REVIEW ARTICLE

Regulatory T cells in the "inflammatory balance" as a response to extracorporeal circulation in cardiac surgery. A narrative review

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Extracorporeal circulation (ECC) offers the benefit of maintaining a bloodless and still surgical field, providing a suitable surgical scenario for the performance of the surgical procedure. It is an essential procedure in virtually all heart surgeries, aiming to temporarily replace the function of the cardiopulmonary system, thus maintaining blood perfusion to organs and body tissues. Unfortunately, the use of this procedure triggers an inflammatory cascade, with endothelial dysfunction being the main triggering mechanism. This damage is a result of the contact between blood components with synthetic plastic surfaces, activating an intense inflammatory response, impacting the postoperative outcomes of patients undergoing this procedure. Regulatory T cells (Tregs) are a subtype of T lymphocytes that play a role in modulating the inflammatory response, specially by activation of a transcription factor called FOXP3. In this revision was identified that the understanding of Treg lymphocytes T and ECC interaction will improve an opportunity to comprehend the physiopathology of development and activation of inflammatory process into cardiac surgery, although ECC has generated an impact on cardiac surgery, also has a price to pay associated to inflammatory phenomenon with negative effect on postsurgical evolution in patients that underwent to cardiac surgery and the recognition of the lymphocytes TregFoxP3 regulatory capacity offer to develop future strategies that promote activation and it´s preservation during ECC through immunomodulatory drugs, such as corticosteroids and adrenergic receptor agonists will to help improve the outcomes of heart surgery.

Key words: *Extracorporeal circulation; Inflammatory response; T regulatory lymphocites; Transcription factor FOXP3.*

La Circulación Extracorpórea (CEC) ofrece el beneficio de mantener un campo quirúrgico exangüe que aporta un escenario quirúrgico apropiado para la realización del procedimiento intracardiaco, condición indispensable en prácticamente todas las cirugías de corazón. Desafortunadamente, este procedimiento desencadena una cascada inflamatoria debido al contacto de la sangre con las superficies de la CEC. Esta inflamación puede tener un impacto negativo en la recuperación del paciente. Los linfocitos T reguladores son un subtipo de linfocitos T que intervienen en la modulación de la respuesta inflamatoria, especialmente a través de la activación de un factor de transcripción denominado FOXP3 que participa como el principal regulador transcripcional de los linfocitos Tregs. En esta revisión se identificó que la comprensión de la interacción entre los linfocitos Tregs y la CEC ofrece la oportunidad de entender la fisiopatología involucrada en la activación y desarrollo de la inflamación en la cirugía cardíaca, que a pesar que la CEC ha generado un gran impacto en el desarrollo de la cirugía a corazón abierto hay un precio que pagar, asociado al fenómeno inflamatorio que desencadena y finalmente afectando la evolución posquirúrgica del paciente sometido a dicho procedimiento y adicionalmente se reconoce que la capacidad reguladora de inflamación de los linfocitos TregFoxP3 ofrece la oportunidad de desarrollar estrategias futuras que propicien su activación, preservación de su función durante la CEC mediante fármacos inmunomoduladores, como corticosteroides y agonistas de receptores adrenérgicos, para coadyuvar en la mejora de resultados de la cirugía cardiaca.

Palabras clave: *Circulación Extracorpórea; Respuesta inflamatoria; Linfocitos T reguladores; Factor de transcripción FOXP3.*

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Cardiac surgery has experienced significant advancements in recent decades, due to the introduction and refinement of surgical techniques and innovative technologies. Among these techniques, extracorporeal circulation (ECC) has become a fundamental tool in performing complex cardiac procedures. ECC allows for the adequate perfusion and oxygenation of vital organs while surgical correction is being performed on the heart, such as in the repair of congenital heart defects, coronary revascularization, heart transplantation, and valve correction [1].

Despite its undeniable utility, ECC triggers a systemic inflammatory response associated with coagulopathy, neurological, pulmonary, and renal dysfunction, with hemodynamic effects and a negative impact on the patient's recovery and outcomes. Therefore, it is crucial to thoroughly understand the technical and pathophysiological aspects of ECC, as well as identify strategies to mitigate and prevent complications.

Recently, the possibility of a regulatory response of the body's inflammatory process has been identified, which may also be present during extracorporeal circulation [2]. This review will examine some components involved in extracorporeal circulation, the inflammatory process it triggers, as well as the role of regulatory T lymphocytes (Tregs) as a possible regulatory response to the immune response triggered by ECC and their potential implications in clinical outcomes.

Components of extracorporeal circulation

ECC is an essential procedure for virtually all interventions in cardiac surgery, temporarily replacing the function of the cardiopulmonary system to maintain blood oxygenation and perfusion of the organs and tissues of the body. The device or pump diverts deoxygenated venous blood from the right atrium of the heart through cannulas (made of polyurethane) and plastic tubing (PVC or polyvinyl chloride) to a reservoir that is connected to a pump. Depending on its mechanism of action, the pump directs the blood either to a membrane oxygenator to carry out gas diffusion or through the tubing and another cannula inserted directly into the ascending aorta or another medium-sized artery, subsequently supplying the entire body, maintaining aerobic metabolism, and ensuring perfusion to all organs. This procedure offers the benefit of maintaining a bloodless and motionless surgical field, providing an appropriate setting for the surgical procedure [1].

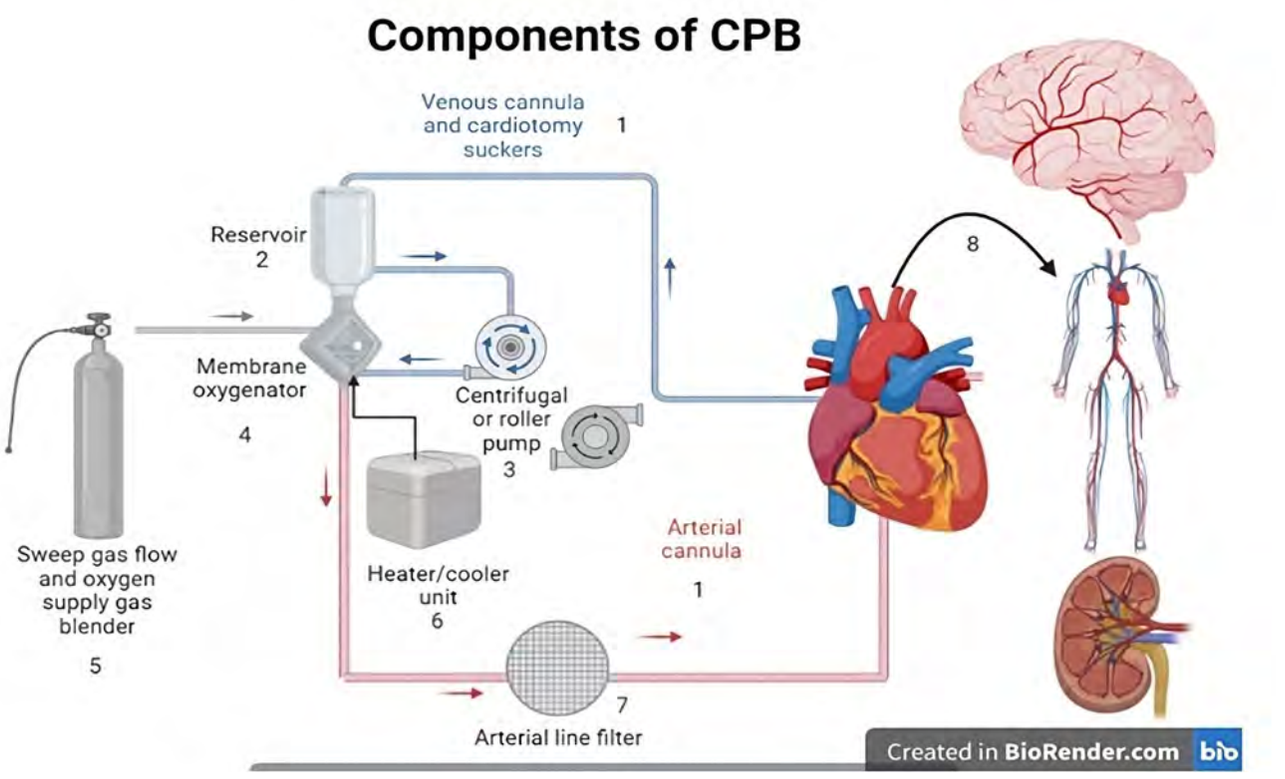

Figure 1. Components of conventional extracorporeal circulation. 1) Venous cannula, cardiotomy suction and arterial cannula. 2) Venous reservoir. 3) Centrifugal/roller pump. 4) Membranae oxygenator. 5) Sweep flow and oxygen mixer blender. 6) Heating/cooler unit device. 7) Arterial line. 8) Systemic blood distribution to vital organs. The components mentioned above are commonly used in conventional extracorporeal circulation. However, variations in the specific equipment and configurations may exist depending on the surgical procedureand individual patient needs.

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In recent decades, numerous advances in equipment and techniques have been introduced, resulting in notable improvements in the morbidity and mortality of patients undergoing ECC (**Fig. 1**) [2-4].

The main components of extracorporeal circulation are:

1. Arterial and venous cannulas: These are flexible PVC (polyvinyl chloride) and/or polyurethane tubes used to connect the extracorporeal circulation system to the patient's arterial and venous system. The venous cannula is inserted into a vein to drain deoxygenated blood to the ECC machine, while the arterial cannula is placed in an artery (ascending aorta in central cannulation or axillary/femoral artery in peripheral cannulation) to return oxygenated blood to the body. The inflammatory response associated with cannulas is primarily due to their interaction with blood and foreign material surfaces. Their surface, especially if made of non-biocompatible materials like PVC, can trigger an immune response. Blood cells and proteins can adhere to such surface, activating inflammatory pathways and leading to the release of inflammatory mediators, initiating a cascade known as the contact activation pathway and promoting leukocyte activation and adhesion [5-6].

The composition of the cannula material can influence the magnitude of the inflammatory response. For example, cannulas made of more biocompatible materials, such as polymers with hydrophilic coatings, have been developed to reduce the inflammatory reaction. Additionally, the design of the cannula can also affect this response. Smooth and rounded cannula tips and a reduced contact surface can minimize blood flow disruption and decrease inflammation [7].

The modification of the circuit surface, aiming to replicate the antithrombotic and anti-inflammatory properties of the endothelium, includes the application of biomimetic surfaces (e.g., using heparin or direct thrombin inhibitors), biopassive surfaces (by using phospholipid-like phosphocholine or albumin), and more experimental attempts at endothelialization of circuit components. The most used biomimetic approach, which seeks to replicate the antithrombotic and anti-inflammatory properties of the endothelium, is heparin coating, which has shown to reduce cellular activation and release of inflammatory mediators in clinical studies of extracorporeal membrane circulation, as well as in in vivo models, and is even associated with better clinical outcomes such as shorter ICU stays and lower incidence of postoperative atrial fibrillation. Preparing the circuit with a heparin-albumin solution can have a similar effect, as PVC can absorb plasma proteins. On the other hand, biopassive approaches aim to make the circuit more inert. A common technique is coating with phospholipid-like phosphocholine, which is the main component of cell membrane phospholipids. It is believed that the formation of a biomembrane-like surface reduces thrombin formation, although its effect on inflammation is not well understood [8].

2. Venous reservoir: It is a reservoir that stores deoxygenated blood returning from the patient. The venous reservoir has the capacity to collect and filter the blood before sending it to the oxygenator for gas exchange. The flow dynamics within the venous reservoir can generate mechanical stress and turbulence, which can contribute to inflammation. Turbulent flow patterns and high shear stress can activate endothelial cells and trigger an inflammatory response. Design modifications in the venous reservoir, such as optimizing flow patterns and reducing turbulence, can help mitigate this effect. Changes in geometry can be made to improve flow and reduce turbulence. Proper sizing and strategic placement of these connections can facilitate more uniform flow and reduce turbulence. The use of biocompatible materials in constructing the reservoir can also reduce the inflammatory response and promote a more laminar flow [9].

3. Blood pump: It is a component responsible for propelling oxygenated blood from the oxygenator back into the patient's body. The blood pump can be either a roller pump or a centrifugal pump, and its function is to maintain adequate blood flow during surgery while the patient's heart is stopped. While both types of pumps are effective in providing blood circulation, they may differ in their impact on inflammation. The roller pump operates by compressing flexible PVC tubes to propel the blood forward. It is a pulsatile pump that generates an intermittent flow. The roller pump has been associated with a higher degree of shear stress and turbulence compared to centrifugal pumps. These factors can activate endothelial cells and trigger an inflammatory response. The increased presence of these factors may contribute to a higher risk of hemolysis and platelet activation, potentially leading to increased inflammation. On the other hand, the centrifugal pump utilizes rotational forces to propel the blood forward. It provides a continuous flow with less pulsatility compared to roller pumps. Centrifugal pumps generally generate less shear stress and turbulence, theoretically resulting in less endothelial cell activation and a potentially milder inflammatory response compared to roller pumps.

It is important to note that the choice between a roller pump and a centrifugal pump in cardiac surgery is based on various factors, including surgeon preferences, patient characteristics, and specific procedure requirements. It should be mentioned that research and some clinical studies have examined the impact of pump types on inflammation, but specific findings and conclusions may vary among studies.

Passaroni et al. [10] analyzed 60 patients undergoing coronary artery bypass grafting (CABG) surgery with ECC. The patients were randomly assigned to two groups: Group 1 (roller pump) and Group 2 (centrifugal pump). Measurements of haptoglobin and lactate dehydrogenase (LDH) were performed to evaluate hemolysis, and levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) were measured to assess the inflammatory response. No significant differences were found in the incidence of hemolysis and inflammatory response between the roller and centrifugal pumps. However, significant differences were observed in haptoglobin, LDH, and CRP levels at different time points, indicating hemolytic and inflammatory changes during the perioperative period.

Keyser et al. [11] conducted a prospective, randomized study involving 240 adult patients undergoing CABG surgery with ECC, where five different types of arterial pumps were used: roller pump, peristaltic pump, Sarns Delphin centrifugal pump, Rotaflow centrifugal pump, and Bio-Medicus Bio-Pump BP 80 centrifugal pump. The results showed a decrease in hemoglobin levels, hematocrit, and red blood cell count after surgery, which then recovered on the third postoperative day. There were no significant differences between the groups in these parameters. Platelet count decreased after surgery and recovered on the third postoperative day, with no significant differences between the groups. In terms of clinical outcomes, there were no significant differences between the groups in terms of mechanical ventilation time, ICU stay, and hospital-

ization duration. There were also no significant differences in intraoperative blood loss, amount of postoperative blood drainage, or transfusion of red blood cell concentrates or fresh frozen plasma.

While one of the studies carrying significant weight is the meta-analysis conducted by Saczkowski et al. [12], where they evaluated 18 randomized clinical trials that met their inclusion criteria and represented 1868 patients (Centrifugal pump= 961, Roller pump= 907). The predominant operation was coronary artery bypass grafting, and fixed-effect pooled estimates were performed for the end of ECC and the first postoperative day for platelet count (ECC: P = 0.51, first postoperative day: P = 0.16), free plasma hemoglobin (ECC: P = 0.36, first postoperative day: P = 0.24), white blood cell count (ECC: P = 0.21, first postoperative day: P = 0.66), and hematocrit (ECC: P = 0.06, first postoperative day: P = 0.51). No difference was demonstrated in postoperative blood loss (P = 0.65) or red blood cell transfusion (P = 0.71). The duration of ICU stay (P = 0.30), hospital stay (P = 0.33), and mortality (P = 0.91) were similar between both groups, with no significant differences in the evaluated variables.

Roller pumps and centrifugal pumps produce non-pulsatile flow (NPF) by default, and this remains the most used mode of perfusion. The development of pulsatile pumps has allowed for comparisons with NPF. Pulsatile flow (PF) mimics the arterial pulse generated by the heart and is considered more physiological by some.

Most of the articles reviewed by Tan et al. [13] in their review article on PF were randomized controlled trials. However, there was wide variation in study methodology, pulse-generating method, and how pulsatility was measured. Most of the evidence in favor of PF showed marginal improvement in renal and pulmonary outcomes. Although there is a lack of high-quality randomized clinical trials that can inform short- and long-term clinical outcomes of PF, further research is needed to reach a conclusion regarding its benefits on organ function. Pulsatility is an important factor for maintaining vascular function and homeostasis during cardiac surgery with ECC. Lack of pulsatility can have detrimental effects on the endothelium and organ perfusion, while pulsatile circulation may be beneficial. This alternating cycle of pressure and flow generates different hemodynamic forces, such as pulse pressure, cyclic shear stress, and cyclic strain, which are sensed at the cellular level and give rise to a variety of physiological responses. The endothelial glycocalyx (EG) is a critical component of endothelial cells and is a primary sensor of shear stress, vital for endothelial nitric oxide (NO) production [14,15], which tends to maintain endothelial homeostasis, including regulation of vasomotor tone, vascular permeability, and acts as an important antioxidant. Additionally, the EG plays a critical role in modulating inflammatory responses, acting as a physical barrier for leukocyte recruitment and extravasation. Loss of pulsatility can induce endothelial injury, demonstrated by degradation and release of the EG through markers such as heparan sulfate and syndecan-1, lasting up to 3 days after an average of approximately 100 minutes of pulsatile-free ECC [16].

At least in theory, pulsatile circulation should avoid the detrimental effects of non-pulsatile circulation on the endothelium.

4. Membrane oxygenator: It is a medical device used in ECC to provide oxygenation and remove carbon dioxide from the blood during cardiac surgical procedures. It consists of a hollow fiber membrane that serves as a gas exchange interface, separating the patient's blood and facilitating the interaction between blood and air, allowing the transfer of oxygen from the gas to the blood and the removal of carbon dioxide from the blood into the gas. The membrane is designed to be gas-permeable, meaning it allows oxygen and carbon dioxide molecules to diffuse through it. This is achieved by selecting suitable materials for membrane fabrication, such as polypropylene, polysulfone, or polymethylpentene. The gas exchange membrane has a porous or microporous structure that provides a large surface area for gas exchange. This structure allows gas molecules to pass through the membrane pores while preventing blood cells or larger particles from doing so [17]. Additionally, advanced oxygenators now incorporate the necessary materials for the heating/cooling unit and arterial line filters within their design, improving outcomes in cardiac surgery by reducing some of the complications triggered by ECC use (macro and micro systemic emboli) [18].

To reduce the inflammatory response during ECC, strategies such as the use of biocompatible surface-coated oxygenators, chemical modifications, and modified perfusion techniques have been implemented. These measures aim to minimize blood cell activation, oxidative stress, and clot formation [19].

Through the history of cardiac surgery with ECC, various types of oxygenators have been developed to facilitate gas exchange and improve oxygenation efficiency. These range from bubble oxygenators, which were the first to be used, to screen oxygenators, disc oxygenators, and the development of membrane oxygenators and high-performance oxygenators used in extracorporeal membrane oxygenation, designed for longer operating times due to their greater surface area for gas diffusion, durability, and biocompatibility in this type of extracorporeal oxygenation therapy [20].

The evolution of oxygenators used in ECC has been driven by the search for more efficient and biocompatible devices that reduce the inflammatory response and improve clinical outcomes. Technological advancements continue in this field, aiming to further enhance the safety and performance of oxygenators in cardiac surgery and other procedures requiring extracorporeal circulation. The latest data demonstrate that there is no single superior product in all aspects. Biochemically, there are small differences among oxygenators that do not translate into clinical differences in outcomes. The design and selection of the ideal oxygenator depend on the specific performance aspects that the perfusion team and surgical team consider relevant in the decision-making process [21–31].

5. Oxygen blender and sweep flow system: The oxygen blender is a critical component of ECC that precisely controls the ratio of oxygen and other gases in the mixture to ensure that the blood receives the appropriate amount of oxygen according to the patient's needs. This is important for maintaining adequate oxygenation levels and preventing hypoxemia (low blood oxygen levels) or hyperoxemia (excessively high blood oxygen levels) during the procedure. While there is no universally accepted strategy for managing oxygen metabolism during ECC, the trend, particularly among surgical teams and perfusionists, leans towards hyperoxemia in a significant number of centers

performing cardiac surgeries with ECC [32]. The discrepancy in preferences has been examined through surveys on oxygen administration during cardiac surgery with extracorporeal circulation. The survey included 317 anesthesiologists and 237 perfusionists, and revealed differences in oxygenation preferences between the two groups. Anesthesiologists were more comfortable with lower oxygen tension (90-250 mmHg PaO2), while perfusionists preferred higher levels (150-325 mmHg PaO2). This discrepancy is due to the availability of real-time peripheral oxygen saturation monitoring for anesthesiologists, which allows for more precise adjustment of oxygen administration. On the other hand, perfusionists lack this advantage during extracorporeal circulation and tend to titrate toward higher oxygen levels to avoid hypoxemia. Additionally, perfusionists also considered the presence of gas microemboli as a factor influencing their preference for higher oxygen levels [33].

There are potential risks and adverse effects associated with hyperoxemia (exposure to elevated oxygen levels) during ECC, with one of the main concerns being the threshold for determining hyperoxemia levels. While it is claimed to have therapeutic benefits such as myocardial preconditioning to better tolerate ischemia, reduced rates of postoperative wound infection, and decreased generation of gas microemboli during ECC, there are concerns about the negative impact of high partial pressures of oxygen on cardiac, vascular, neurological, respiratory, and renal function, as well as the possibility of exacerbating ischemia-reperfusion injury by altering the production of reactive oxygen species (ROS) that can accelerate the established inflammatory process [34].

One recent study by Douin et al. [35], a multicenter cohort study involving 21,632 patients undergoing ECC, demonstrated that hyperoxemia occurred over 96% of the time before, during, and after extracorporeal circulation. Cumulative intraoperative exposure to hyperoxemia, assessed continuously as the area under the curve, was associated with the development of postoperative pulmonary complications in a linear relationship during ECC. Increasing exposure to hyperoxemia before and during ECC was associated with a higher risk of postoperative pulmonary complications, while lower levels of hyperoxemia exposure after ECC were associated with a lower risk. Prospective clinical trials are needed to determine the causal relationship between hyperoxemia and not only postoperative pulmonary complications but also to establish optimal oxygenation targets during cardiac surgery. The upcoming "Risk of Oxygen during Cardiac Surgery" trial [36] may reveal optimal oxygenation goals for both cardiothoracic anesthesiologists and perfusionists.

Based on current evidence, normoxemic management may also reduce oxygen-derived free radicals during ECC, as well as reduce inflammatory cytokines. Completely preventing systemic inflammatory response syndrome (SIRS) is challenging as it is related to multiple factors, including direct contact of blood cells with artificial surfaces followed by leukocyte activation, ischemia-reperfusion injury to the heart and lungs, and oxidative injury. However, we can minimize SIRS by reducing oxidative injury, ischemia-reperfusion injury, and the production of anti-inflammatory cytokines [38].

The sweep flow system refers to a component used to remove exhaled carbon dioxide (CO2) and other residual gases from the ECC circuit during blood oxygenation. It works by extracting a small amount of gas from the oxygenator or venous return line and subsequently eliminating it from the circuit by connecting it to a CO2 removal device such as a CO2 absorber or filter. While this is not directly related to inflammation, efficient removal of CO2 and residual gases can help maintain proper homeostasis and reduce oxidative stress in the cardiovascular system. The gas removed through the sweep flow system contains CO2 exhaled by the patient and other residual gases. Its elimination helps maintain adequate CO2 levels in the oxygenated blood that is returned to the patient during ECC. This contributes to maintaining acid-base balance and ensures that the circulating blood is properly oxygenated and free from undesirable residual gases.

Some authors follow strategies for pH management through sweep flow and have found differences in pediatric and adult management. Thus, the trend is to make the necessary adjustments and modifications based on goal-directed therapy, which in this case would involve maintaining a pH range of 7.35-7.45 depending on the clinical context. Karabulut et al. [39] evaluated thirty patients undergoing isolated coronary artery bypass grafting and randomly and equally assigned them to three groups. The sweep flow to the oxygenator was maintained at 1.35 Lt/min/m2 in Group 1, 1.60 Lt/min/m2 in Group 2, and 2.0 Lt/min/m2 in Group 3. Blood gas samples were taken at the following time points: T1: before ECC; T2: 5 minutes after the start of ECC; T3: just before rewarming; and T4: at the end of rewarming. At 5 minutes after the start of ECC (T2), pCO2 significantly decreased in Groups 2 and 3 compared to Group 1 ($p < 0.02$). With the addition of hypothermia (T3), changes in pH and pCO2 became more profound, and during this period, levels in Group 3 exceeded physiological limits, with pCO2 and pH values of 28 ± 3 mmHg and 7.50 ± 0.04, respectively. At the end of the rewarming period (T4), despite increased carbon dioxide production, pCO2 values were below physiological limits in Groups 2 and 3. They concluded that the gas sweep flow to the oxygenator should be maintained between 1.35 and 1.60 L/min/m2 during ECC to avoid hypocapnia, which leads to alkalosis and has detrimental effects on pulmonary, cerebral blood flow, and the cardiovascular system.

On the other hand, Clingan et al [38]. retrospectively analyzed 1,077 cases in which PaCO2 values were not lower than 30 mmHg or higher than 50 mmHg in preoperative blood gas results. They examined the respiratory-to-blood flow ratio (V/Q) within the first few minutes of initiating ECC. A V/Q of 0.6 had an odds ratio (OR) of 1.57 for achieving a PaCO2 value between 35 and 45 mmHg in the initial blood gas analysis during ECC compared to a V/Q of 0.4. A V/Q of 0.9 had an OR of 1.76 compared to a V/Q of 0.4 and an OR of 1.12 compared to 0.6. Using a V/Q ratio of 0.6 achieved a PaCO2 value within normal physiological limits without a significant advantage compared to a higher V/Q ratio overall. However, younger or smaller patients required a higher V/Q ratio to achieve similar odds and PaCO2 values compared to larger or older patients. They contrast this ratio with the previous study by Karabulut [39] and compare sweep flow rates of 1.35, 1.6, and 2 Lt/min/m2, which would translate to V/Q ratios of 0.675, 0.8, and 1, respectively.

Although these are observational studies, the information described allows for an analysis of the situation. Depending on the experience of the surgical team, hospital infrastructure, and available resources, goal-directed therapy based on

physiological parameters should be the trend in managing ECC circuit components.

6. Heating/Cooling Devices: During ECC, the blood circulating outside the patient's body tends to cool down. To maintain proper body temperature, a device is used to heat the blood before reintroducing it into the body. This helps prevent hypothermia and maintain normal metabolic function.

These first-generation devices control temperature by heating or cooling water and circulating that water through water lines to a disposable heat/cold exchanger located in the ECC oxygenator. Typically, they consist of at least two circuits: a patient circuit, responsible for maintaining the patient's body temperature, and a cardioplegia circuit, responsible for cooling a solution directly administered to the heart [40]. Due to the presence of a water reservoir in these devices, they have long been postulated as a potential source of infection, especially Mycobacterium chimaera, a member of the Mycobacterium avium complex, a group of slow-growing nontuberculous mycobacteria [41]. In 2015, a deadly outbreak of Mycobacterium chimaera was attributed to the use of heating/cooling units during extracorporeal circulation [42]. It was confirmed that the transmission route for these bacteria was aerosolization through the device's exhaust fan, which dispersed bacteria into the operating room air. Since this discovery, multiple cases of M. chimaera infections have been attributed to heating/cooling units, causing significant harm and even death to patients [43].

As a result, the US Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) recommended strictly following a cleaning, disinfection, and maintenance protocol provided by the device manufacturers, as well as water sampling and monitoring. The protocol involves cleaning and disinfecting the equipment following the manufacturer's instructions, environmental testing, measures to be taken in case of positive results, reporting instructions, task allocation among hospital departments (preventive medicine department, clinical microbiology and parasitology department, and cardiac surgery department), and case identification standards. According to the protocol, the Sorin system (LivaNova) cleaning and disinfection include the following: surface and water circuit disinfection (before first use, before storing the device, and during regular use), surface disinfection after each use, water replacement (adding hydrogen peroxide to tanks), and overflow bottle disinfection every 7 days, water circuit disinfection every 14 days, tube replacement every year, and annual cleaning and disinfection by the manufacturer [43].

The second-generation glycol exchange system is a widely accepted technology used in applications requiring biostatic capacity. The solution involves reformulating the biostatic thermal fluid into a biocidal thermal fluid. This is achieved by adding monomeric glutaraldehyde (Quantum, Medtronic) and has the potential to eliminate aerosolization-related infections, such as those caused by M. chimaera, avoiding the use of chemical agents for disinfection. Although it requires the use of an additional disposable heat exchanger and manipulation of the glycol by the operator, it offers greater control and lower risk of malfunctions. However, its recharge is not automated and requires the physical presence of the user. These technological improvements are important for safety and efficiency during cardiac surgery [43].

Regarding inflammation during ECC, the patient's body is cooled to a lower temperature to decrease metabolic demand and protect vital organs. This hypothermia can have anti-inflammatory effects by reducing the release of inflammatory mediators and attenuating the immune response. Low temperatures can also decrease cellular metabolism, reducing tissue injury and inflammation. On the other hand, warming the patient after the hypothermic period can trigger an inflammatory response. The sudden increase in temperature during rewarming can activate inflammatory pathways and promote the release of pro-inflammatory cytokines. This response is known as reperfusion injury and can contribute to inflammation and tissue damage. The use of this device in ECC allows precise control of the patient's body temperature. Gradual rewarming is often employed instead of rapid rewarming to minimize the inflammatory response. By controlling the rewarming rate and maintaining a stable temperature, the inflammatory cascade can be attenuated, reducing the risk of complications associated with excessive inflammation [44-46].

7. Arterial line filter: It is a device used to remove any particles or microemboli before they return to the patient, helping to prevent systemic macro and microembolism during cardiac surgery. The efficacy of the arterial line filter in ECC has been the subject of research, and studies have been conducted to evaluate its impact on various aspects, including the inflammatory response. According to the available evidence, the use of an arterial line filter during ECC can help reduce the burden of microemboli and particles in the patient's circulation. This can have a beneficial effect by decreasing the inflammatory response and preventing potential complications related to inflammation [47].

The particles present in the bloodstream during ECC can vary in size. Generally, smaller particles are considered to have a greater potential for causing harm as they can pass through filters and access organs and tissues. The retention capacity of these filters typically ranges from particles of approximately 40 micrometers (μm) to particles of around 20 μm [48].

The oxygenator and arterial line filter have been integrated into a single device as a method to reduce priming volume and surface area, as mentioned earlier. The instructions for use of a currently available oxygenator with an integrated arterial line filter recommend incorporating a distal recirculation line at the outlet of the oxygenator. However, according to a non-scientific survey, 70% of respondents use ECC circuits that incorporate these integrated filters without a distal recirculation pathway at the oxygenator outlet. Considering this circuit design, the ability to quickly eliminate a large air bubble in the blood path distal to the oxygenator outlet may be compromised. Reagor et al. [49] concluded in that a distal recirculation line to an oxygenator with an integrated arterial line filter significantly reduces the time required to remove an air bubble from the ECC circuit and may be safer for clinical use than the same circuit without a recirculation line.

8. Anticoagulants: ECC is a process in which blood flow is diverted outside the body to perform complex cardiac surgical procedures. During ECC, heparin is used as a systemic anticoagulant to prevent clot formation in the extracorporeal circuit and ensure adequate blood flow. Heparin belongs to the family of glycosaminoglycan (GAG) molecules, which consist of repeated disaccharide units of uronic acid residues (L-iduronic acid or D-glucuronic acid) and N-acetyl-D-glucosamine. Un-

fractionated heparin (UFH) is the least processed form of natural GAG and is derived from purified porcine intestinal tissue. It has a molecular weight of 3 to 30 kDa [50].

The pentasaccharide sequence-containing unfractionated heparin is responsible for its interaction with antithrombin (AT) on thrombin. Heparin is anionic and binds to the positively charged residues of the protease inhibitor AT. This causes a conformational change in the reactive arginine center of AT and an increase in the rate and binding activity of AT by up to 1000-fold. Furthermore, the reactive arginine center of AT covalently binds to the active serine protease center of thrombin (factor IIa), factor Xa, and other serine proteases, irreversibly inhibiting their procoagulant activity. Heparin molecules containing the pentasaccharide sequence have strong anticoagulant effects through their binding with AT, facilitated by binding to exosite II. Because access to exosite II is obstructed, heparin does not act on fibrin-bound thrombin, unlike direct thrombin inhibitors [51].

Recent guidelines from the Society of Thoracic Surgeons (STS) and the Society of Cardiovascular Anesthesiologists (SCA) in 2018 have provided recommendations on the dosing and monitoring of heparin for CPB. The key principles from this document are as follows [52-55]:

Before initiating CPB, adequate anticoagulation should be demonstrated through an activated clotting time (ACT). Heparin doses for CPB start at 300-400 IU per kg of total body weight, but individual response to heparin is heterogeneous. Adequate anticoagulation is considered when the activated clotting time (ACT) is above 480 seconds. There is significant molecular variability in unfractionated heparin (UFH); therefore, the dose-response relationship is complicated.

Alternative methods exist to calculate the initial heparin dose, such as ex vivo heparin response curves, which compare ACTs with added UFH concentrations. The HepCon heparin response model is based on adding two heparin concentrations, 1.7 IU/ml and 2.84 IU/ml, to the patient's blood plasma and assumes a linear dose-response relationship. It then estimates the heparin dose needed to achieve concentrations of 2 IU/ml, which falls between the two used heparin concentrations. However, studies have shown poor correlation between the calculated in vitro heparin response curve and the actual patient response to heparin.

Activated clotting time (ACT) is considered the "standard of care" for assessing anticoagulation during CPB. In the clinical context of an ACT for safe anticoagulation during CPB, heparin concentration and ACT maintain an approximately linear relationship. All tests operate with different methodologies (amount/type of activator).

Protamine reverses the anticoagulant effect of heparin by forming an ionic bond between the anionic charge of heparin and the cationic charge of protamine. This new complex prevents heparin from binding to antithrombin (AT) and causes dissociation of heparin already bound to AT, allowing AT function to return to normal. The neutralization of heparin by protamine is amplified by platelet factor 4 (PF4) activity. Platelet factor 4 is released by platelets that are activated during CPB and acts to stabilize the heparin-protamine complex. The protamine-heparin complex is cleared through the reticuloendothelial system. The elimination half-life is 7.4 minutes, so most protamine is cleared from the body after 15 minutes.

Protamine has a range of unwanted effects that vary in severity and morbidity. The rate of adverse reactions is documented between 0.1% and 13% and includes hypotension, pulmonary hypertension, and anaphylaxis. Most severe reactions occur within the first 10 minutes of injection. Independent risk factors for protamine reaction include the use of insulin containing protamine (NPH insulin), previous reaction to protamine, allergy to protamine or fish, and any history of non-protamine drug allergies.

Hypotension is the most common hemodynamic effect and varies in severity from mild instability to cardiovascular collapse. It is defined as a systolic blood pressure (SBP) <100 mmHg or a reduction in mean arterial pressure (MAP) >10 mmHg.

Anaphylaxis associated with protamine has an incidence of 0.19%. Both immunoglobulin E (IgE)-mediated and IgG-mediated anaphylaxis have been described. Severity and incidence are related to the presence of specific antibodies against protamine. Heparin-protamine complexes are known to activate the classical complement pathway, leading to basophil and mast cell degranulation through C3a and C5a.

To achieve successful anticoagulation during CPB, it is necessary to reverse anticoagulation both at the end of CPB and during the postoperative period. Insufficient doses of protamine have been shown to increase postoperative bleeding; however, high doses of protamine have also been associated with increased postoperative bleeding.

Regimens based on the initial heparin dose result in prolonged clotting times and microvascular bleeding compared to protamine based on the measured heparin concentration. Additionally, protamine/heparin ratios greater than 1.3 are associated with increased postoperative bleeding compared to 0.8, without affecting ACT or heparin rebound. Furthermore, a protamine/heparin ratio of 0.6 may be better than a ratio of 0.8. At lower doses, a protamine/heparin ratio <0.6 is associated with increased blood loss in the first 12 hours after surgery.

The recommendations from the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA) [64] advise a lower total dose and emphasize that the protamine dose should match the actual heparin concentration after CPB. They also suggest low-dose protamine infusion (25 mg/h) for up to 6 hours to reduce the risk of heparin rebound.

The EACTS and EACTA guidelines recommend a total dose lower than the dose recommended by the STS/SCA [64] and stress that the protamine dose should match the actual heparin concentration after CPB. It is also advised that the protamine dose not exceed a ratio of 1:1 with respect to the initial heparin bolus.

9. Monitoring and Control: During extracorporeal circulation, it is crucial to monitor and control various parameters to ensure patient safety and well-being. This includes monitoring blood pressure, temperature, blood flow, gas concentration, and other vital indicators. Monitoring and control

devices provide real-time information to the medical team to make appropriate decisions during surgery [56].

This leads us to one of the main pillars within the multidisciplinary surgical team responsible for managing ECC, which is the perfusionist. Considered a specialist technician, the perfusionist is a clinical scientist who directs extracorporeal circulation towards goal-directed perfusion. This involves maintaining hemodynamic stability by keeping mean arterial pressure (MAP) above 65-70 mmHg, cardiac index >2.4 l/min/m2 and ensuring an adequate oxygen supply essential for tissue metabolism with indexed oxygen delivery (iDO2) >272 ml/min/m2. Monitoring parameters such as arterial oxygen saturation (SaO2) >94%, central or mixed venous oxygen saturation (SvO2) >65-70%, adjusting pump flow rate to meet the patient's metabolic demands, and maintaining an appropriate hematocrit level above 25% during ECC are important for oxygen transport capacity. Achieving optimal body temperature without compromising tissue perfusion and oxygenation through mild hypothermia and/or normothermia, as well as evaluating the function of end organs during ECC, such as renal function with urine flow >0.5 ml/kg/min and neurological function using near-infrared spectroscopy (NIRS), all this parameters help to identify any perfusion-related complications and guide interventions to optimize tissue perfusion in a preventive rather than corrective manner [24,57-60]. Continuous monitoring and adjustment of parameters help ensure tissue perfusion and prioritize preventive measures over correcting alterations in these objectives, focusing on the support of clinical guidelines for temperature management (61), anticoagulation management, blood component management [62], as well as the most recent guidelines for ECC management and conduct [63,64], in order to timely perform interventions and reduce potential complications that can be triggered by poor practice.

Understanding all relevant aspects of technological advancements for better clinical outcomes is of fundamental importance in evidence-based medicine applied to the science of extracorporeal circulation in cardiac surgery.

So far, some of the most important innovations in the clinical practice of conventional cardiac surgery with extracorporeal circulation have been reaffirmed. However, over the past two decades, an exceptional practice has emerged and has been increasing in developed countries, mainly due to the good results obtained in cardiac surgery. Despite being a low, intermediate, or high-risk intervention, it is associated with complications and postoperative sequelae that affect the quality of life of patients. This technique, known as Minimally Invasive Extracorporeal Circulation (MiECC), aims to minimize the invasiveness of ECC procedures (**Fig. 2**) [65], involving the use of specialized equipment and strategies to reduce the size of conventional circuits and the associated inflammatory response.

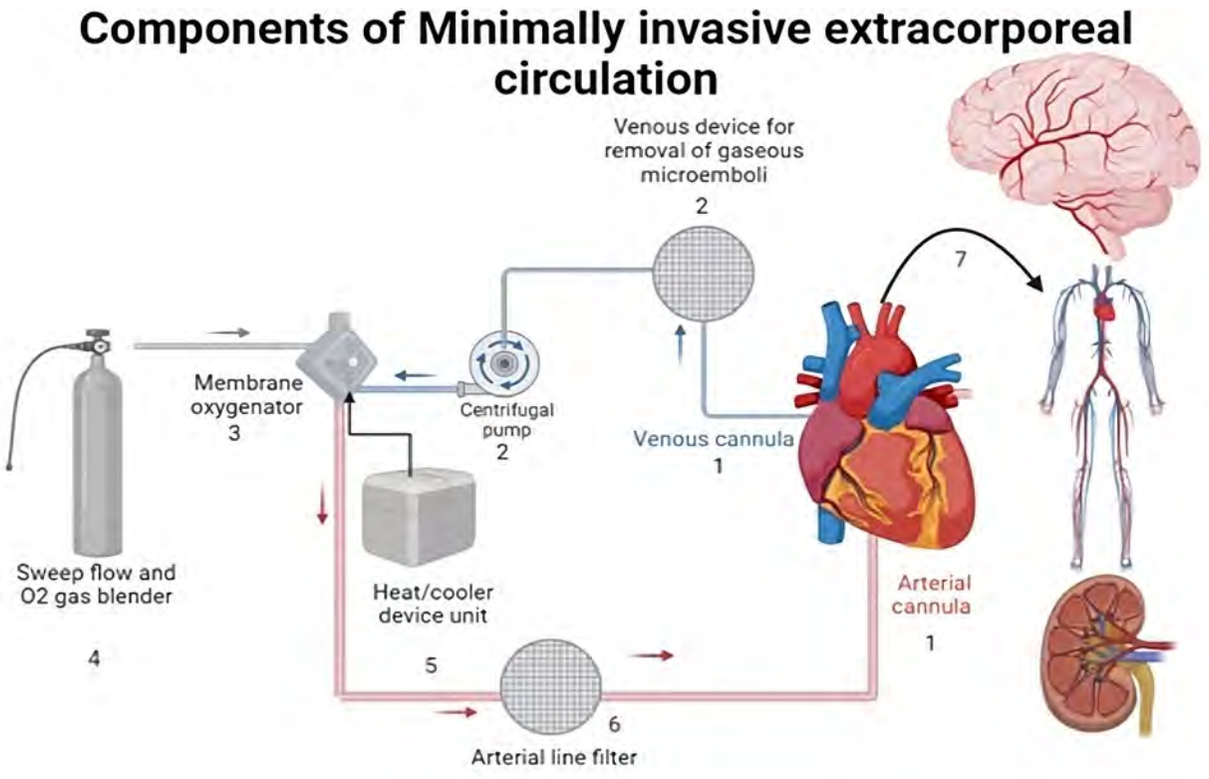

Figure 2. Components of Minimally Invasive Extracorporeal Circulation. This illustration depicts the configuration of this technique, particularly one of the most used circuits, which is Circuit II (Air Management). Circuit I, on the standard circuit, lacks the venous air removal device. Circuit III adds a collapsible venous reservoir to the Circuit I configuration and is used for volume management. Finally. Circuit IV (Blood Volume Management) adds a rigid reservoir as an additional component ingertated into the venous cannula, allowing it to convert to an open circuit and facilitate blood volume management in case of an emergency. 1) Venous and arterial cannulae. 2) Venous air removal device. 3) Centrifugal pump. 4) Membrane oxygenator. 5) Sweep flow and oxygen blender. 6) Heating/cooler device unit. 7) Arterial line filter. 8) Systemic blood distribution to vital organs.

The techniques and strategies of MiECC focus on minimizing circuit size, primordiality reducing the alteration of microcirculation triggered by conventional ECC, such as decreased blood contact with non-endothelialized surfaces, blood/air interface contact, patient hemodilution, use of cardiotomy suction and venous reservoir. All of these contribute to reducing blood trauma and decreasing the activation of inflammatory mediators, resulting in better outcomes in terms of renal function by reducing the incidence of renal injury, neurological function with reduced neurocognitive disability, postoperative arrhythmias, especially atrial fibrillation, erythrocyte physiology by reducing hemolysis and hemodilution, minimizing the need for blood transfusion and its related complications, immune function by reducing the activation of proinflammatory factors, and coagulation physiology by decreasing activation of both the intrinsic pathway in response to contact activation with non-endothelialized surfaces and the extrinsic pathway by reducing tissue factor response in this closed circuit. Furthermore, without the use of blood from cardiotomy suction, which contains large amounts of tissue factor, there is a decrease in thrombin generation, resulting in reduced platelet activation and, therefore, lower consumption of coagulation factors. Despite the extensive scientific literature available on ECC pathophysiology, better results in cardiac surgery are achieved when the surgical team applies these techniques [66-72].

Another vitally important specialty in cardiac surgery is cardiovascular anesthesia, which plays a fundamental role in ECC as it is necessary to ensure patient safety and well-being during the surgical procedure. It is primarily involved in anesthetic induction, monitoring and management of hemodynamic parameters, maintenance of an appropriate anesthetic level, among others [73-76].

Myocardial protection

Myocardial protection is a fundamental measure in initiating CPB in cardiac surgery procedures. During CPB, a variety of strategies are used to safeguard the cardiac tissue and prevent ischemic-reperfusion injury. These strategies are designed to preserve the function and viability of the myocardium during the period when the heart is disconnected from the blood flow and include temperature management, cardioplegia, and controlled ischemia-reperfusion environment, among others.

Among these strategies, Yamamoto [77] describes a series of experimental studies on myocardial protection, and one of the main techniques used is the induction of hypothermia [78]. By reducing the body temperature below 35°C, the metabolism of the heart is decreased, which helps protect it against ischemic-reperfusion injury. Hypothermia also reduces the oxygen demand of the myocardium and prolongs the time that the heart can tolerate the lack of blood flow [79]. However, this can have metabolic consequences that may affect the postoperative evolution of patients. Abassciano et al. [80], in their systematic review and meta-analysis, concluded that the protective effects of hypothermia in CPB are inconsistent and of low quality. Regardless, the strategy depends on the surgical team and the conditions and pathology of the patient. In some types of surgery, temperature management during CPB is divided into mild hypothermia (32°-35°C), moderate hypothermia (26°-31°C), and deep hypothermia (<25°C) (81). In a cohort study of 6,525 patients, Bianco et al. [82] found that patients with mild hypothermia (3,148) compared to normothermia (3,337) during CPB experienced increased postoperative renal failure (3.7% vs. 2.4%; P = .03) and longer stay in the intensive care unit (46.5 hr vs. 45.1 hr; p=0.04). However, they did not observe differences in long-term survival (82.6% vs. 81.6%; p=0.81). In addition to hypothermia, cardioprotective agents are used to minimize myocardial damage. These agents can include cardioplegia solutions, which are crystalloid, or blood solutions administered directly to the heart to induce temporary cardiac arrest and protect the tissue. Cardioplegia contains a combination of nutrients and chemicals that help preserve cardiac function [83].

Here are the key aspects of cardioplegia solutions:

Composition: They usually contain a combination of components that have various protective effects. This includes agents that stop the electrical and metabolic activity of the heart, such as adenosine and calcium channel blockers. They may also contain antioxidants to combat oxidative stress and energy substrates to provide nutrients to the myocardium during cardiac arrest.

Cooling: They are usually administered in the form of cold solutions (4°C) to cool the heart and reduce its metabolism during cardiac arrest.

Administration: They are administered directly into the coronary arteries to ensure adequate distribution in the myocardial tissue. This can be achieved through infusion of the solution into the aorta or by placing special cannulas in the coronary arteries.

Duration of action: They have a limited duration of action and, therefore, must be administered periodically during the period of cardiac arrest to maintain myocardial protection. The frequency of administration depends on various factors determined by the manufacturer, such as the temperature and composition of the solution [84].

Selection of the solution: The choice depends on the type of cardiac surgery, surgeon preference, and patient characteristics. There are different formulations of cardioplegia solutions available in the market, and the surgical team will select the most suitable one for each case. Zhou et al. [85], in their meta-analysis, included a total of 47 studies with 4,175 patients evaluating up to 7 types of cardioplegia solutions. They concluded that all solutions had protective effects after CPB, although the use of terminal warm blood cardioplegia had a lower concentration of markers of myocardial necrosis such as CK-MB at 2 hours (Mean Difference: 213.56; 95% CI: -25.79 to -1.59) and cTnT at 24 hours (Mean Difference: -1.50; 95% CI: -2.69 to -0.31) post-surgery when compared to crystalloid cardioplegia.

Inflammatory response triggered by cardiopulmonary bypass.

As discussed throughout this review article, cardiac surgery with cardiopulmonary bypass is one of the most physiopathological phenomena in medical literature, and the development of inflammation is practically involved in every component that has been developed and innovated over the past seven decades. Multiple cellular and humoral components are altered and contribute to systemic inflammatory response syndrome (SIRS) triggered by CPB, including blood contact with non-endothelial surfaces, changes in pressure and reduced tempera-

ture activating pathophysiological cascades within the body. This results in the production of an inflammatory storm characterized by the release of proinflammatory cytokines (IL-1, IL-6, and TNF-α) and activation of endothelial cells, neutrophils, macrophages, lymphocytes, and platelets. Prolonged exposure to these effects leads to disturbances in redox processes, resulting in increased production of oxygen free radicals with a negative impact, particularly on the cardiovascular, neurological, renal, and respiratory systems, leading to a scenario of multiorgan dysfunction and consequently increased postoperative morbidity and mortality.

As previously described, the combination of all these interrelated factors required to perform cardiac surgery leads to a myriad of outcomes that determine the likelihood of successful cardiac surgery. However, the injury to the vascular endothelial layer, coupled with blood components contacting the CPB circuit, intensifies the inflammatory process. The initial local inflammatory response eventually disseminates and becomes systemic [86-89].

This is an inherently unnatural process that magnifies this reaction. The pump and oxygenator function in a non-physiological manner, without feedback from normal homeostatic mechanisms, resulting in deviations from normal intravascular pressures and blood gas composition. Significant blood dilution occurs, leading to changes in intracellular/extracellular compartments, significant fluid retention, dilution, and denaturation of important plasma proteins. Blood encounters non-endothelial surfaces and experiences abnormal shear stress, which activates blood elements to produce various vasoactive mediators, altering capillary permeability and causing hemolysis. Simultaneously, the coagulation system is both activated and inhibited.

In summary, the body's homeostatic mechanisms become imbalanced, resulting in systemic inflammatory response syndrome (SIRS) [90,91].

Bone [92] postulated that there is already a powerful anti-inflammatory response to balance the destructive proinflammatory response, and agents that disrupt the balance in either direction could lead to death, either through uncontrolled inflammation or an inability to defend against infectious organisms. Unlike previously thought, SIRS is not a single, uncontrolled response; a compensatory anti-inflammatory response (CARS) occurs alongside SIRS. CARS is considered a late response to SIRS, although some argue it occurs simultaneously with the onset of SIRS. The concept of CARS was proposed in 1997 and is defined as an adaptive reprogramming of the immune state that attempts to regulate the acute proinflammatory response. The compensatory phase appears to play a prominent role in generalized postoperative immunosuppression and the development of infectious complications after CPB. It is speculated that regulatory T cells (Tregs) may be the main trigger of CARS. Tregs are a specialized subset of T cells that play a crucial role in maintaining immune homeostasis, controlling acute and chronic inflammation, and are characterized by the presence of the transcription factor FOXP3 [93-95].

Systemic inflammation following major surgery is the initial result of the highly conserved innate immune response.

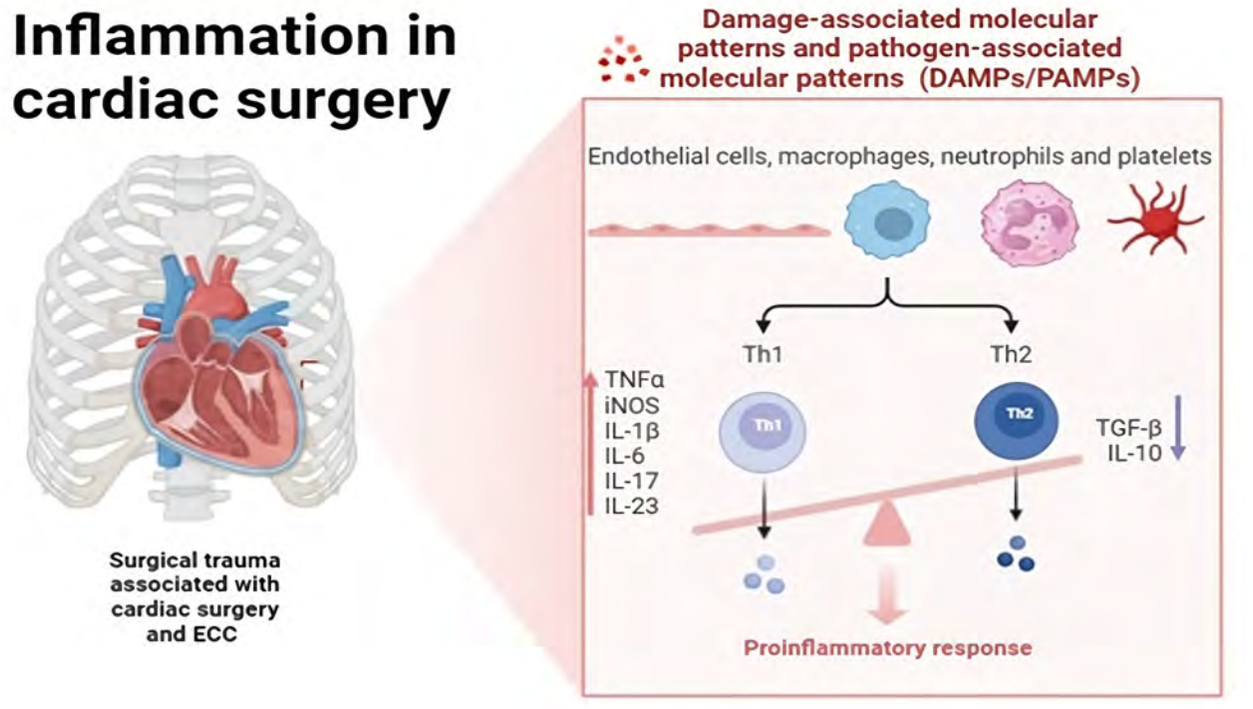

Figure 3. Cellular components in inflammation in cardiac surgery. Inflammation in cardiac surgery triggers a cascade of proinflammatory phenomena, disrupting the physiological balance when blood and its formed elements encounter proinflammatory stimuli, such as the surgical stress response, activation of cellular subgroups, and the release/activation of humoral factors, leading to a series of pathophysiological events throughout the body. If not self-limiting, this process can result in multiorgan failure and death. TNF-α: Tumoral Necrosis factor-alpha; iNOS: inducible Nitric Oxide Shyntase; IL-1ß: Interleukin-1beta; IL-6: Interleukin-6; IL-17: Interleukin-17; IL-23: Interleukin-23; TGF-ß: Transformig Growth Factor-beta; IL-10: Interleukin-10.

The magnitude of the response varies widely depending on the surgical environment and is proportional to the degree of surgical injury [96]. Cellular injury is detected at the molecular level by pattern recognition receptors in innate immune cells. These receptors recognize molecules released by damaged and necrotic cells, known as damage-associated molecular patterns (DAMPs) or alarmins. They also recognize highly conserved molecules derived from exposed microorganisms, known as pathogen-associated molecular patterns (PAMPs) [97]. DAMPs are the key molecular ligands responsible for triggering the inflammatory and immune response to surgical injury [98]. At the site of injury, DAMPs bind to pattern recognition receptors, activating multiple signaling pathways that result in the production and release of proinflammatory cytokines and chemokines. This leads to increased production and recruitment of immune cells, such as neutrophils and monocytes, to the site of injury [99].

Natural killer cells are also activated, reactive oxygen species are released, and endothelial permeability is modified. The inflammatory and immune response is balanced as immune suppression processes are simultaneously activated. Interleukin-6 (IL-6) is the dominant inflammatory cytokine in this response, and its levels strongly correlate with the severity of the injury and the synthesis and secretion of acute-phase reactants, such as C-reactive protein (CRP) and procalcitonin. However, along with other proinflammatory cytokines, IL-6 directly stimulates the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol secretion and influencing cortisol-mediated immune regulation. Additionally, IL-6 induces the release of prostaglandin E2, a potent immunosuppressor, from macrophages, which negatively regulates the function of monocytes, macrophages, and T cells. The balance between type 1 helper T cells (Th1) and type 2 helper T cells (Th2), represented by the Th1/Th2 ratio, is an important factor in maintaining immunological balance, and suppression of Th1-mediated immunity has been associated with an increased risk of infectious complications [100]. IL-10 plays a significant role in regulating the Th1/Th2 balance, limiting excessive immune activation and uncontrolled inflammation. However, IL-10 can also induce profound immunosuppression by deactivating monocytes and cytotoxic T cells, as well as affecting antigen presentation [101]. (**Fig. 3**)

During CEC, different phases of activation occur, triggering inflammatory and other biological responses. These phases can be classified as early and late activation [90].

Early activation phase

The early phase of the inflammatory response occurs at the initiation of extracorporeal circulation and is believed to be caused by the contact of blood components (both cellular and humoral) with the synthetic material of the extracorporeal circuit. Under normal circumstances, blood only meets the endothelial cell lining of blood vessels, a surface with an important role in maintaining circulatory balance. By producing balanced amounts of procoagulant and anticoagulant substances, en-

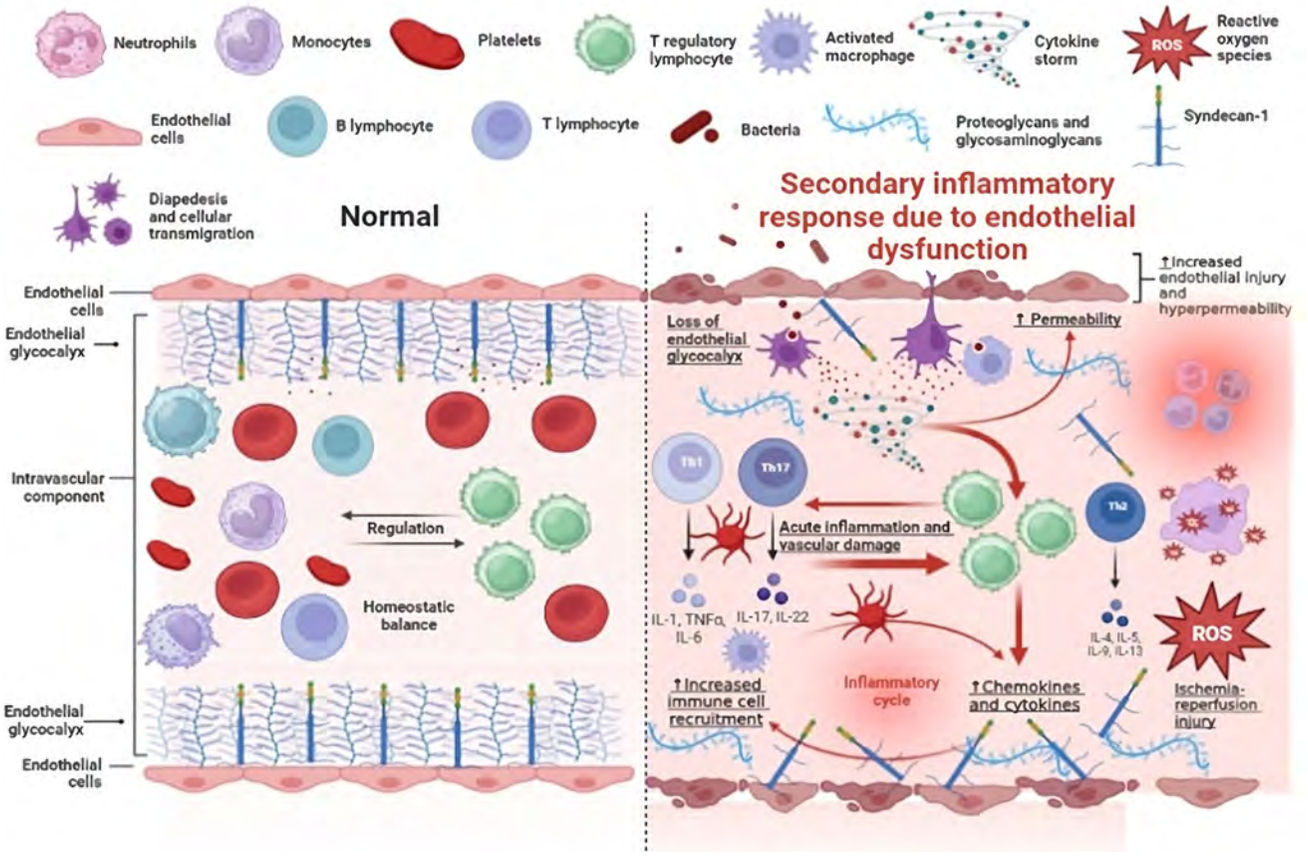

Figure 4. Early and Late Activation Phases in Cardiopulmonary Bypass. Read the text for a more detailed description [90].

dothelial cells ensure that blood remains in its fluid state until vascular injury occurs, and blood clot formation is favored. The non-endothelial surfaces of the extracorporeal circulation machine disrupt this balance towards thrombosis, making it essential to administer appropriate doses of heparin before initiating extracorporeal circulation. When heparinized blood encounters the tubing of the extracorporeal circulation circuit, plasma proteins instantaneously adsorb to the circuit, forming a monolayer. Some of these proteins undergo conformational changes that expose receptors to circulating proteins and cells in the blood. This leads to the activation of 5 plasma protein systems (contact system, intrinsic and extrinsic coagulation cascade, fibrinolytic system, and complement cascade) and 5 cellular groups (endothelial cells, lymphocytes, monocytes, neutrophils, and platelets). The roles of these protein systems and cellular groups are interconnected, complex, and not yet fully understood. However, vasoactive substances, enzymes, and microemboli produced by these activated mediators initiate the "systemic inflammatory response" and are responsible for the major complications associated with extracorporeal circulation, such as coagulopathy, tissue edema, and temporary organ dysfunction (**Fig. 4**) (**Fig. 5**).

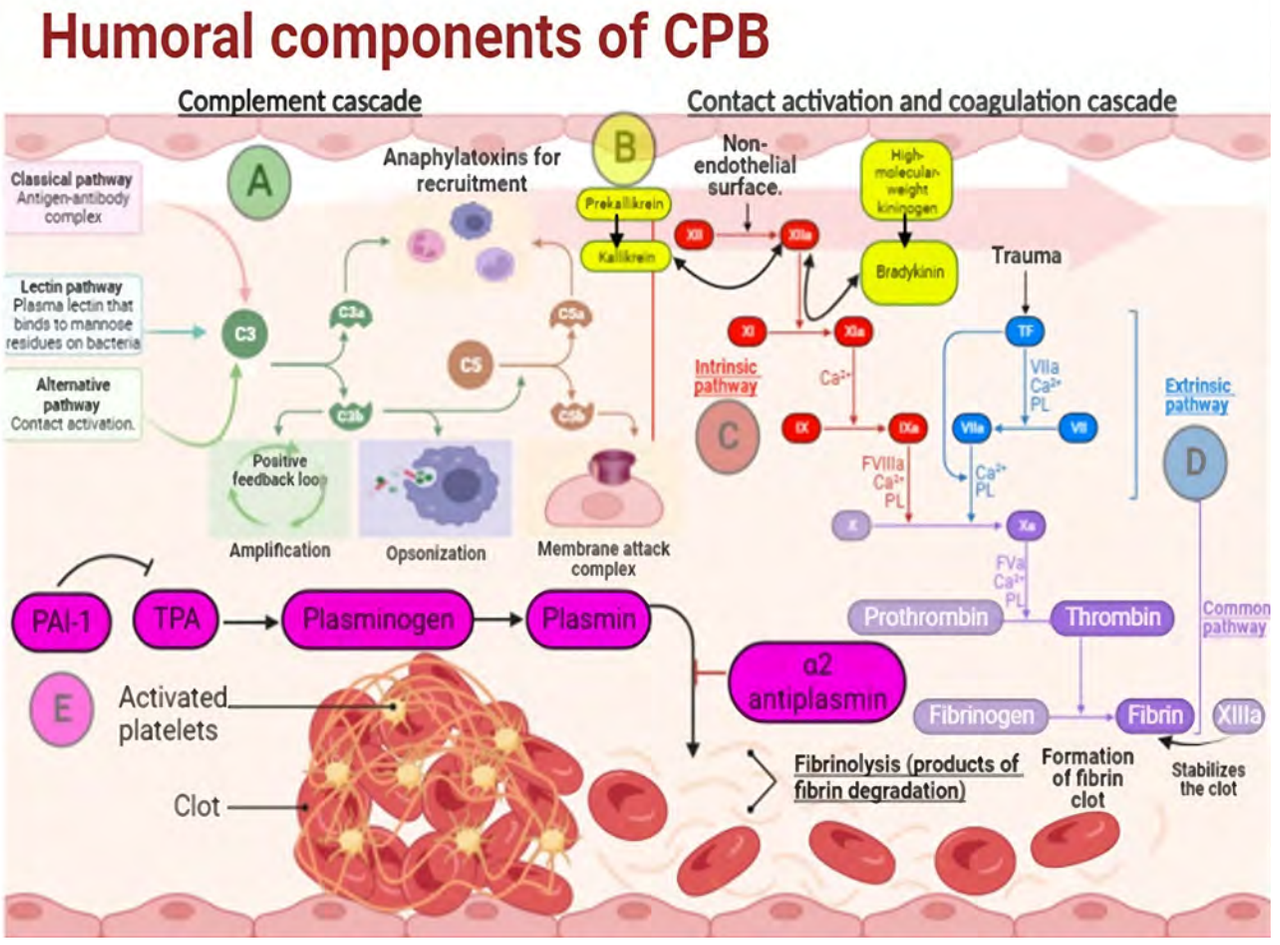

Figure 5. Humoral Components in CPB. A. Complement Cascade: It is a system of over 35 plasma proteins activated by all three pathways in ECC; however, the alternative pathway is predominantly activated due to contact of proteins with non-endothelial surfaces, the common pathway is triggered by the formation of heparin/protamine complexes with C1q, and the lectin pathway through mannose residues with plasma lectins. B. Contact Cascade: The contact system consists of 4 plasma factors activated when blood meets a non-endothelial cell surface. This activation triggers a series of reactions including the generation of vasoactive peptides, coagulation activation, and amplification of the inflammatory response. Bradykinin, generated from the activation of high molecular weight kininogen, causes vasodilation and smooth muscle contraction. Additionally, kallikrein activation promotes neutrophil activation and accelerates factor XII degradation. C. Intrinsic Coagulation Pathway: Activation of the contact system initiates the intrinsic coagulation pathway when blood contacts a non-endothelial surface. This pathway involves the activation of factors like factor XII and XI, prekallikrein, and high molecular weight kininogen. Activation of this pathway leads to thrombin generation, which plays a crucial role in blood clot formation and the inflammatory response. Thrombin has multiple effects, including the activation of coagulation factors, stimulation of smooth muscle cells, and production of substances that promote inflammatory cell adhesion and increase vascular permeability. D. Extrinsic and Common Coagulation Pathway: This pathway is activated when there is damage to the wall of a blood vessel and is the primary pathway involved in wound hemostasis. It begins when tissue factor (TF), present in exposed tissue cells, binds to circulating factor VII to form a TF-FVIIa complex. This complex catalyzes the conversion of factor X into its active form (Xa), which is crucial for thrombin formation. TF can come from various sources, such as blood cells from the pericardium or soluble fragments. The generation of factor Xa and thrombin triggers a cascade of coagulation that can result in consumption coagulopathy and complications of thrombosis and bleeding. E. Fibrinolysis Cascade: This fifth system of plasma proteins limits this process, localizing blood clot formation at the site of tissue or vascular injury and preventing widespread thrombotic occlusion of vessels and secondary tissue ischemia. Plasminogen, an inactive protein, is converted to plasmin, an enzyme that breaks down fibrin in blood clots. Fibrinolysis occurs continuously, especially at the pericardial wound, and is regulated by t-PA and other proteins. Fibrinolysis activation is associated with higher levels of bleeding during surgery. t-PA: Tissue Plasminogen Activator; PAI-1: Plasminogen Activator Inhibitor 1.

Late activation phase (**Fig. 4**)

As the duration of extracorporeal circulation increases, the activation of the previously described humoral and cellular components decreases. However, a second phase of the inflammatory response has been demonstrated, which is believed to be related to ischemia-reperfusion injury during and after extracorporeal circulation and endotoxemia, likely following the release of endotoxins by the intestinal microflora. During surgery, aortic clamping interrupts the blood supply to the heart and, to a lesser extent, the lungs, resulting in ischemia. Once the clamp is released, reperfusion occurs, involving the restoration of blood flow to these organs. However, this reperfusion also triggers an additional inflammatory response. Ischemia and reperfusion cause injury to the vascular endothelium, leading to activation and sequestration of neutrophils at the site of injury. Additionally, the generation of highly toxic reactive oxygen species (ROS), such as superoxide anions and hydrogen peroxide, occurs.

These ROS, along with the release of other molecules, amplify the already implemented inflammatory process. The reintroduction of oxygen during reperfusion creates a highly oxidative environment within the cells that experienced ischemia, leading to cellular damage. Endothelial cells in the microcirculation are particularly susceptible to damage caused by ROS. These free radicals can damage cell membranes and denature proteins, contributing to endothelial dysfunction and local structural alterations.

Endotoxin, which is a component of gram-negative bacterial cell walls, is considered a significant stimulus for the development of SIRS. The magnitude of endotoxin elevation during extracorporeal circulation can vary in different studies, which may be due to the heterogeneity in the existing literature. One possible source of endotoxin release during extracorporeal circulation is intestinal translocation, due to splachnic vasoconstriction that occurs during this procedure, which can lead to ischemia of the enteric mucosa and changes in microbial viability and intestinal permeability. However, it should be noted that establishing a clear relationship or causality between variables such as the duration of extracorporeal circulation, intestinal permeability levels, and endotoxin levels at the end of extracorporeal circulation has proven to be a challenge in research. Although it is recognized that elevated levels of endotoxin during extracorporeal circulation can activate the complement system, stimulate the release of proinflammatory cytokines, and increase postoperative oxygen consumption, further research is still needed to fully understand the underlying mechanisms [102-105].

Microcirculatory dysfunction resulting from endothelial dysfunction

CEC is associated with microvascular changes in various pathological aspects. Endothelial cell injury and subsequent acute inflammation with vascular damage, impairment of the coagulation cascade, ischemia-reperfusion injury, endothelial hyperpermeability, glycocalyx impairment, and gas microemboli all work together on the same team towards CEC-induced organ dysfunction [106].

Several studies in animal models and patients have demonstrated that cardiac surgeries, especially those involving cardioplegia and CPB, induce extensive vascular dysfunction. This dysfunction affects both large and medium-sized vessels, as well as the microcirculation, which is the terminal vascular network of the circulatory system comprising a wide variety of microvessels with a diameter of less than 200 micrometers. Microvessels can be subdivided into arterioles, capillaries, and venules, all of which play important roles in maintaining organ function. Microvascular dysfunction following cardiac surgery is characterized by changes in myogenic and vasomotor tone, as well as generalized endothelial dysfunction that clinically manifests as systemic hypotension and organ damage. For example, intra- and postoperative inflammation in the microcirculation triggers leukocyte activation, initiating the coagulation cascade in venules. Alternatively, coagulation cascade activation in capillaries restricts the available surface for diffusion, resulting in impaired nutrient and gas exchange. Patients may require vasopressors and/or aggressive fluid therapy to overcome these clinical consequences (**Fig. 6**).

Endothelial cell injury can be dependent and independent of neutrophils. In the former case, neutrophils express adhesion molecules on their surface, such as the integrins CD11a/CD18 (LFA1) and CD11b/CD18 (Mac1). The specific endothelial cell molecule, endocan, represents a novel endothelial cell stress signal and is released when the cells are activated. Free endocan binds to human leukocytes via the LFA1 integrin, inhibiting the interaction of LFA1 with ICAM1 and thus protecting endothelial cells from binding to inflammatory leukocytes [107]. Under physiological conditions, low levels of Mac-1 and LFA-1 are expressed. Neutrophil activation leads to the fusion of cytoplasmic granules with the cell membrane and an increase in Mac-1 expression on the surface. Mac-1 and LFA-1 interact with their endothelial "counter-receptor," ICAM-1. If the endothelial cell meets cytokines such as tumor necrosis factor-alpha (TNF-α) and/or interleukin-1 (IL-1), the expression of ICAM-1 significantly increases, facilitating adhesive interactions with neutrophils. Neutrophil-released elastase penetrates endothelial cells, where it converts xanthine dehydrogenase (x.d.) to xanthine oxidase (x.o.). In turn, x.o. can react with its substrate, xanthine (a breakdown product of ATP), leading to intracellular generation of superoxide anion (O_2^-), which then causes the conversion (reduction) of ferritin-bound Fe^{3+} to Fe^{2+}, an unstable and transient form of iron [108].

Neutrophil-mediated endothelial cytotoxicity can also be influenced by intracellular mechanisms involving nitric oxide synthase (NOS) present in endothelial cells. NOS interacts with L-arginine to generate nitric oxide (NO), which is known to decrease the expression of adhesion molecules on endothelial cells and reduce adhesive interactions between neutrophils and endothelial cells. Additionally, NO can "scavenge" O_2^- by reacting with it to form the peroxynitrite anion ($ONOO^-$). Therefore, if O_2^- is eliminated through this mechanism, the ability to reduce intracellular Fe^{3+} to Fe^{2+} may be compromised, resulting in increased resistance of endothelial cells to neutrophil-induced cytotoxicity.

In the case of a neutrophil-independent pattern, endothelial cells can also be directly damaged by soluble mediators produced during acute inflammation. In vitro studies have demonstrated that proinflammatory cytokines such as TNF-α and IL-1 directly harm endothelial cells, resulting in increased monolayer permeability. The direct injury of endothelial cells by these mediators can occur through the induction of apoptosis, especially in the case of TNF-α. All these observations may

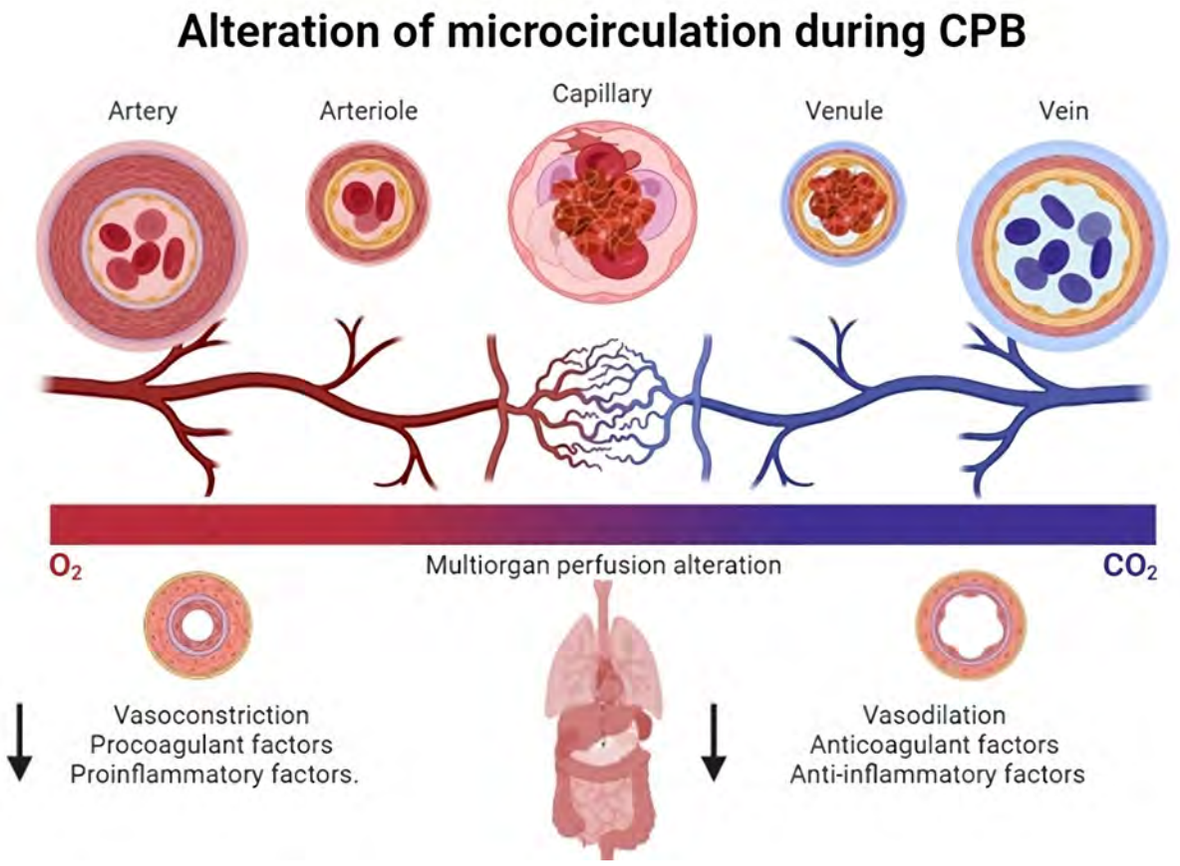

Figure 6. Impairment of microcirculation in cardiopulmonary bypass. The consequences of endothelial dysfunction and microcirculatory impairment during cardiopulmonary bypass include reduced blood flow to organs and tissues, increased risk of thrombosis, decreased tissue oxygenation, and enhanced inflammatory response. These factors can contribute to complications following cardiac surgery, such as organ dysfunction, postoperative bleeding, and prolonged recovery times.

be related to intracellular production of oxidants in stimulated endothelial cells triggered by TNF-α or IL-1. Furthermore, the production of cyclooxygenase products by endothelial cells increases when they meet TNF-α or IL-1. Several studies have revealed that angiopoietins-1 and -2 (Ang-1 and Ang-2) target key mechanisms contributing to the maintenance of endothelial barrier function. Ang-1 promotes junctional integrity by regulating the accumulation of adhesion proteins, especially VE-cadherin, at endothelial cell-cell junctions. Conversely, Ang-2 is increasingly expressed during endothelial activation and, by competing with Ang-1, may counteract endothelial stabilization [109].

The endothelial glycocalyx (EG) is a layer that coats endothelial cells inside blood vessels and organs. It is composed of glycoproteins that retain a non-circulating plasma volume of approximately 700 to 1,000 mL. This intraluminal layer maintains its own colloid osmotic pressure (COP) due to its content of plasma proteins, primarily albumin, which become trapped within the endothelial glycocalyx. The EG is estimated to contribute approximately 60% of intravascular COP. Structurally, the EG is a gel-like layer with a negative charge composed of an intricate matrix of oligosaccharide and polysaccharide chains called glycosaminoglycans, which covalently bind to glycosylated membrane proteins called proteoglycans, as well as membrane proteoglycans such as syndecans, glypicans, perlecans, and other plasma proteins. In the presence of an intact EG, water and electrolytes can freely pass through this layer and beyond the endothelial cells via intercellular gaps. Except for albumin, this exclusion zone also prevents high molecular weight colloids (>70 kDa) from contacting the endothelial cells. Albumin is the only significant plasma protein that can easily move between plasma and the EG due to the selectively permeable nature of the glycocalyx to naturally occurring colloids with molecular weights <70 kDa. However, it is noteworthy that the EG is susceptible to damage and degradation, especially under conditions of high transendothelial pressures. This may result in the loss of its protective function and the release of colloids into the extravascular space [110, 111].

Recently, it has been shown that loss of the endothelial glycocalyx, including syndecan-1, is associated with microcirculatory perfusion disorders following coronary artery bypass surgery [15]. Robisch et al. [112] found that prolonged CPB time contributes to elevated levels of syndecan-1, which may promote the mobilization of neutrophils from the bone marrow, resulting in leukocytosis. Neutrophils are equipped with a wide variety of bioactive factors that can contribute to the amplification of local inflammation. These neutrophils can access vulnerable endothelial cells, bypassing the compromised protective barrier of the endothelial glycocalyx and transmigrating into the extracellular space through intracellular gaps. There-

fore, it is speculated that prolonged CPB-associated cardiac surgery is associated with loss of the endothelial glycocalyx and mobilization of neutrophils from the bone marrow, contributing to and amplifying a systemic inflammatory response.

Understanding the fundamental aspects of the pathophysiology involved in CPB, such as microcirculatory alteration due to endothelial dysfunction, highlights several mechanisms that contribute to it. Far from the balance of proinflammatory factors against the anti-inflammatory factors analyzed in this review, there is an alteration in the response of vasoactive mediators, disturbances in contact and coagulation cascades, but primarily the shedding of the glycocalyx and subsequent endothelial activation, disrupting the balance between vasodilatory and vasoconstrictive factors in the microcirculation, negatively affecting adequate tissue and organ perfusion. Hypoperfusion, ischemia-reperfusion, and microvascular inflammation are identified as common underlying themes in post-cardiac surgery kidney, brain, and lung injuries. These mechanisms can have significant consequences on organ function and integrity, increasing the risk of postoperative morbidity and mortality.

REGULATORY T LYMPHOCYTES IN INFLAMMATION

Regulatory T lymphocytes, also known as Treg cells, are a subtype of T cells in the immune system that play a crucial role in regulating and suppressing immune responses. In the body, there are modulatory mechanisms of inflammatory processes as a response to reduce the negative impact on organ function. Lymphocytes expressing cellular markers CD4, CD25, and the transcription factor FoxP3 participate in the modulation of the inflammatory response triggered by multiple causes. These regulatory T lymphocytes (Tregs) produce anti-inflammatory cytokines (IL-10 and TGF-β) that attenuate the activation of pro-inflammatory effector T lymphocytes and induce their apoptosis [113-115].

In the early 1970s, it was recognized that T cells not only had a helper function but could also modulate the inflammatory response, identifying a subpopulation of T cells with the ability to modulate excessive immune responses [116]. As an initial discovery, researchers began to identify the presence of suppressor cells in the immune system, which had the ability to inhibit excessive immune responses. In the early 1980s, studies in mice showed the existence of CD4+ T lymphocyte suppressor cells that could prevent autoimmune diseases. Through experiments in mice and other animals, researchers observed the existence of CD4+ T lymphocyte suppressor cells. These cells were shown to be capable of preventing autoimmune diseases in the animal models studied [117].

In the 1990s, significant advances were made in the characterization of regulatory T cells. It was discovered that these cells expressed the transcription factor FoxP3, which became a key marker for identifying and distinguishing Tregs. It was demonstrated that the absence or dysfunction of FoxP3 result-

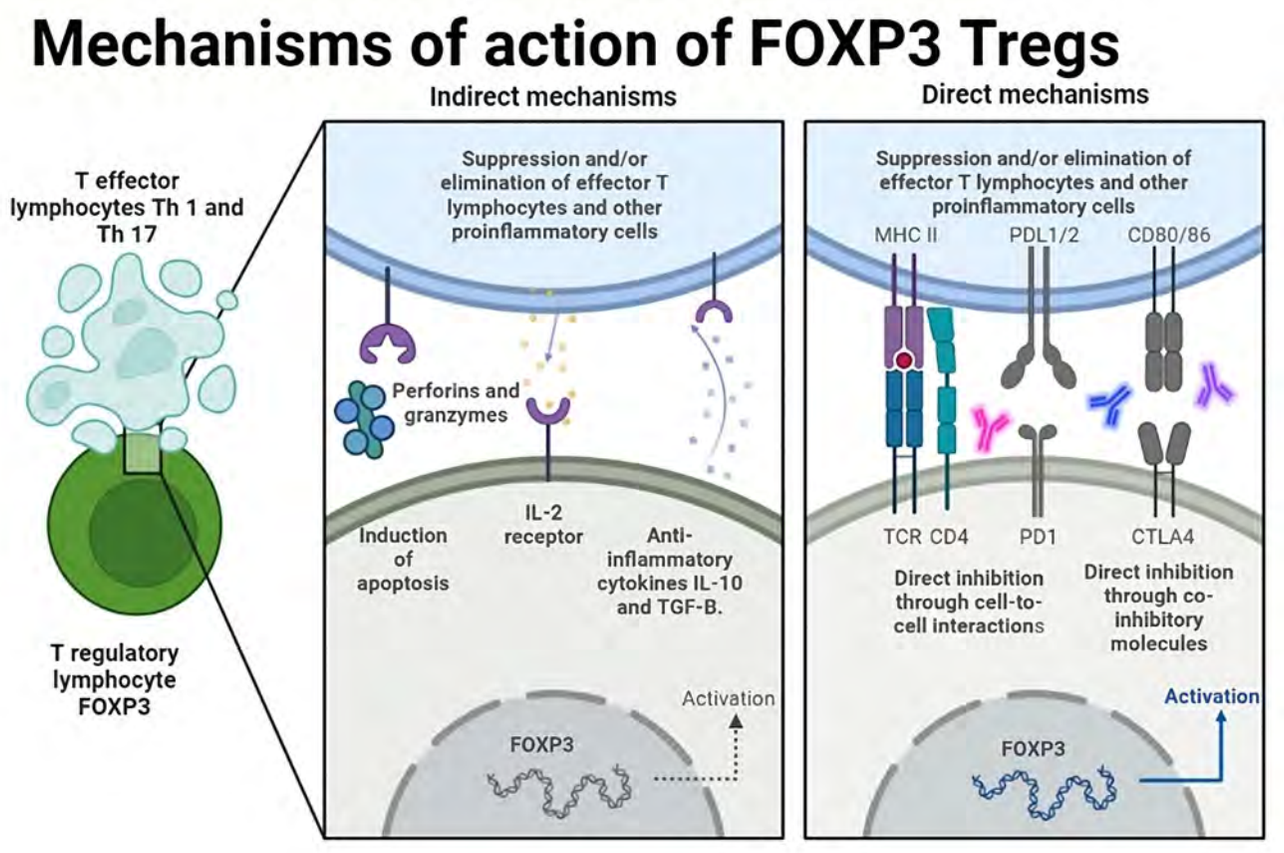

Figure 7. Mechanisms of action of FOXP3 Tregs. Tregs lymphocytes can suppress the immune response of effect cells through direft and indirect mechanisms.

ed in severe autoimmune disorders in animal models [118]. In the first decade of the 21st century, numerous studies were conducted to understand the mechanisms by which Tregs exert their suppressive function. It was found that Tregs can suppress the immune response in different ways, including the release of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), as well as direct inhibition of other immune cells [119].

In the past decade, there has been growing interest in the role of Tregs in various diseases, including autoimmune diseases, allergies, organ transplantation, and cancer. It has been shown that Tregs play a key role in maintaining immune tolerance and preventing excessive immune responses in these conditions. Furthermore, advances have been made in identifying specific biomarkers of Tregs and developing therapies based on the manipulation of these cells [120].

Lymphocytes marked with FoxP3 act as a transcription factor that regulates the expression of various suppressor genes, including anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Additionally, FoxP3 can suppress the expression of pro-inflammatory genes and co-stimulatory molecules in Tregs, thus contributing to their suppressive function through cytokine signaling pathways and interaction with other immune cells (Fig. 7) [121,122].

FoxP3 was discovered in 2001 by the research team led by Dr. Shimon Sakaguchi in Japan. It was identified as an essential gene for the function and stability of Tregs. FoxP3 expression was found primarily in Tregs, which helped distinguish them from other subsets of T cells. FoxP3 plays a fundamental role in the differentiation of Tregs in the thymus during the development of the immune system. Its expression is necessary for the generation of functional Tregs and proper immune suppression. The absence or dysfunction of FoxP3 results in severe autoimmune disorders in animal models and in the autoimmune immunodeficiency syndrome called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) [123].

The FoxP3 signaling pathway is crucial for the differentiation and function of regulatory T lymphocytes (Tregs), and activation of the FoxP3 signaling pathway is triggered through a combination of intracellular and extracellular signals. T cell receptor (TCR) signaling plays a fundamental role in FoxP3 activation. The interaction of the TCR with the major histocompatibility complex (MHC) on antigen-presenting cells (APCs) and the presentation of specific antigens are crucial for triggering the signaling pathway [124].

Activation of the mTOR pathway has been shown to be essential for Treg differentiation. mTOR signaling promotes the expression of the transcription factor FoxP3, which is a distinctive feature of Tregs. Additionally, the mTOR pathway is involved in the regulation of other transcription factors and key molecules in Treg differentiation and function, such as interferon regulatory factor 4 (IRF4) and interleukin-2 (IL-2). Manipulation of the mTOR pathway in Tregs has emerged as a potential therapeutic approach in various diseases. For example, mTOR inhibition in Tregs can be used in the treatment of autoimmune diseases to enhance the suppressive function of Tregs and reduce dysregulated immune response. Furthermore, mTOR activation in Tregs can be explored in the context of cardiopulmonary bypass (CPB) against the secondary inflammatory response to the activation of multiple interrelated factors in cardiac surgery to improve the understanding of the anti-inflammatory immune response [125-127].

Metabolism plays a crucial role in the function and survival of Tregs. These cells show a preference for aerobic metabolism, which is highly efficient in energy generation. This involves the utilization of glucose as the primary fuel source and energy production through glycolysis and oxidative phosphorylation in the mitochondria. The high activity of oxidative phosphorylation in Tregs enables efficient production of adenosine triphosphate (ATP), the main cellular energy source [128]. In addition to glucose, Tregs heavily depend on the amino acid glutamine to maintain their suppressive function. Glutamine is metabolized in the citric acid cycle in the mitochondria, generating key metabolic intermediates such as alpha ketoglutarate, which are necessary for Treg function and proliferation. Glutamine deficiency can compromise Treg function [129]. The mTOR signaling pathway plays a crucial role in Treg metabolism. mTOR activation promotes Treg proliferation and differentiation, as well as their suppressive function. The mTOR pathway regulates nutrient uptake, protein and lipid biosynthesis, and cytokine production in Tregs. Proper balance in mTOR activity is essential for maintaining Treg homeostasis and proper function [130]. Tregs interact with dendritic cells (DCs) and can modify their metabolism. It has been observed that Tregs can suppress the metabolism of DCs, reducing their capacity to effectively activate other T cells and thus promoting immune tolerance. This metabolic interaction between Tregs and DCs is important for maintaining immune system balance and preventing autoimmunity [131]. The composition and diversity of the gut microbiota can also impact Treg metabolism. It has been shown that the gut microbiota can influence Treg metabolism through the production of specific metabolites, such as short-chain fatty acids. These metabolites can directly affect Treg function and stability, as well as modulate the immune response in the gut [132,133].

Treg metabolism during cardiac surgery with CPB can be affected due to factors such as ischemia-reperfusion, the presence of numerous pro-inflammatory mediators, and metabolic stress. Stress can affect the regulation of key metabolic pathways, such as the mTOR pathway, which is critical for Treg function. Changes in stress response can influence the ability of Tregs to maintain their suppressive function and modulate the immune response during surgery.

Perspectives of Treg Lymphocytes

Tregs have promising therapeutic potential in the context of cardiac surgery with CPB. Manipulation of Tregs, either by increasing their numbers or enhancing their function, could be a therapeutic strategy to mitigate the inflammatory response and improve clinical outcomes in patients undergoing cardiac surgery with CPB [134]. Research is being conducted to identify specific biomarkers that can predict the inflammatory response during CPB and Treg function. This could enable more precise and personalized patient stratification, as well as the development of targeted therapeutic approaches. Furthermore, therapeutic approaches involving the expansion and activation of Tregs prior to surgery have been explored, aiming to enhance their ability to modulate the inflammatory response and protect against organ injury during CPB [135].

Pharmacological modulation of Tregs: Drugs and compounds that can directly modulate the function of Tregs, improving their suppressive and regulatory capacity, are also under investigation. These approaches could provide new therapeutic strategies to control the inflammatory response during CPB [136].

CONCLUSIONS

Understanding the interaction between Tregs and ECC provides an exciting opportunity to comprehend the pathophysiology involved in the activation and development of inflammation in cardiac surgery with the use of this device. While ECC has had a significant impact on the development of open-heart surgery, there is a price to pay due to its capacity to generate an inflammatory component that affects the postoperative evolution of patients undergoing this procedure. Several studies have explored strategies to preserve Treg function during ECC, including the use of immunomodulatory drugs such as corticosteroids and adrenergic receptor agonists, as well as modulating perioperative environmental conditions. Gaining more knowledge about the fascinating cellular biology of these regulatory T lymphocyte subtypes can provide relevant information on their interaction with all the factors required to perform heart surgery, ranging from identifying single-nucleotide polymorphisms in proinflammatory genes to the therapeutic potential in myocardial protection and ischemia-reperfusion mechanisms, as well as postoperative management and behavior in high-risk patients prone to developing an uncontrolled inflammatory response. Understanding the inflammatory balance in ECC and its potential outcomes on the morbidity and mortality of patients undergoing heart surgery can be of great significance.

It is worth noting that despite the numerous innovations in ECC components and techniques in cardiac surgery over the past years discussed in this review, there is limited information that considers the behavior of these important immune system cells and their relationship with each pathophysiological aspect triggered by these procedures, particularly in relation to inflammation, coagulation, and oxidative stress pathways.

In developed and some developing countries, minimally invasive cardiac surgery has been practiced, performed through small incisions instead of a full sternotomy, and using video-assisted thoracoscopy or robot-assisted techniques, reducing trauma and accelerating patient recovery. On the other hand, minimally invasive extracorporeal circulation, previously discussed, addresses some of the issues triggered by hemodilution, blood transfusions, and mainly inflammation due to the reduction in the contact surface area of these components with blood, resulting in better outcomes when compared to conventional ECC. The incorporation of both techniques can drive the evolution of minimally invasive cardiac surgery towards a more physiological approach aligned with current trends in cardiac care, known as physiological cardiac surgery [70].

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