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REVIEW

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Cardiopulmonary bypass and VA-ECMO induced immune dysfunction: common features and differences, a narrative review

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Abstract

Cardiopulmonary bypass (CPB) and veno-arterial extracorporeal membrane oxygenation are critical tools in contemporary cardiac surgery and intensive care, respectively. While these techniques share similar components, their application contexts differ, leading to distinct immune dysfunctions which could explain the higher incidence of nosocomial infections among ECMO patients compared to those undergoing CPB. This review explores the immune modifications induced by these techniques, comparing their similarities and differences, and discussing potential treatments to restore immune function and prevent infections. The immune response to CPB and ECMO involves both humoral and cellular components. The kinin system, complement system, and coagulation cascade are rapidly activated upon blood contact with the circuit surfaces, leading to the release of pro-inflammatory mediators. Ischemia–reperfusion injury and the release of damage-associated molecular patterns further exacerbate the inflammatory response. Cellular responses involve platelets, neutrophils, monocytes, dendritic cells, B and T lymphocytes, and myeloid-derived suppressor cells, all of which undergo phenotypic and functional alterations, contributing to immunoparesis. Strategies to mitigate immune dysfunctions include reducing the inflammatory response during CPB/ECMO and enhancing immune functions. Approaches such as off-pump surgery, corticosteroids, complement inhibitors, leukocyte-depleting filters, and mechanical ventilation during CPB have shown varying degrees of success in clinical trials. Immunonutrition, particularly arginine supplementation, has also been explored with mixed results. These strategies aim to balance the inflammatory response and support immune function, potentially reducing infection rates and improving outcomes. In conclusion, both CPB and ECMO trigger significant immune alterations that increase susceptibility to nosocomial infections. Addressing these immune dysfunctions through targeted interventions is essential to improving patient outcomes in cardiac surgery and critical care settings. Future research should focus on refining these strategies and developing new approaches to better manage the immune response in patients undergoing CPB and ECMO.

Keywords Cardiopulmonary bypass, Extracorporeal membrane oxygenation, Acquired immune dysfunctions

Graphical abstract

Although often considered similar, CPB and ECMO have distinct immune repercussions. Numerous immunomodulatory strategies have been tested in cardiac surgery patients undergoing CPB to mitigate the induced immunoparesis,

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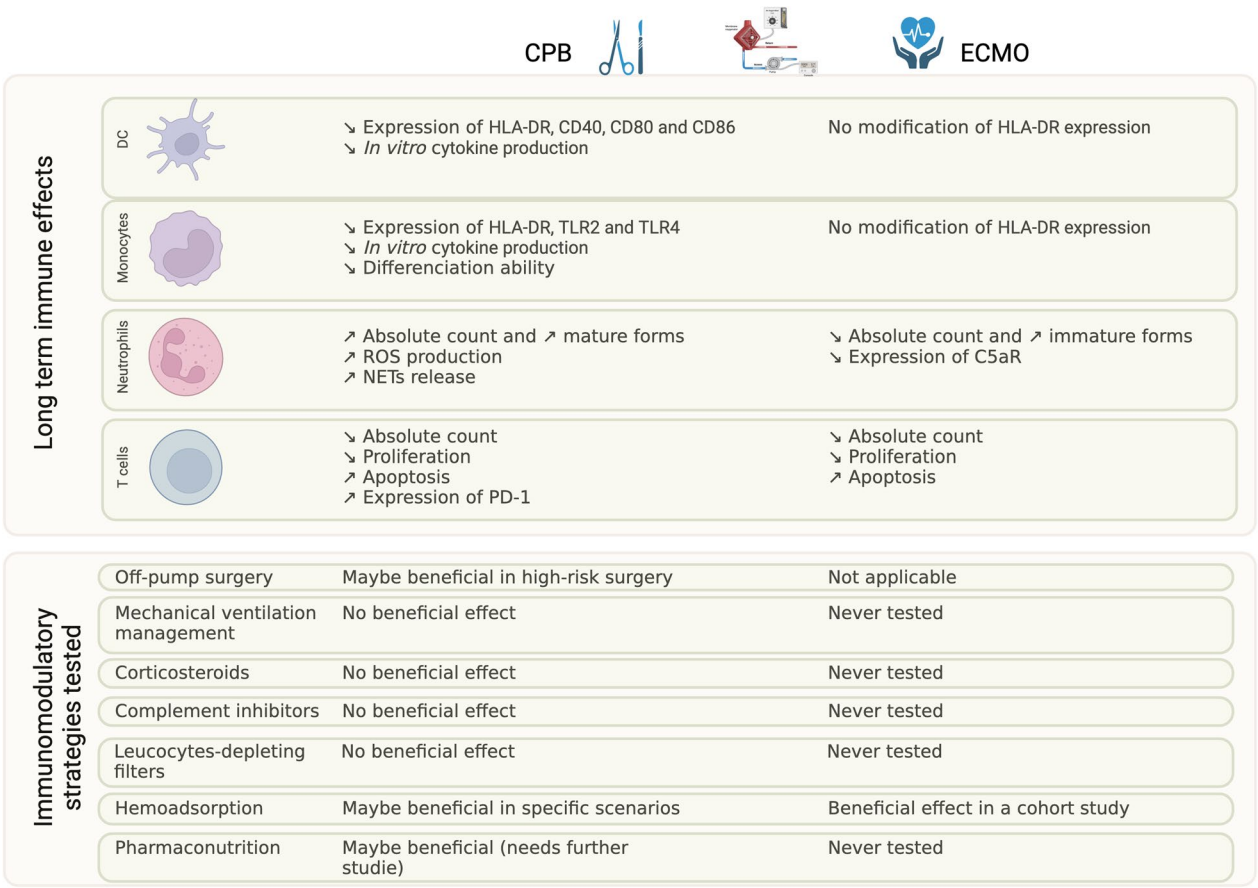
but no clinical trials have been conducted for patients on ECMO. C5aR (complement component 5a receptor), CPB (cardiopulmonary bypass), DC (dendritic cells), ECMO (extracorporeal membrane oxygenation), HLA-DR (human leukocyte antigen-DR isotype), NETs (neutrophil extracellular traps), PD-1 (program cell death protein 1), ROS (reactive oxygen species), TLR (toll-like receptor). Created with BioRender.com



Introduction

Cardiopulmonary bypass (CPB) is commonly used in the operating room during cardiac surgery since its first use in 1953 by Gibbon [1]. It has been miniaturized and adapted for the Intensive Care Unit (ICU) as a critical tool for treating refractory cardiogenic shock and various other conditions, a method known as veno-arterial extracorporeal membrane oxygenation (ECMO) [2]. For instance, coronary artery bypass grafting (which is mainly done with CPB) has an incidence rate of 62 per 100,000 inhabitants in western European [3] countries and nearly 40,000 patients worldwide were treated with VA-ECMO [4] in 2022. However, postoperative infections are frequent after cardiac surgery and, nosocomial infections among those patients increase hospital length of stay, cost and mortality [5, 6]. Acquired immune dysfunctions, also known as immunoparesis, are associated with the occurrence of nosocomial infections in the ICU [7]. Consequently, several studies have focused on CPB-associated inflammatory response, describing both humoral and cellular immunodepression features associated with acquired infections and applying this knowledge to patients under ECMO. Nonetheless, despite similarities, CPB and ECMO exhibit significant differences that lead to variations in immune responses. A comprehensive examination of the immune disorders induced by these two techniques will highlight the knowledge gap concerning ECMO's immune repercussions and underscore the need for dedicated translational research on ECMO alone. Therefore, the objective of this narrative review is to elucidate the immune modifications triggered by these two techniques and investigate

potential treatments aimed at restoring immune functions and preventing nosocomial infections.

Why exclude VV-ECMO from this narrative review?

Although veno-venous ECMO (VV-ECMO) and VA-ECMO share the same circuit, their applications and implications significantly differ. VV-ECMO is primarily used for Acute Respiratory Distress Syndrome (ARDS) caused by viral and/or bacterial infections [8]. These infections are known to elicit distinct immune responses. For instance, viral infections might trigger a robust interferon response, whereas bacterial infections often involve substantial activation of the innate immune system with elevated levels of pro-inflammatory cytokines [9, 10]. Additionally, VV-ECMO is not limited to infectious causes but can also be employed in non-infectious settings. Conditions such as hypercapnic ventilatory failure, which includes diseases like asthma and chronic obstructive bronchopathy [11], present with specific immune alterations. Asthma, for example, is often associated with eosinophilic inflammation and a skewed Th2 immune response, whereas chronic obstructive bronchopathy involves a more complex interplay of neutrophilic inflammation and systemic immune modulation [12]. The patient population treated with VV-ECMO is markedly heterogeneous, encompassing a wide range of etiologies and immune responses. This diversity contrasts sharply with the indications for VA-ECMO, which is typically used for cardiogenic shock, conditions with more homogenous pathophysiological mechanisms. The fundamental differences in the underlying conditions and the consequent immune responses make direct comparison between VV-ECMO and VA-ECMO impractical.

CPB and ECMO: similarities and differences

Similarities

Both of these devices share the same objective: to sustain blood circulation and ensure organ perfusion. They share common components, including a heparin-coated circuit, a primarily arterial pump, an oxygenator, and a heat exchanger (which is not always used during ECMO). These components lack endothelialization, leading to an inflammatory response that will be elaborated upon later. Nonetheless, CPB and ECMO have quite major differences thus leading to different immune modifications.

Differences

Patient factor

Initially, cardiopulmonary bypass (CPB) is employed in the context of cardiac surgery, whereas ECMO is utilized within the Intensive Care Unit (ICU) to address diverse medical conditions. In most cases, CPB is specifically used in patients undergoing surgical interventions who have not been subjected to any pre-existing immune challenges. Cardiac surgery with CPB can be performed in elective, urgent, or emergent situations. Most surgeries (around 60%) are elective, followed by urgent cases (35%) where the procedure is needed during the same hospitalization as the diagnosis. Emergent surgeries (5%) are conducted when the patient does not respond to medical treatment [13]. CPB in emergent situations could be considered a "second hit," but most studies on the immune impact of CPB exclude these patients. Even if the surgery and the anesthesia can induce immune changes [14, 15], the CPB, contrary to the ECMO, does not act as a "second hit". Indeed, ECMO is usually used as part of the treatment of refractory cardiogenic shock (from acute coronary syndrome, myocarditis, cardiac arrhythmic storm) as a bridge to "recovery", "transplantation" or "decision" in some cases [16]. Nonetheless, it is also implemented for the support of refractory cardiac arrests [17] or during septic shock [18] as well as other causes detailed in Table 1. All of these diseases induce immune changes and the ECMO could act as a "second hit". Furthermore, patients on ECMO often experience additional organ dysfunctions, such as acute kidney injury, gastrointestinal or cannula site bleeding, and hemolysis [19]. These complications are less common during CPB [20], leading to a prolonged immune response and immune dysfunction in ECMO patients.

Machine factor

CPB commonly last for 1 to 2 h while the median duration of ECMO is 4 days [21]. Additionally, CPB necessitates a bypass of the heart and lungs, resulting in ischemia. Following the conclusion of CPB, reperfusion occurs in these organs, initiating an ischemia–reperfusion process that will be explained later on. A similar process can occur, albeit to a lesser extent, during ECMO, given the multi-organ ischemia until ECMO initiation. On the other hand, ischemia–reperfusion can still occur during ECMO support due to the patient's hemodynamic status and/or ECMO malfunction (pump malfunction, oxygenator failure, canula problem). This prolonged ischemia can impact specific organs such as the brain, lungs and heart and impact patient's long term quality of life [22]. Finally, during cardiac surgery with cardiopulmonary bypass (CPB), there is direct blood-air contact, unlike with ECMO. The typical CPB circuit includes an open venous reservoir and cardiotomy suction, which continuously expose the blood to atmospheric air and negative pressure. This exposure triggers neutrophil activation and cytokine release due to the direct contact between blood and air, contributing to the inflammatory response observed in patients undergoing CPB [23]. Hence, the adoption of minimally invasive surgical

Table 1 CPB and ECMO differences

	CPB	ECMO
Patient factors		
Terms of use	Operating room	ICU
Indication	Cardiac surgery	Refractory cardiogenic shock from: Acute coronary syndrome Myocarditis Refractory cardiac arrhythmic storm Sepsis with profound cardiac depression Drug overdose/toxicity with profound cardiac depression Pulmonary embolism Cardiac trauma Acute anaphylaxis Post cardiotomy Post heart transplant Refractory cardiac arrest
Machine factors		
Ischemia–reperfusion	Yes	Yes (to a lesser level but can be prolonged)
Volume of blood into the circuit	700–1800 ml	600 ml
Surgical approach	Yes	No (a surgical approach of the scarpa can be needed for the ECMO implantation but is shorter than CPB)
Cardiac protection	Yes (cardioplegia solution)	No
Air/blood interface	Yes (no air/blood interface in minimal extracorporeal circuit)	No
Filters and reservoirs	Yes	No
Reinfusion of aspirated blood	Yes	No
Management		
Duration (median)	1–2 h	4 days
Complications related associated treatment	Rare	Frequent
Anticoagulation	High levels	Low levels

procedures, involving reduced extracorporeal circulation and no air-blood contact, is increasingly common across various medical operations. These techniques have been shown to provoke lesser immune responses and reduced mortality rates [24].

Management differences

As mentioned above, CPB is shorter and has fewer complications than ECMO. Therefore, patients on CPB receive less additional therapy, such as analgesics and sedatives, transfusions, or other extracorporeal support like renal replacement therapy [19, 20]. However, the anticoagulant dose during cardiac surgery is higher than during ECMO [25]. These differences, and other minors, are summarized in Table 1.

These differences lead to distinct induced immune dysfunctions which could explain the higher incidence of nosocomial infections among patients under ECMO than CPB. Indeed, 5% of patients will develop a nosocomial infection after cardiac surgery with CPB [5] whereas these infections occur in 65% of patients with ECMO [6]. Considering the elevated mortality associated with acquired infections [26, 27], addressing immune functions could potentially mitigate morbidity linked to both CPB and ECMO. Consequently, evaluating immune dysfunctions becomes imperative in each unique clinical scenario.

Immunoparesis induced by CPB and ECMO

The immune system is traditionally categorized into humoral and cellular components. The humoral segment encompasses various tools, including the kinin system, the complement system, the coagulation cascade, and antibodies. Conversely, the cellular segment of the immune system involves various cell types such as platelets, neutrophils, monocytes, dendritic cells, lymphocytes, and others. The alterations induced by CPB/ECMO on the immune system are summarized in Table 2. The immune response to CPB/ECMO initiates shortly after blood comes into contact with the non-endothelial surface of the circuit, primarily through the humoral

response. Additionally, the subsequent ischemia–reperfusion process further influences this response. These two mechanisms influence the cellular components of the immune system. Additionally, the underlying disease that necessitated the ECMO placement also impacts the immune system (cardiac surgery also, though to a lesser extent). This review aims to provide a comprehensive analysis of the similarities and differences of the immune alterations induced by CBP and ECMO. The interaction between the CPB/ECMO and the immune system is elaborated in the Fig. 1.

The humoral immune response

Kinin system

The kinin system is a plasma protease cascade which activates the proinflammatory kallikrein-kinin system and the procoagulant intrinsic coagulation pathway. The first step is the activation of the coagulation factor XII (FXII) into FXIIa as it encounters the negatively charged surfaces of the circuit. Afterwards, FXIIa converts Prekallikrein into Kallikrein which also activates FXII into FXIIa creating a positive feedback loop. This activation of FXII is quick as its peak is obtained within the first 10 min

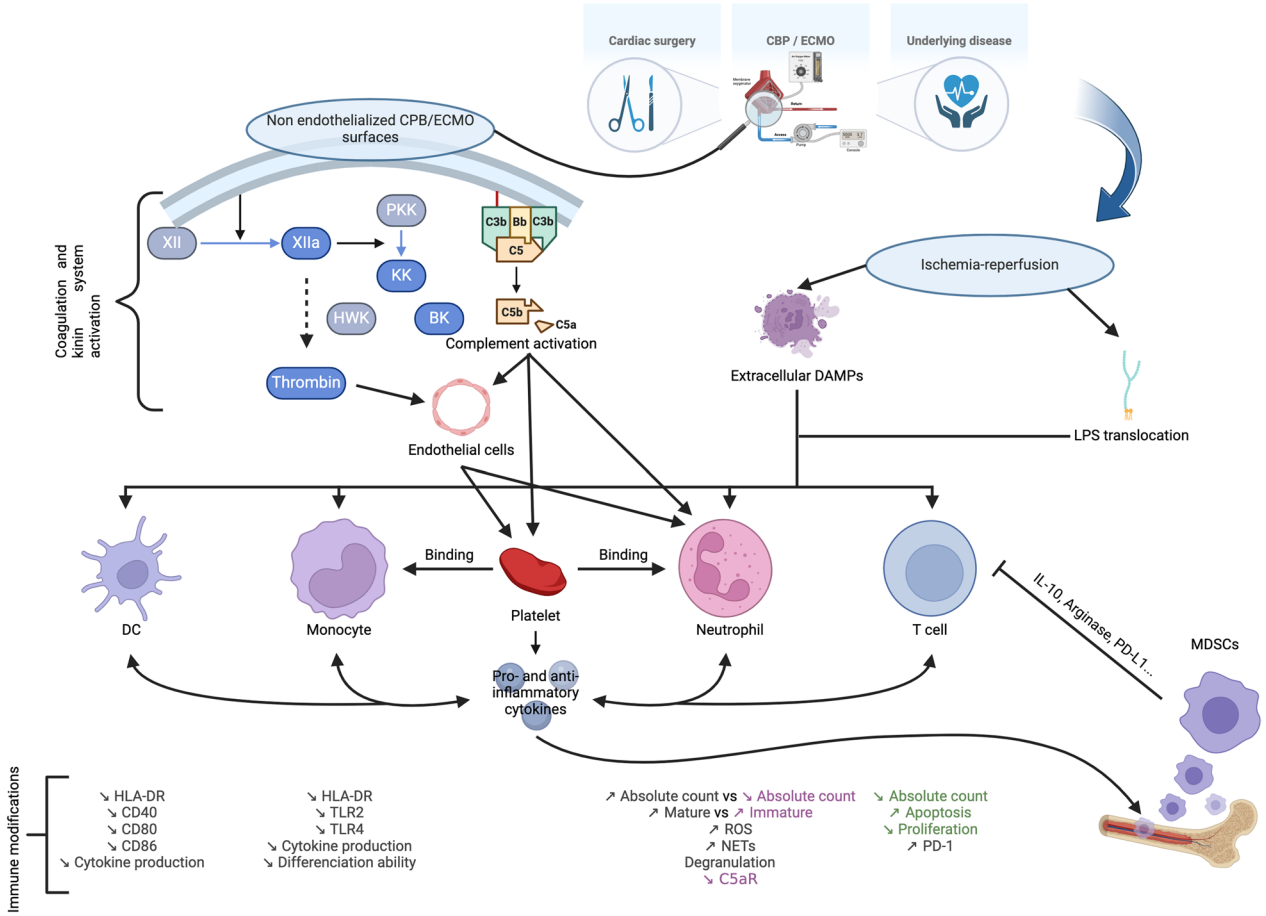


Fig. 1 CPB/ECMO immune response. In the initial moments following blood contact with non-endothelial surfaces within circulatory circuits, activation of the kinin system, complement system, and coagulation cascade occurs. This triggers the activation of endothelial cells, platelets, and neutrophils. Platelets form direct bonds with neutrophils and monocytes, while also releasing both pro- and anti-inflammatory cytokines. Furthermore, the ischemia-reperfusion process prompts the release of damage-associated molecular patterns and translocation of LPS from the gut, activating various cellular components of the immune system (including dendritic cells, monocytes, neutrophils, and T-cells). These cells also release pro- and anti-inflammatory cytokines, elucidating the interplay among cellular components. Ultimately, Myeloid Derived Suppressor cells are mobilized from the bone marrow, inhibiting T-cell functions. The immune modifications induced by CPB/ECMO are summarized at the bottom of the figure (gray: observed only after CPB, purple: observed only after ECMO, green: observed in both). BK (bradykinin), C5aR (complement component 5a receptor), CPB (cardiopulmonary bypass), DAMPs (damaged associated molecular patterns), DC (dendritic cells), ECMO (extracorporeal membrane oxygenation), HLA-DR (human leukocyte antigen-DR isotype), HWK (high weigh kininogen), KK (kallikrein), LPS (lipopolysaccharide), MDSCs (myeloid derived suppressor cells), NETs (neutrophil extracellular traps), PD-1 (program cell death protein 1), PD-L1 (program death ligand 1), PKK (prekallikrein), ROS (reactive oxygen species), TLR (toll-like receptor). Created with BioRender.com

Table 2 Immune modifications during CPB/ECMO

Humoral immune components

	CPB		ECMO		References
	Upregulation/ downregulation	Immune interaction	Upregulation/ downregulation	Immune interaction	
Kinin system	Upregulation	Coagulation cascade Endothelial cells	–	–	[28, 29]
Complement system	Upregulation	Neutrophils Endothelial cells Platelets	Upregulation	Neutrophils Endothelial cells Platelets	[31, 34]
Coagulation cascade	Upregulation	Platelets Endothelial cells	Upregulation	Platelets Endothelial cells	[36, 37]

Cellular immune components

	CPB			ECMO			References
	Number	Phenotype	Function	Number	Phenotype	Function	
Platelets	↓	↑ CD40 ↑ CD62P	↑ Release secretory granules	↓	–	–	[49, 49, 53]
Neutrophils	↑	Mature	↑ ROS production ↑ NETs release ↑ Degranulation	↓	Immatures ↓ C5aR	–	[55, 56, 57, 58, 61, 62]
Monocytes	→	↓ HLA-DR ↓ TLR2 ↓ TLR4	↓Cytokine production ↓Differenciation ability	→	→HLA-DR	–	[62, 65, 66, 68, 69, 72, 73]
Dendritic cells	→	↓ HLA-DR ↓ CD80 ↓ CD40 ↓ CD86	↓ Cytokine production	→	→HLA-DR		[62, 74]
B cells	↓	–	↑ Antibodies production	–	–	–	[76, 77]
T cells	↓	↑ PD1 ↓ CD25 ↓ CD45RO ↓ CD11 ↓ ICAM	↑ Apoptosis ↓ Proliferation	↓	–	↑ Apoptosis ↓ Proliferation	[62, 77, 78, 79, 80, 81, 93, 94, 96]
MDSCs	↑	↑ PD-L1	↑ IL-10 production ↑ Arginase activity ↓ T cells proliferation	↑	–	–	[62, 93, 96]

after CPB is started [28]. Kallikrein activates neutrophils and produces bradykinin from high mass weight kininogen. Finally, bradykinin enhances vascular permeability after binding to the B2 receptor on endothelial cells. The activation of the kinin system is transient as bradykinin levels return to baseline 24 h after surgery with CPB [28]. While the activation of the kinin system has been extensively investigated during surgeries involving CPB, there is currently a lack of data pertaining to ECMO. We can assume that the surfaces of the circuit can activate FXII, however, as bradykinin is degraded mainly in the lungs (which is not bypassed during ECMO), its concentration may be lower than during surgery with CPB [29].

The complement system

The complement system is a group of proteins that can be activated by three different pathways [30]. In the course of CPB, the alternative pathway undergoes rapid activation (within 1 h) due to the interaction between C3 and the surfaces of the circuits lacking inhibitory proteins specific to this activation pathway [31]. Therefore, C3 activation leads to the production of C3a and C5a which are pro-inflammatory as they activate neutrophils and increase vascular permeability [32]. Moreover, the complement activation finally leads to the formation of the C5b-9 membrane attack complex which activate platelets [33]. Research on complement activation during ECMO traces back to the 1990s, a period marked by less biocompatible circuits that exhibited complement activation in vitro [34]. Furthermore, while cardiogenic shock is known to activate the complement system [35], there is a lack of data comparing complement system activation between patients admitted for cardiogenic shock with and without ECMO support.

Coagulation activation

The contact between blood and the circuit surfaces initiates the activation of FXII, marking the initial phase of the intrinsic pathway within the coagulation cascade. Additionally, the extrinsic pathway is triggered. For instance, during cardiac surgery, endothelial cells release tissue factor due to vascular injuries [36] and even in the absence of endothelial damage during ECMO, complement system activation prompts monocytes and endothelial cells to generate tissue factor [37]. Consequently, the coagulation system is activated, ultimately leading to thrombin production. Thrombin, apart from its role in thrombus formation, also induces the expression of P- and E-selectin on endothelial cells, thereby activating neutrophils and platelets.

Ischemia–reperfusion, damaged associated molecular patterns (DAMPs) and endotoxemia

DAMPs are molecular patterns released during tissue damage, they initiate an inflammatory response after being recognized by receptors expressed by all immune cells such as Pattern Recognition Receptors (PPR) (Toll-like Receptors and Nod-like Receptors) and Non-PPR (CD44, CD91 and Receptor for Advanced Glycation End products) [38]. This leads to the production and release of pro-inflammatory cytokines (TNF-α and IL-1), vasoactive amines (histamine and serotonin) and Reactive Oxygen Species (ROS) by immune cells. In cardiac surgery involving CPB, the circuit bypass both the heart and lungs, resulting in ischemia for these organs, even though the heart is safeguarded by a cardioplegia solution [39, 40]. Moreover, the surgical procedure itself contributes to tissue damage and the release of DAMPs. Before ECMO implantation, the refractory cardiac shock induces a multi-organ ischemia [41]. Cell metabolism is therefore switched to anaerobic glycogenolysis which may induce multiple ionic modifications (such as the accumulation of H+ and Ca^{2+} inside the cells) [42, 43], thus weakening immune cells and leading to the production of ROS. Once CPB is over, or ECMO is started, reperfusion of the organs occurs with enriched oxygen blood, increasing ROS production [44], which is responsible for cell damages and DAMPs release. Ischemia–reperfusion also disrupts the intestinal barrier, enabling the translocation of lipopolysaccharide (LPS) into the bloodstream [45]. This endotoxemia activates the complement system [46], many components of the cellular immune system and promotes the production of pro-inflammatory cytokines [47].

The cellular immune response

Platelets

Platelets play a crucial role in in the inflammatory response by bridging humoral and cellular immune responses. They release pro-inflammatory molecules and directly interact with other immune cells to activate them. Platelets are activated by the coagulation cascade and the complement system during CPB [48]. They release secretory granules which contain chemokine C-X-C motif ligand 1 (CXCL1), CXCL4 and CXCL7 which increase neutrophils recruitment and other pro-inflammatory molecules such as platelets-activating factor, thromboxane A2 and IL-1ß which activate neutrophils, monocytes, dendritic cells and T-lymphocytes [49]. Moreover, activated platelets express CD40L and CD62P which allow them to bind to monocytes and neutrophils. This interaction activates the latter and facilitates their extravasation through the endothelium [50, 51]. There is a notable absence of data concerning the impact of ECMO on the immune aspects of platelets. Existing studies predominantly concentrate on thrombocytopenia during ECMO support and the pro-aggregation activity of these cells [52]. Additionally, assessing the interaction between platelets and leukocytes through flow cytometry poses challenges, as ex-vivo platelet activation is common and may result in the subsequent formation of platelet-leukocyte aggregates [53].

Neutrophils

Neutrophils are the first leucocytes to be recruited to an inflammatory site and they can eliminate countless pathogens by different means [54]. In cardiac surgery with CPB, there is a notable increase in the number of neutrophils within the initial 24 h. Intriguingly, flow cytometry analysis revealed a predominance of mature neutrophils in the bloodstream in this situation [55]. Furthermore, examination of the bone marrow compartment and neutrophil progenitors in the same study showed no alterations induced by CPB. Consequently, the mature neutrophils observed 24 h post-CPB are recruited through a demargination process [55]. Neutrophils are also activated during CPB. Multiple studies have shown an increase of Reactive Oxygen Species (ROS) production [56], a higher Neutrophils Extracellular Traps (NETs) release and blood levels of elastase and lactoferrin, which are contained in neutrophils' granules, were greater after CPB [57]. All of these functions are essential for killing bacteria. However, when exposed to

Staphylococcus aureus, neutrophils' phagocytosis and bactericidal activities were not heightened [55]. As previously mentioned, the complement system becomes activated shortly after the commencement of CPB. In the context of sepsis, it is established that C5a promotes the activation of neutrophils [58], and it can be inferred that a similar mechanism occurs during CPB. Moreover, pro-inflammatory cytokines which activate neutrophils such as IL-6, IL-8 and TNF-α are released during CPB [59]. Finally, the ischemia–reperfusion process induces the release of Damaged Associated Molecular Patterns (DAMPs) [60] which also activate neutrophils.

The studies on the impact of ECMO on neutrophils were mainly done in newborns and they show opposite effects compared to CPB. The number of circulating neutrophils decreases within the first 24 h after initiation and regains 7 days after [61]. In our study, we investigated phenotypic changes in major cellular immune subset, including neutrophils, dendritic cells, monocytes and T lymphocytes, among patients undergoing ECMO for cardiogenic shock. We assessed these changes just before ECMO initiation and at 1 and 7 days afterward. Additionally, we compared these findings to patients admitted for cardiogenic shock but treated without ECMO. We confirmed the decrease of circulating neutrophils among adults but most importantly, flow cytometry analysis showed that neutrophils were immature and their C5a receptors expression was decreased as well [62]. This alteration in phenotype has also been observed during sepsis and has been linked to a diminished capacity to eliminate gram-positive bacteria [63].

Monocytes

Monocytes migrate towards the inflammation site where they differentiate into dendritic cells and macrophages who will fill multiples roles (pathogens eradication, antigen presentation, healing orchestration…) [64]. The number of monocytes does not fluctuate after CPB. Nevertheless, there is a shift in their phenotype characterized by a reduced expression of TLR2 and TLR4 [65, 66]. TLR are essential for the activation of monocytes as they allow these cells to recognize Pathogens Associated Molecular Patterns (PAMPs) [67]. In the same study, the ex-vivo production of IL-6, IL-8 and TNF-α by the monocytes was reduced after CPB. Moreover, TLR2 expression was associated with the occurrence of nosocomial pneumonia after surgery [66]. At the surface of monocytes, another receptor is down-regulated after CPB: the Human Leucocyte Antigen D-related (HLA-DR) [68, 69]. This receptor is crucial for antigen presentation, playing a mandatory role in the activation of the cellular adaptive immune response. The monocyte's decrease expression of HLA-DR has also been widely studied during sepsis and is one key feature of the sepsis induced immunoparesis [70]. It has been associated with nosocomial infections among ICU patients [71]. Finally, the ability of monocytes to differentiate into dendritic cells is also impaired ex-vivo up to three months after CPB [72]. As for neutrophils, data about the impact of ECMO on monocytes come from one study on neonates. In this study where both VV-ECMO and VA-ECMO were analyzed, the authors observed a down-regulation of HLA-DR was during the whole time of the ECMO support compared to healthy subjects [73]. However, analyzing cardiogenic shock with and without ECMO among adults, there was no difference in the absolute number of monocytes or in their HLA-DR expression between the two groups or during ECMO support [62].

Dendritic cells

Dendritic cells play a sentinel role as they infiltrate nearly all organs and are antigen presenting cells. The number of dendritic cells remains stable during cardiac surgery with CPB, but significant phenotypic and functional dysfunctions emerge afterwards. First of all, the expression of HLA-DR at their surface is down-regulated as well as the expression of other receptors such as CD80, CD40 and CD86 [74]. These receptors act as co-stimulatory receptors crucial for the activation of lymphocytes by dendritic cells and their down-regulation attests a weakened immune response [75]. Moreover, the ex-vivo ability to produce pro-inflammatory cytokines such as IL-6 and TNF-α is decreased after CPB [74]. In the sole study focusing on dendritic cells during ECMO, no disparities were observed in either the absolute number or the expression of HLA-DR at their surface [62].

B lymphocytes

Although the number of B lymphocytes was lower after cardiac surgery with CPB [76, 77], patients who underwent cardiac surgery without CPB had an even lower absolute count of B lymphocytes compared to those undergoing cardiac surgery with CPB [76]. This suggests that these cells are more sensitive to surgery itself than to CPB itself. Additionally, the production of antibodies, which is one of the main functions of B-cells, was enhanced after CPB [77]. Finally, there is currently no data regarding the impact of ECMO on these cells.

T lymphocytes

CPB and ECMO share similarities regarding their impact on T lymphocytes. The number of T lymphocytes decreases after CPB [77–80] and 24 h after the initiation of the ECMO [81]. With the elevated neutrophil count following CPB, the neutrophil/lymphocyte ratio has been employed and found to be correlated with organ failures,

including acute kidney injury and atrial fibrillation, as well as with the length of hospital stay [82]. Moreover, persistence of lymphopenia 5 days after its initiation was associated with mortality among patients with ECMO [81]. The observed T-cell lymphopenia can be attributed to increased apoptosis of T-cells occurring both after cardiac surgery with CPB [76] and during the initial four days of ECMO [62]. T-cell apoptosis is also noted during sepsis and has been linked to poor outcomes among patients admitted to the ICU for sepsis [83]. In-vitro studies have demonstrated that macrophages and dendritic cells produce fewer pro-inflammatory cytokines and more anti-inflammatory cytokines after engulfing apoptotic bodies [84]. Moreover, in a mouse model of sepsis, the translocation of apoptotic bodies resulted in decreased survival [85]. Surgery itself [86–88] and medications used during the procedure such as propofol [89] or opioids [90] can induce T-cell apoptosis. However, Shi et al. have compared T-cell apoptosis among children undergoing cardiac surgery with and without CPB and have shown an increased apoptosis in the CPB group [91]. Besides, dobutamine, which is used as the treatment for cardiogenic shock, is known to induce T-cell apoptosis [92]. However, in our study, we compared T-cell apoptosis between patients with cardiogenic shock treated with ECMO and those treated without ECMO. Our findings demonstrated that the T-cell apoptosis was higher in patients receiving ECMO support than in those who did not undergo ECMO [62]. Besides T-cell apoptosis, cardiac surgery with CPB also induces phenotype alteration such as an increased expression of Program cell Death 1 (PD1), which is correlated to the duration of CPB [93], and a decreased expression of activation markers (CD25 and CD45RO) and adhesion markers (CD11 and ICAM) [94]. PD1 has been widely studied in the cancer field is known to promotes T-cell exhaustion [95]. Finally, CPB and ECMO decreases T-cell proliferation ex-vivo [62, 93, 96]. This phenomenon has also been extensively observed during sepsis and has been correlated to nosocomial infection and mortality among ICU patients [97, 98].

Myeloid derived suppressor cells (MDSCs)

MDSCs are immunosuppressive myeloid cells that were first described in the tumor microenvironment [99]. They have also been identified during sepsis and are correlated to nosocomial infections among ICU patients [100]. There are two types of MDSCs: monocytic MDSCs (M-MDSCs) and granulocytic MDSCs (G-MDSCs). They are recruited from the bone marrow in response to a significant and/or prolonged inflammatory stimulus. Indeed, GM-CSF and IL-6 are both released during the immune response in order to recruit neutrophils and monocytes from the bone marrow. However, these two cytokines also recruit MDSCs. MDSCs mainly impact T-cells and inhibit their activation through different mechanisms. They release anti-inflammatory cytokines such as IL-10 and TGF-β and express Program Death Ligand 1 (PD-L1) that inhibits T-cell activation. Moreover, they catabolize nutrients (arginine, tryptophan) that are essential for T-cell proliferation. MDSCs also produce ROS and nitric oxide that degrade T-cell receptor which is vital for antigen recognition. Finally, they release adenosine which decrease T-cell cytotoxic activity and degrade T-cell receptor (CD62L, CD44 and CD164) which prevent their endothelium adhesion and their migration towards lymphatic nodes [101].

The total number of MDSC increases after cardiac surgery with CPB and is correlated with nosocomial infections [93]. Interestingly, only M-MDSC are recruited during cardiac surgery whereas the number of G-MDSC remains unchanged [96]. Along these lines, arginine levels in blood are decreased after CPB such as tryptophan whereas IL-10 in increased. Finally, MDSC upregulate their PD-L1 expression. Interestingly, when MDSC are depleted in-vitro, T-cells functions improve leading to the conclusion that CPB induces the recruitment of MDSC that inhibits T-cells. In our study, we inhibited MDSC main function with IL-10 antibody, PD-L1 blocking antibody, Indoleamine 2,3 dioxygenase (which catabolize tryptophane) inhibitor and arginine supplementation in the culture media. Arginine supplementation was the only treatment that restored T-cell proliferation in-vitro. MDSCs are also recruited during ECMO but their impact on T-cells remain unclear [62].

Acquired immune dysfunction under CPB/ECMO: perspectives

Both CPB and ECMO trigger an initial inflammatory immune response followed by an immunoparesis phase, potentially contributing to the susceptibility of nosocomial infections. Consequently, two strategies have been explored to reduce infection acquisition in these patients. Numerous clinical trials have sought to either restrain the inflammatory response during CPB to mitigate its anti-inflammatory repercussions or enhance the compromised immune system to restore its functions.

Limiting the immune response during CPB/ECMO

The limited data from patients under ECMO

There is a substantial disparity in the available data between CPB and ECMO. Immune responses during cardiac surgery with CPB have been extensively documented, providing both phenotypic changes and mechanistic insights due to the homogeneous population studied. Conversely, data on ECMO are sparse, primarily

because most studies have focused on neonates. In the sole study comparing immune responses in patients with cardiogenic shock with and without ECMO, we demonstrated that the immune response differs from that observed in CPB patients [62]. Therefore, it is essential to distinguish between CPB and ECMO in terms of immunoparesis. Consequently, various experimental immunomodulation strategies have been investigated through clinical trials in patients undergoing cardiac surgery with CPB. In contrast, the data concerning patients on ECMO primarily consists of retrospective analyses, case reports and cohort studies.

The "off-pump" surgery

Since CPB induces an inflammatory response that ultimately led to an immunoparesis state, the idea of cardiac surgery without CPB has emerged. Indeed, some surgery can be done without the opening of the heart (e.g. coronary artery bypass). Therefore, numerous studies have shown that "off-pump" cardiac surgery reduces cytokines levels [102], complement activation [103], as well as the activation of neutrophils [104] and of the endothelium [105]. Those results were correlated with decreased blood transfusion rates, lower cardiac damages and shorter hospital stay [106, 107]. However, those studies were tested among young patients without comorbidities. Recent studies among older patients failed to show any benefits with "off-pump" surgery [108].

Corticosteroids

Corticosteroids are commonly used for numerous inflammatory states as they reduce both cellular and humoral immune response [109]. Although corticosteroids decrease cytokines levels [110], complement activation [111] and endothelial damage [112] during cardiac surgery with CPB, numerous clinical trials have failed to show any clinical improve. Indeed, among 13 randomized clinical trials, only 2 concluded to a diminution of postoperative complications with corticosteroids whereas all of the other failed to show any improvement concerning mortality, organ dysfunction and length of hospital stay [113]. Moreover, a meta-analysis published in 2011 concluded that corticosteroids during cardiac surgery with CPB does not improve the mortality nor do they reduce the cardiac and pulmonary damages [114]. Since then, multiple meta-analysis have been made and only one found a decreased incidence of atrial fibrillation and kidney injury with a low dose of corticosteroids [115] which was only seen in small trials [116]. However, mortality was the same regardless of the use of steroid [115–118].

Complement inhibitors

As described before, the complement activation is one of the first step of the immune response during cardiac surgery with CPB. Therefore, pexelizumab, which inhibits the production of C5a and C5b which are essential for the formation of the membrane attack complex, has been studied in cardiac surgery with CPB. Two clinical trials showed no differences in term of mortality and postoperative infarcts compared to placebo [119].

Leucocytes-depleting filters and hemoadsorption

In order to remove the most abundant activate cells during cardiac surgery with CPB, leucocytes-depleting filters, which reduces the number of activated neutrophils, have been developed in the late 90s. Numerous studies have conflicting results on both biological and clinical variables. Moreover, depending on the type of filter and its position on the CPB circuit, the effects are different and summarized in other specific reviews [120, 121]. Hemoadsorption is designed to remove low molecular weight molecules such as cytokines. The CytoSorb® sorbent has been evaluated in a clinical trial, which showed that cytokine levels remained consistent regardless of CytoSorb® usage; however, IL-10 demonstrated a more prolonged anti-inflammatory effect [122]. Furthermore, no differences in clinical outcomes were observed [122], a finding corroborated by a recent systematic review [123]. Nonetheless, case reports and smaller studies have reported positive outcomes in high-risk patients [124]. These studies suggest that hemoadsorption may be beneficial in specific scenarios by enhancing hemodynamic stability and lowering cytokine levels, though more comprehensive research is required to universally validate these findings. In a recent cohort study, the use of hemoadsorption during ECMO support was associated with an accelerated recovery of multiorgan and microcirculatory dysfunction and lower risk of early death [125].

Mechanical ventilation during CPB

Since CPB mechanically circulates and oxygenates blood bypassing the heart and lungs, usual procedure during CPB is to stop mechanical ventilation. However, Gaudriot et al. suggested that maintaining mechanical ventilation may improve immune dysfunction parameters such as the expression of monocytic HLA-DR [69]. Additionally, the application of low tidal volume—low frequency ventilation could decrease the production of pro-inflammatory cytokines such as interleukin 10 and tumor necrosis factor-α [126]. In two clinical trials, maintaining mechanical ventilation did not decreased nosocomial infections

after cardiac surgery with CPB [127, 128]. However, these studies did not use the occurrence of postoperative infections as their primary endpoints. Therefore, the clinical relevance of maintaining the mechanical ventilation during CPB is still on debate although recommended [129] (ClinicalTrials.gov Identifier: NCT0337217).

Restoring immune functions during CPB/ECMO: immunonutrition for patients under cardiac surgery with CPB

Immunonutrition (mainly Arginine supplementation) has already been investigated among patients with cardiac surgery with CPB and showed conflicting results. Indeed, in a prospective, randomized, monocentric, double-blind, placebo-controlled study, patients were treated with 5 days of Arginine (or placebo). There was a significant reduction of nosocomial infections among treated patients and a higher expression of monocytic HLA-DR compared to the placebo group [130]. However, these results have never been confirmed in other studies and arginine supplementation have failed to correct hypoargininemia in other inflammatory situations [131].

Conclusion

Despite shared characteristics between immunoparesis induced by CPB and immune dysfunction brought about by ECMO, it is essential to address these two situations separately, considering ECMO as a "second hit." Furthermore, attempts to limit the inflammatory response to reduce immunoparesis have not yielded to conclusive results over the past decade. Therefore, strategies focused on restoring immune functions should be considered for clinical trials, mirroring approaches for other patients in the intensive care unit (ICU) [132].

Abbreviations

CPB	Cardiopulmonary bypass
CXCL	Chemokine (C-X-C motif) ligand
DAMPs	Damage associated molecular patterns
ECMO	Extracorporeal membrane oxygenation
FXII	Coagulation factor XII
GM-CSF	Granulocyte–macrophage colony-stimulating factor
HLA-DR	Human leucocyte antigen-DR isotype
ICU	Intensive care unit
IL	Interleukin
LPS	Lipopolysaccharide
MDSCs	Myeloid derived suppressor cells
PAMPs	Pathogen associated molecular patterns
PD-1	Programmed cell death 1
PD-L1	Programmed death ligand 1
ROS	Reactive oxygen species
TNF	Tumor necrosis factor
TGF-β	Transforming growth factor beta
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation

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Declarations

Competing interests

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