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Health Review

Influence of Extracorporeal Circulation on The Inflammatory Cascade

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Abstract: Extracorporeal circulation (ECC) represents a major technological advance in modern cardiac surgery, enabling complex procedures by temporarily replacing cardiac and pulmonary functions. However, its use is closely associated with a multifactorial systemic inflammatory response that contributes to several postoperative complications, such as multiple organ dysfunction, bleeding, acute kidney injury, neurological changes, and pulmonary inflammation. This narrative literature review aimed to analyze the main pathophysiological mechanisms involved in the inflammatory activation induced by ECC, as well as to discuss strategies for modulating this response. Topics addressed include activation of the complement system, release of pro-inflammatory cytokines (such as IL-6 and TNF-α), leukocyte recruitment, and the impact of mechanical, hemodynamic, and biochemical factors occurring during the procedure. Furthermore, the study explores technological advances aimed at mitigating these effects, including the use of heparin-coated circuits, biocompatible membrane oxygenators, cytokine hemoadsorption, thermal control, pharmacological strategies with corticosteroids, anti-inflammatory agents and antioxidants, as well as minimally invasive approaches (MiECC) and individualized nutritional support. The rational use of these strategies is essential to reduce morbidity and mortality, shorten hospital stays, and improve clinical outcomes in patients undergoing cardiac surgery with ECC. This review also highlights the need for further clinical studies to support greater standardization of therapeutic approaches, especially regarding drug selection, optimal ECC duration, the impact of circuit coatings, and interdisciplinary integration between perfusionists, surgical teams, and intensive care providers. A multidisciplinary approach is key to developing safer, more effective, and personalized practices. The data synthesized here reinforces the critical role of understanding inflammatory mechanisms and implementing advanced technologies and nutritional interventions as strategies to optimize surgical patient care.

Keywords: Extracorporeal Circulation; Systemic Inflammation; Cardiac Surgery; Cytokines; Heparin-coated Circuits; Hemadsorption; Clinical Nutrition.

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1. Introduction

Extracorporeal circulation (ECC) has revolutionized modern cardiac surgery by enabling the performance of complex intracardiac procedures through the temporary replacement of heart and lung functions. Since the first experiments with artificial blood

oxygenation in the late 19th century, scientists and physicians have sought to develop methods capable of providing effective circulatory support during surgical interventions [1,2]. The creation and successful clinical implementation of the heart-lung machine by John Gibbon in 1953 marked a turning point in cardiovascular surgery, allowing intracardiac corrections to be performed with greater safety and control [2,3].

With the advancement of ECC technologies, it became clear that the interaction between blood and the artificial surfaces of the circuit triggers a pronounced systemic inflammatory response. This phenomenon, known as the systemic inflammatory response induced by ECC, is mediated by complex biochemical cascades involving activation of the complement system, release of pro-inflammatory cytokines, and stimulation of innate immune cells [4]. In particular, activation of the classical and alternative complement pathways leads to the generation of anaphylatoxins (C3a and C5a), promoting leukocyte adhesion to the endothelium, increased vascular permeability, and postoperative organ dysfunction [1].

Understanding the mechanisms underlying this inflammatory response has led to the development of therapeutic strategies aimed at mitigating its harmful effects. These include the use of membrane oxygenators instead of bubble models, heparin-coated extracorporeal circuits, and anti-inflammatory pharmacological interventions. More recently, minimally invasive extracorporeal circulation (MiECC) has emerged as a promising alternative, combining advanced technology with a closed and self-regulated system that significantly reduces blood-air interaction and the associated adverse effects of conventional ECC [4].

Given the persistence of inflammatory complications related to ECC, this study aims to conduct a narrative literature review on the pathophysiological mechanisms involved in the inflammatory cascade triggered by extracorporeal circulation in cardiac surgery, as well as to explore technological advancements and therapeutic strategies designed to reduce its harmful effects. This review seeks to consolidate current knowledge, support clinical practice, and highlight future perspectives for safe and effective extracorporeal perfusion.

2. Materials and Methods

This study was developed as a narrative literature review aimed at synthesizing and critically discussing the evidence on the role of ECC in triggering the systemic inflammatory response and its clinical repercussions in cardiac surgery. The review was guided by the following research question: Which factors influence the inflammatory response in patients undergoing cardiac surgery with extracorporeal circulation, and what are the main consequences and mitigation strategies described in the literature?

A literature search was conducted in PubMed, Scopus, ScienceDirect, and SciELO, covering publications from 2000 to 2024, in English and Portuguese. The search strategy combined controlled descriptors, when available, with free-text terms related to ECC and inflammation. The main search terms included “extracorporeal circulation,” “cardiopulmonary bypass,” “systemic inflammatory response,” “cardiac surgery,” “cytokines,” “complement activation,” and “anti-inflammatory strategies,” as well as their respective synonyms and spelling variations. Boolean operators (AND, OR, and, when necessary, NOT) were applied according to the specific characteristics of each database.

The selection of publications was guided by their relevance to the proposed topic (Figure 1). Original studies, clinical trials, and review articles, whether systematic or narrative, were considered when they addressed the relationship between ECC and systemic inflammation in the context of cardiac surgery. Particular emphasis was placed on studies reporting: mechanisms and biomarkers of inflammation, such as cytokine release, complement activation, leukocyte activation, and oxidative stress; clinical outcomes potentially associated with the inflammatory response, including neurological complications, renal dysfunction, bleeding, infection, length of hospital stay, and mortality; and strategies aimed at attenuating inflammation, such as pharmacological interventions,

circuit technologies, biocompatible coatings, adsorption techniques, perfusion-related modifications, and supportive care measures, including nutritional approaches.

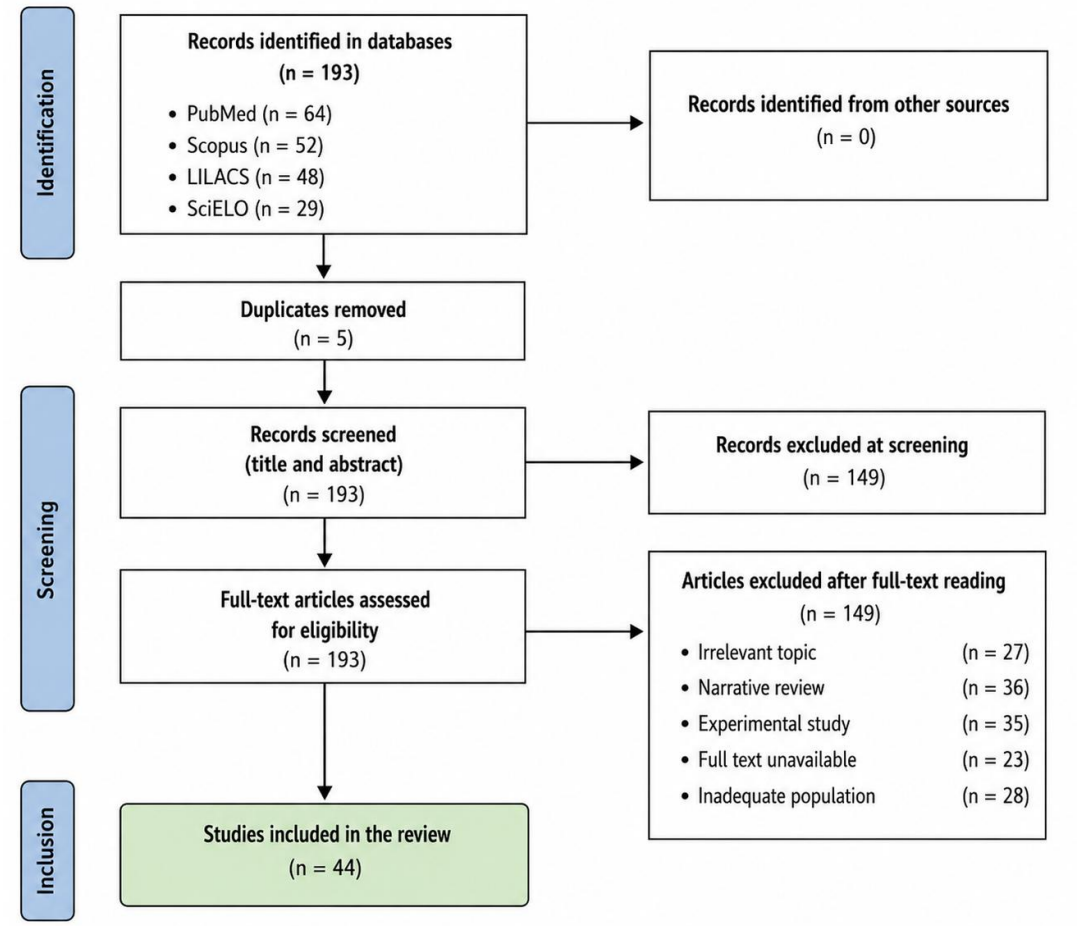

Figure 1. Flowchart of study selection process.

Duplicate references, incomplete publications, studies unrelated to cardiac surgery with ECC, and articles that did not substantially address inflammatory mechanisms, consequences, or mitigation strategies were excluded from the final analysis. After identification of the references and removal of duplicates, titles, abstracts, and, when necessary, full texts were examined according to their thematic relevance and their contribution to the objectives of this review. The final selection was based on the potential of each study to support a broad and clinically meaningful discussion of the topic. For the purpose of analysis, the selected studies were reviewed in a structured manner, considering, whenever available, aspects such as author and year of publication, study design, population or sample, ECC or cardiopulmonary bypass characteristics, inflammatory markers and timing of assessment, evaluated clinical outcomes, and main findings.

Given the heterogeneity among studies regarding design, biomarkers, timing of measurement, and reported outcomes, the findings were synthesized descriptively rather than quantitatively. The discussion was organized into thematic categories: historical and conceptual aspects of ECC/CPB; inflammatory mechanisms involved in ECC, including cytokine release, complement activation, cellular responses, and oxidative stress; clinical complications related to systemic inflammation; factors capable of modulating this response, such as patient profile, surgical complexity, CPB duration, and circuit biocompatibility; and strategies proposed to reduce inflammatory burden and related complications.

In addition to summarizing the available literature, this review sought to provide a critical interpretative analysis of the evidence, taking into account the methodological characteristics of the studies, the consistency of the reported findings, and the main limitations observed across the literature, including variability in inflammatory markers, differences in timing of measurement, heterogeneity of surgical procedures, small sample sizes, and possible sources of bias. Areas of uncertainty and knowledge gaps were also identified, particularly regarding the comparative effectiveness of different anti-inflammatory strategies and ECC-related technologies, highlighting topics that warrant further investigation.

Nevertheless, to minimize the risk of selective or confirmation-driven citation, several safeguards were adopted. The search was structured around an explicit research question and performed across four complementary databases (PubMed, Scopus, ScienceDirect, and SciELO), using predefined descriptors and Boolean combinations. Screening of titles, abstracts, and, when necessary, full texts were carried out by more than one author, with disagreements resolved by consensus and, when needed, by a senior reviewer. Predefined inclusion and exclusion criteria were applied uniformly, and both confirmatory and discordant findings were deliberately incorporated, for example, the trials reporting no significant clinical benefit of cytokine hemoadsorption (RECCAS and the CytoSorb pilot trial) and the mixed results of leukocyte filtration, so that the synthesis reflects the existing uncertainty rather than a predetermined conclusion.

3. General Aspects of Extracorporeal Circulation (ECC)

Since the early experiments conducted by John Gibbon in the 1930s, ECC has evolved significantly, culminating in the first successful surgery using this technology [5]. Since then, substantial advances in biomedical engineering and refinements in perfusion techniques have considerably reduced complication rates, improved clinical outcomes, and expanded the therapeutic possibilities in cardiovascular surgery.

The ECC system comprises essential components, including a membrane oxygenator, a centrifugal or roller pump, microaggregate filters, and a venous reservoir. During perfusion, venous blood is drained from the venae cavae and directed to the oxygenator, where carbon dioxide is removed and oxygen is diffused in a controlled manner. The pump then propels the oxygenated blood back to the arterial system, ensuring adequate tissue perfusion [6]. Precise calibration of blood flow and rigorous control of metabolic parameters are imperative to mitigate hemodynamic instability and biochemical complications.

4. Extracorporeal Circulation and Its Implications

ECC revolutionized cardiovascular surgery by enabling complex procedures. However, its use is associated with a series of physiological and metabolic implications, particularly regarding the systemic inflammatory response and postoperative organ dysfunction [7].

Exposure of blood to the components of the extracorporeal circuit triggers an inflammatory cascade mediated by cytokines and vasoactive factors. Studies have shown a significant increase in interleukins, such as IL-6 and IL-10, shortly after the procedure, reflecting an exacerbated immune response that may lead to complications such as circulatory, hematological, and pulmonary dysfunction [8]. Macrophage migration inhibitory factor (MIF) has also been identified as a central mediator of the ECC-related inflammatory response, directly correlating with the severity of organ dysfunction [7].

The repercussions of the inflammatory response can affect various organ systems. Renal function may be compromised due to hemodynamic alterations and endothelial injury induced by inflammatory mediators, leading to acute kidney injury in some patients [9]. In addition, cerebral perfusion may be impaired, increasing the risk of transient or permanent neurological alterations. Hematological dysfunctions are also frequent, in-

cluding thrombocytopenia and coagulation disturbances related to platelet activation and consumption of coagulation factors [10].

Furthermore, studies indicate that the duration of ECC is a determining factor in the magnitude of the inflammatory and hemodynamic changes observed postoperatively. Patients exposed to prolonged ECC times present a higher risk of pulmonary complications, circulatory failure, and multiple organ dysfunction, reinforcing the need to optimize perfusion strategies to minimize these adverse effects [7].

5. Inflammatory Cascade and ECC

The exposure of blood to the non-endothelial surfaces of the ECC circuit activates the complement system, initiating an inflammatory cascade mediated by anaphylatoxins such as C3a and C5a. These mediators increase vascular permeability and facilitate leukocyte recruitment, intensifying the inflammatory response. Moreover, activation of the alternative complement pathway may lead to the formation of the membrane attack complex (C5b-9), inducing cell lysis and endothelial dysfunction [11].

Blood contact with artificial surfaces and complement activation promotes the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, which play key roles in the ECC-associated inflammatory response. IL-6, for example, is a well-established biomarker of inflammation and has been correlated with postoperative complications in cardiac surgery [12].

Endothelial cells, even without direct contact with the extracorporeal circuit, respond to the changes induced by ECC through increased expression of adhesion molecules such as ICAM-1 and VCAM-1, facilitating leukocyte migration into tissues. Additionally, activated neutrophils release proteolytic enzymes and reactive oxygen species, promoting endothelial damage and exacerbating inflammation [12]. Studies have shown that leukocytes are excessively activated during ECC, contributing to endothelial injury, organ dysfunction, and worse clinical outcomes. Consequently, leukocyte filtration has been proposed as a strategy to attenuate this inflammatory response.

Leukocyte filtration has been proposed as a strategy to attenuate the inflammatory response associated with extracorporeal circulation by reducing the number of activated neutrophils and limiting the release of proteolytic enzymes, reactive oxygen species, and pro-inflammatory mediators. Experimental and small clinical studies have demonstrated reductions in inflammatory biomarkers and improvements in surrogate measures of pulmonary and endothelial function following leukocyte depletion during cardiopulmonary bypass [12].

However, the translation of these biological effects into consistent clinical benefits remains uncertain. Several clinical trials and meta-analyses have generally failed to demonstrate significant reductions in mortality, duration of intensive care unit stay, incidence of acute kidney injury, neurological complications, or overall postoperative morbidity [14]. Several factors may explain this discrepancy. First, leukocyte activation represents only one component of a multifactorial inflammatory process that also involves complement activation, platelet–leukocyte interactions, coagulation pathways, endothelial dysfunction, ischemia–reperfusion injury, and cytokine release. Second, the timing and duration of filtration, differences in filter technology, and patient heterogeneity may influence outcomes. Therefore, although leukocyte filters are capable of reducing inflammatory activation at a biological level, current evidence does not support their routine use solely for the purpose of improving major clinical outcomes. Future studies should focus on identifying patient subgroups most likely to benefit from this strategy and on integrating leukocyte filtration into multimodal approaches aimed at controlling the systemic inflammatory response associated with extracorporeal circulation [14].

The systemic inflammatory response induced by ECC can lead to various clinical complications, such as pulmonary dysfunction, renal insufficiency, hemodynamic compromise, and systemic inflammatory response syndrome (SIRS). The increased incidence

of SIRS is closely associated with the contact of blood with non-endothelial surfaces during ECC. This mechanical interaction leads to the release of anaphylatoxins, which in turn promote the secretion of IL-1, IL-6, and TNF-α. These mediators are responsible for fever, neutrophilia, increased neutrophil adhesion to the endothelium, and further cytokine release by monocytes and leukocytes, especially IL-6 and IL-8—the latter being a key mediator of acute respiratory distress syndrome and central nervous system inflammatory processes.

Strategies to mitigate this response include the use of biocompatible-coated circuits, corticosteroid administration, and strict temperature control during the procedure [12]. Therefore, understanding the inflammatory mechanisms associated with ECC is essential for developing therapeutic strategies that minimize its deleterious effects and improve clinical outcomes in cardiac surgery [14].

6. Clinical Impacts of the Inflammatory Response to ECC

The inflammatory cascade is intensified and may lead to the onset of symptoms such as fever, cardiac dysfunction (caused by mechanical, ischemic, or immunological injury), and/or vasoplegia, resulting in hypotension, signs of low cardiac output, reduced blood flow, and inadequate tissue oxygenation [14].

Other complications include acute kidney injury, acute lung injury, severe respiratory distress syndrome, hematological alterations, neurological problems, and fluid retention, which may result in weight gain due to damage to the vascular walls. When these manifestations occur, the length of stay in the intensive care unit (ICU) and hospital may be prolonged due to the associated complications. In more severe situations, multiple organ failure may occur, or even extreme cases resembling septic shock [14].

Several complications may arise from ECC due to factors such as blood contact with artificial materials, continuous flow, hemodilution, hypothermia, and anticoagulation, which can lead to complications either during surgery or in the intensive care unit. The main complications of ECC include hemorrhage, low cardiac output, arrhythmias, respiratory failure, renal failure, neurological or neuropsychiatric alterations, hydroelectrolytic imbalances, abdominal complications, hemolysis, and inflammation.

Pulmonary complications may result from the inflammatory response, ischemia-reperfusion injury, the release of reactive oxygen species, and a loss of coherence between macro- and microcirculation. Because of post-ECC hemodilution, there is a loss of capillaries filled with red blood cells and an increased diffusion distance between erythrocytes and tissues.

Among pulmonary complications, postoperative hypoxemia is one that is linked to cardiac or pulmonary insufficiency and is exacerbated by a period of hypoperfusion in the lungs. When blood flow is restored, an ischemia-reperfusion injury occurs that worsens the inflammatory response initiated by ECC. Moreover, the inflammatory process, including complement activation and the release of pro-inflammatory cytokines, can partly increase the permeability of the alveolar-capillary membrane, leading to a higher risk of developing Acute Respiratory Distress Syndrome (ARDS).

Acute postoperative bleeding is a significant complication of cardiopulmonary bypass, deriving from activation of the coagulation pathway during ECC, which induces a combination of thrombocytopenia and platelet dysfunction after contact with artificial surfaces or surgical trauma. ECC also causes dilution of coagulation factors and reduces factor V and VII levels, although these are rarely the main causes of postoperative bleeding. The primary cause of bleeding related to heparin is inadequate neutralization of heparin with protamine.

The use of ECC may also contribute to hemolysis, which is associated with factors such as exposure to non-endothelial surfaces, air exposure, positive and negative pressures, and shear stresses. Mechanical trauma to red blood cells triggers an inflammatory response and reduces vasomotor reactivity, which, when combined with hypotension, increases the risk of acute kidney injury (AKI). Excess free hemoglobin in the plasma,

resulting from hemolysis that overwhelms circulating haptoglobin, can further increase the risk of AKI.

Intraoperative hypotension (defined as a mean arterial pressure below 65 mmHg) is a significant complication during ECC, as it has been shown that if it persists for more than 10 minutes during the post-ECC phase, the risk of stroke, AKI, or death increases. Conversely, maintaining mean arterial pressure within a range between 65-85 mmHG may balance the risks of hypoperfusion and hyperperfusion, thereby optimizing cerebral blood flow and potentially reducing postoperative complications.

7. Factors Influencing the Inflammatory Response

The initial phase of the inflammatory response is triggered by blood contact with the synthetic material of the ECC circuit, due to its passage through the non-epithelialized surfaces of extracorporeal systems. This contact leads to changes in the immune response, as well as increased venous tone, alterations in hydroelectrolytic balance, and myocardial and pulmonary dysfunction [17]. Currently, there are two types of ECC circuit surface coatings: bioactive (e.g., heparin, nitric oxide) and biopassive (e.g., albumin, polyethylene oxide [PEO], phosphorylcholine) [17]. Beyond procedural factors, the patient's baseline inflammatory status is increasingly recognized as an important determinant of the magnitude of the inflammatory response to cardiopulmonary bypass. Older patients frequently exhibit chronic low-grade inflammation ("inflammaging"), characterized by persistent elevation of inflammatory mediators, endothelial dysfunction, and innate immune priming, which may amplify the inflammatory response to surgical stress and extracorporeal circulation [35,36].

Likewise, chronic conditions such as cardiovascular disease, diabetes mellitus, obesity, and chronic kidney disease contribute to a pre-existing pro-inflammatory phenotype. Emerging evidence also suggests that clonal hematopoiesis of indeterminate potential (CHIP), frequently observed in elderly individuals, may further enhance inflammatory signaling through increased production of IL-1β and IL-6, although its specific contribution to extracorporeal circulation (ECC)-induced inflammation remains to be fully established [37]. Consequently, ECC may act as a "second-hit" stimulus, amplifying complement activation, cytokine release, endothelial injury, and postoperative organ dysfunction in susceptible patients [36]. Therefore, the inflammatory response to ECC reflects not only the characteristics of the extracorporeal circuit but also the patient's preoperative inflammatory phenotype and biological susceptibility.

A study evaluating the use of pediatric membrane oxygenators with heparin-coated surfaces demonstrated that these systems showed significantly higher platelet counts, lower platelet factor release, reduced contact activation (factor XIIa and kallikrein), and lower neutrophil elastase levels ($p < 0.05$) compared to uncoated oxygenator systems [18]. The technical comparison between phosphorylcholine (PC) and heparin coatings centers on their roles as passive vs. active strategies for managing Factor XII (Contact Phase) activation.

7.1. Phosphorylcholine (PC) and the Contact Phase

Phosphorylcholine is a zwitterionic polymer that mimics the outer layer of erythrocyte membranes. Its interaction with Factor XII is primarily preventive and passive [19]:

- Hydration Barrier: PC possesses a strong water-binding ability due to its polar zwitterionic group [19]. This creates a tightly bound hydration layer that acts as a physical and free energy barrier, keeping plasma proteins at a distance from the material surface [19].

- Prevention of Adsorption: The activation of Factor XII (autoactivation) depends on its direct contact and adsorption onto a foreign surface [20,34]. By preventing the initial protein adsorption, the PC coating effectively blocks the trigger of the contact phase [19].

- Electrical Neutrality: Unlike negatively charged surfaces that are known to promote Factor XII activation, PC is electrically neutral at physiological pH [19]. This neutrality reduces the electrostatic interactions that would otherwise initiate the intrinsic pathway [19,34].

7.2. Standard Heparin Coatings

Heparin coatings function as an active, bioactive strategy, primarily targeting the products of the coagulation cascade rather than preventing the initial contact:

- Active Inhibition: Heparin acts by binding to antithrombin, dramatically accelerating its capacity to inactivate enzymes like thrombin and Factor Xa [19,34].

- Limited Impact on Contact Trigger: Although heparin-coated circuits may reduce some inflammatory factors, they often fail to completely prevent the initial activation of the blood system. Heparinization primarily aims to inhibit thrombin generation and fibrin formation after the cascade has already been initiated [19].

- Dependency on Cofactors: Heparin's effectiveness is catalytic and requires the presence of endogenous antithrombin, whereas PC functions independently based on the physical chemistry of its polymer structure [34].

Table 1. Technical comparison between phosphorylcholine and heparin coatings used in extracorporeal circulation [19, 34].

Feature	Phosphorylcholine (PC)	Heparin
Strategy type	Passive (anti-fouling)	Active (antithrombotic)
Action on Factor XII	Prevents protein adsorption and contact activation through a hydration barrier.	Inhibits downstream coagulation products (e.g., thrombin and factor Xa) after the coagulation cascade has already been initiated.
Physical mechanism	Biomimetic interface that polarizes and retains water molecules on the surface, reducing protein adhesion.	Covalent or ionic immobilization of a bioactive molecule on the biomaterial surface.
Cofactor dependency	Independent; effect is based on surface chemistry.	Dependent on antithrombin to exert catalytic anticoagulant activity.

In summary, while phosphorylcholine alters the contact phase physically excluding Factor XII from the surface through an energetic water barrier, heparin acts by neutralizing the proteolytic enzymes generated once the contact phase has already begun. It is well known that the inflammatory response is closely associated with ECC duration; however, there is no consensus on the ideal duration of extracorporeal support.

Nonetheless, studies indicate that patients who underwent ECC for the shortest possible time had fewer complications within the first 72 postoperative hours [21]. Another important point highlighted in the literature is that several other factors, beyond

ECC itself, may influence the systemic inflammatory response, such as patient age, presence of comorbidities, and the type of surgery performed [15, 22].

8. Strategies for Modulating the Inflammatory Response

Hypothermia during ECC has demonstrated beneficial effects such as the reduction of inflammatory markers like TNF-alpha and NF-kB, although it does not completely eliminate them. Additionally, it increases IL-10 levels, confirming its anti-inflammatory effect, while also reducing leukocyte counts and histological injury [23-25]. There is no standardized ideal temperature during cardiopulmonary bypass, as it varies according to physiological goals. However, some studies have shown that hypothermia at 30°C offers no additional neurological protection compared to 35°C. Importantly, during the re-warming phase, temperatures should not exceed 37°C, as this has been associated with neurological damage [23,24].

Heparin-coated circuits are extremely beneficial. Heparin molecules bound to the circuit surface resemble the heparan sulfate glycosaminoglycans present on endothelial cells, minimizing direct blood contact with artificial materials. This allows inhibition of contact system activation, complement, and neutrophils, reduces and modulates platelet activity, and decreases the release of pro-inflammatory cytokines such as TNF-alpha, IL-6, IL-8, and soluble TNF receptors [23, 24, 26]. Additional benefits include reduced hospital and ICU stay durations, decreased need for transfusion and re-sternotomy, lower incidence of pulmonary and renal dysfunction, shorter mechanical ventilation times, and reduced rates of postoperative atrial fibrillation [23, 24, 26]. Despite these advantages, these circuits are costly and therefore not routinely used [23, 24, 26].

The activation of immune system cells, especially neutrophils, plays a central role in ECC-induced inflammation. The use of leukocyte filters has been shown to not only reduce leukocyte counts but also decrease IL-8, plasma elastase, and myeloperoxidase levels, resulting in lower pulmonary vascular resistance, reduced myocardial and renal injury, and improved cardiac function [23-26]. It is important to note that leukocyte filtration with arterial line filters shows mixed results, while venous line filtration appears to attenuate inflammation more effectively. Additionally, some studies have not demonstrated clear clinical changes related to leukocyte filter use, indicating the need for further research to confirm their benefits [23, 24, 26].

Hemofiltration involves ultrafiltration (UF), a process that removes fluids and low molecular weight substances from plasma by creating a hydrostatic pressure gradient. This approach is particularly beneficial in reducing inflammation, especially in pediatric patients. Conventional ultrafiltration (CUF) occurs during ECC, while modified ultrafiltration (MUF) begins after ECC ends [23-25]. UF has the potential to remove pro-inflammatory substances during ECC (e.g., TNF-alpha, IL-1, IL-6, IL-8, C3a, and myeloperoxidase), as well as reduce cytokine concentrations in the postoperative period. Benefits include reduced need for transfusion, decreased postoperative bleeding, improved hemodynamic stability, early postoperative oxygenation, and shorter mechanical ventilation duration [23-25].

MUF has proven especially beneficial by lowering IL-6 and IL-8 levels, reducing pulmonary vascular resistance, and decreasing respiratory, neurological, and gastrointestinal complications. It also reduces transfusion needs, improves left ventricular systolic function and diastolic compliance, and increases arterial pressure [23-25].

Regarding flow regulation during ECC, the goal is to maintain physiological compatibility and minimize damage. Pulsatile versus non-pulsatile flow does not show significant differences in mediators such as IL-6 and IL-1. However, reductions in flow below standard levels are associated with decreased tissue PO_2 [25]. Hemoadsorption consists of extracorporeal blood filtration to attenuate the cytokine storm responsible for systemic inflammation. This filtration occurs through a solid sorbent agent and may help prevent acute kidney injury (AKI) after ECC by reducing circulating free hemoglobin levels [27].

The CytoSorb hemoadsorption device was developed to adsorb hydrophobic and medium molecular weight molecules, including cytokines, based on size exclusion and non-specific surface adsorption in peripheral blood. The sorbent is composed of porous divinylbenzene polymer beads encased in a polycarbonate cartridge [28]. This device enables the reduction of circulating pro-inflammatory cytokines, provides prolonged anti-inflammatory effects via IL-10, and reduces C3a and C5a levels, as well as free hemoglobin and bilirubin. It also strengthens the endothelial glycocalyx and contributes to improved hemodynamic and metabolic stabilization in the postoperative period [23]. Recent clinical trials involving patients undergoing elective surgery with CPB found no significant differences in pro- or anti-inflammatory interleukin levels. Moreover, while the procedure proved safe and feasible, it did not yield any meaningful improvement in clinical outcomes, presenting no significant differences in parameters such as SOFA scores, lactate, C-reactive protein (CRP), and procalcitonin [32, 33].

Minimally Invasive Extracorporeal Circulation (MiECC) represents a significant technological advancement designed to reduce the systemic inflammatory response and the complications associated with conventional cardiopulmonary bypass (CPB) [44]. MiECC systems are closed circuits characterized by a reduced priming volume, the absence of an open venous reservoir, and minimal blood–air contact, thereby decreasing complement activation and leukocyte activation. In addition, these systems incorporate centrifugal pumps, heparin-coated tubing, and highly biocompatible oxygenators, contributing to a more physiological perfusion [43, 44].

Studies have demonstrated that MiECC is associated with:

- Reduced levels of IL-6, TNF-α, and IL-8;
- Lower requirements for blood transfusion;
- Reduced pulmonary and renal dysfunction;
- Faster postoperative recovery and shorter intensive care unit (ICU) stays [4].

The multicenter randomized COMICS trial compared MiECC with conventional CPB and reported a 25% reduction in major postoperative adverse events in the MiECC group. However, the potential benefits of MiECC remained uncertain due to limitations in sample size [43].

Conversely, a meta-analysis by Anastasiadis et al. [44] demonstrated that MiECC is associated with significantly lower postoperative mortality, as well as a reduced incidence of major adverse events, including postoperative myocardial infarction and cerebrovascular events. Furthermore, MiECC was associated with lower rates of postoperative atrial fibrillation, reduced blood transfusion requirements, decreased blood loss, and fewer reoperations. These benefits translated into a significantly reduced need for mechanical ventilation and shorter ICU length of stay [43, 44]. Based on the findings of this meta-analysis, there is now compelling evidence (Class I, Level of Evidence A) supporting the adoption of MiECC as a safe and effective alternative to conventional CPB, particularly in coronary artery bypass grafting and elective valve surgery.

9. Nutritional Aspects

Among the key factors contributing to the inflammatory state induced by ECC are blood contact with non-endothelialized surfaces of the extracorporeal circuit, the release of pro-inflammatory mediators, and complement activation, which ultimately lead to a hypercatabolic state and increased metabolic demand in patients [29]. In this context, clinical nutrition emerges as a fundamental strategy for modulating the inflammatory response, preventing malnutrition, and optimizing clinical outcomes. Patients undergoing ECC present a hypermetabolic state characterized by increased protein catabolism,

insulin resistance, and alterations in splanchnic perfusion, compromising gastrointestinal function and nutrient absorption [30]. This condition is exacerbated by prolonged preoperative fasting and delayed initiation of nutritional support, increasing the risk of iatrogenic malnutrition and worsening surgical outcomes [29].

Nutritional therapy for patients undergoing ECC must be individualized and initiated early, taking into account the metabolic particularities of this population. Enteral nutrition is preferred whenever possible, as it preserves the integrity of the intestinal barrier, reduces bacterial translocation, and improves the immune response [31]. Nevertheless, the early enteral nutrition (EN) requires caution in the immediate post-ECC phase, as it depends heavily on the patient's hemodynamic stability. The severe systemic inflammatory response syndrome (SIRS) induced by ECC often leads to the vasoplegia, which requires aggressive resuscitation with escalating doses of alpha1-adrenergic vasopressors like norepinephrine [38]. These catecholamines cause intense splanchnic vasoconstriction and compromise mesenteric blood flow [39].

If the EN is initiated under these conditions, the presence of nutrients increases the oxygen demands of enterocytes. However, this metabolic demand cannot be met by the already restricted arterial supply [40]. This local mismatch of supply and demand can rapidly jeopardize mucosal viability and lead to non-occlusive mesenteric ischemia (NOMI) and bowel necrosis [41]. Therefore, international guidelines recommend delaying the initiation of EN in patients with uncompensated shock and on high and increasing doses of vasoactive drugs. Perfusion should be optimized and the abdomen carefully observed before the initiation of feeding [40, 41].

Diet composition also directly influences the inflammatory response. Diets enriched with omega-3 fatty acids, for example, have been shown to reduce the production of pro-inflammatory eicosanoids derived from arachidonic acid, promoting an anti-inflammatory profile [29]. Furthermore, antioxidant supplementation with selenium and vitamin C has been studied as a strategy to reduce oxidative stress induced by ECC, although the clinical evidence supporting their benefits remains limited [30].

10. Conclusion

Extracorporeal circulation, although a major advance in cardiovascular surgery, is intrinsically linked to a complex systemic inflammatory response, which may result in various postoperative clinical complications. The processes involved in this inflammatory cascade are diverse, including activation of the complement system, release of pro-inflammatory cytokines, leukocyte activation, oxidative stress, and the subsequent development of multi-organ dysfunction. In this context, several technological, pharmacological, and procedural tactics have been suggested and applied to attenuate this response and optimize patient outcomes. The progress of methods such as heparin-coated circuits, hemoadsorption, minimally invasive extracorporeal circulation (MiECC), and adequate nutritional support highlights the relevance of a multidisciplinary approach. However, important gaps in research still restrict the strength and comparability of current evidence, which affects the consistency with which these tactics can be translated into standardized perioperative practice.

The main gaps in the literature include: (i) limited direct comparisons between mitigation strategies in standardized extracorporeal circulation settings; (ii) inconsistent reporting of extracorporeal circulation variables (for example, circuit type/coating, flow parameters, temperature targets, and ultrafiltration strategy); (iii) heterogeneity in biomarker selection and sampling windows; and (iv) insufficient integration of mechanistic markers with clinically meaningful outcomes. Filling these gaps is crucial to increase reproducibility and determine which interventions offer a clear clinical benefit beyond reductions in laboratory indicators of inflammation.

From a clinical standpoint, the evidence gathered in this review helps connect mechanisms to bedside decisions. Recognizing extracorporeal circulation as a trigger for complement activation and cytokine release supports the selection of more biocompatible

circuits when available, limiting unnecessary blood–air interface, preventing excessive rewarming, and anticipating organ-specific complications (renal, pulmonary, neurologic, and hemorrhagic), especially in prolonged or complex procedures. In addition, early nutritional assessment and individualized support can be incorporated into perioperative planning for higher-risk patients, with the aim of attenuating catabolism and promoting postoperative recovery.

Therefore, a thorough understanding of the underlying pathophysiology, combined with protocol-based preventive measures and multidisciplinary coordination, represents a central pillar for increasing the safety and recovery of patients undergoing extracorporeal circulation. Future research should prioritize well-designed prospective studies and pragmatic comparative trials with harmonized reporting and outcome definitions to establish feasible, evidence-based anti-inflammatory bundles for routine clinical practice.

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