The criteria for inclusion in the study were pathology of the gastrointestinal tract and clinical manifestations of necrotizing enterocolitis.

The presence of NEC was established by anamnestic, clinical, laboratory, mi-

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