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Inflammatory response and extracorporeal circulation

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Patients undergoing cardiac surgery with extracorporeal circulation (EC) frequently develop a systemic inflammatory response syndrome. Surgical trauma, ischaemia–reperfusion injury, endotoxaemia and blood contact to nonendothelial circuit compounds promote the activation of coagulation pathways, complement factors and a cellular immune response. This review discusses the multiple pathways leading to endothelial cell activation, neutrophil recruitment and production of reactive oxygen species and nitric oxide. All these factors may induce cellular damage and subsequent organ injury. Multiple organ dysfunction after cardiac surgery with EC is associated with an increased morbidity and mortality. In addition to the pathogenesis of organ dysfunction after EC, this review deals with different therapeutic interventions aiming to alleviate the inflammatory response and consequently multiple organ dysfunction after cardiac surgery.

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Introduction

During cardiac surgery, extracorporeal circulation (EC) enables surgeons to treat a wide range of heart diseases while circulation and oxygenation of human blood are maintained by machines. While the first successful cardiopulmonary bypass (CBP) during a ventricular septum repair in 1953 by Gibbon was still an experimental procedure, CPB has in the meantime emerged as a well-established procedure, used worldwide in more than half a million people per year [1,2]. Blood trauma and the creation of embolic particles were initially common adverse effects of EC. However, through the development of new biomaterial technologies and implementation of pharmacologic drugs, these potential side effects were reduced, linked to a rapid improvement of patients' outcome. Nevertheless, despite the encouraging successes, patients undergoing cardiac surgery continue to frequently develop post-operative complications arising from the inappropriate activation of inflammatory pathways [3].

Inflammation is the response of the organism to several noxious stimuli. During cardiac surgery, different stimuli, such as blood exposition to the nonendothelial surface of the CPB, ischaemia–reperfusion injury and endotoxaemia, may trigger an inflammatory response. The activation of humoral and cellular cascades leads to an increase of pro-inflammatory cytokines in the circulating blood and to enhanced leucocyte recruitment [4]. The resulting systemic inflammatory response syndrome (SIRS) is associated with post-operative complications including myocardial dysfunction, respiratory failure, acute kidney injury (AKI), neurologic dysfunction, bleeding disorders and, finally, multiple organ failure (MOF). MOF is strongly associated with increased morbidity and mortality rates among patients undergoing cardiac surgery.

Mediators of the inflammatory response

Coagulation linked to inflammation

In the vascular system, endothelial cells produce pro- and anticoagulation factors, which together maintain the equilibrium of blood fluidity. The exposure of blood components to artificial surfaces within the extracorporeal circuit leads to an activation of coagulation cascades. These pathways, classically divided into an intrinsic and extrinsic pathway, consist of a series of enzyme cascades and lead to the generation of activated thrombin (Fig. 1) [5].

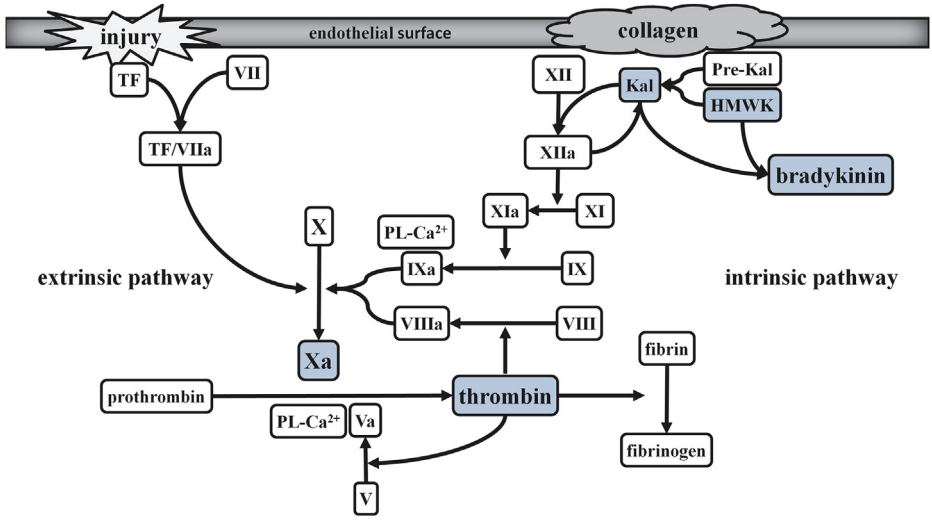

Fig. 1. Schematic overview of the intrinsic and extrinsic coagulation pathway. Coagulation factors that contribute to inflammatory cell activation are coloured blue. TF, tissue factor; Pre-Kal, prekallikrein; Kal, kallikrein; HMWK, high molecular weight kininogen; PL, phospholipids; and coagulation factors, V,VII, VIII, IX, X, XI and XII (a indicating active form).

The intrinsic pathway is initiated by the exposure of negatively charged, nonendothelial surfaces to factor XII (Hageman factor), whose autoactivation requires the presence of prekallikrein and high-molecular-weight kininogen (HMWK). Factor XIIa contributes to an enzyme cascade that leads to the generation of thrombin. Thrombin subsequently cleaves fibrinogen to fibrin, which is able to form fibrin strands in a polymerised form [6]. Active factor XII enables the activation of prekallikrein to kallikrein, a serine protease-releasing bradykinin through the cleavage of HMWK. Bradykinin is a potent vasoactive peptide that alters vascular endothelial permeability and smooth muscle tone level. In addition, binding to the bradykinin receptor on leucocytes may alter their activation state and cytokine production of leucocytes [7].

Tissue trauma initiates the extrinsic coagulation pathway. Injured vessel walls enable the exposure of blood to tissue factor (TF), an integral membrane glycoprotein (GP) of perivascular cells [8]. Binding of the circulating factor VII to TF enables its activation to factor VIIa. Depending on Ca^{2+} and phospholipids, the factor VIIa–TF complex promotes the activation of factor X to factor Xa. Production of Factor Xa is the point of convergence of both coagulation pathways leading to thrombin generation and cleavage of fibrinogen.

In addition to their pro-coagulation properties, factor Xa and thrombin have pleiotropic effects on inflammatory processes, tissue remodelling and development of atherosclerosis [9,10]. Both factors bind and activate protease-activated receptors (PARs). These G-protein-coupled receptors (GPCRs) activate intracellular signalling cascades leading to platelet and leucocyte activation. *In vitro* studies revealed that factor Xa induces cytokine expression and surface expression of adhesion molecules on leucocytes, thereby linking coagulation to inflammation [11,12].

During cardiac surgery with the use of EC, both the intrinsic and extrinsic pathways of the coagulation cascade are activated. To prevent intravascular clot formation, anticoagulation therapy is indispensable [13]. Systemic heparinisation has evolved as the current standard therapy, largely because of the easy monitoring of its anticoagulant effect. Despite full heparinisation, thrombin generation still occurs, as indicated by elevated levels of thrombin–antithrombin III complexes in patients undergoing CPB [13]. This may cause a consumptive coagulopathy, which is responsible for thromboembolic events and non-surgical haemorrhage after CPB [14]. Thus, increased levels of biomarkers of activated coagulation pathways are associated with negative outcomes after cardiac surgery [15].

Cytokines and chemokines

Cytokines and chemokines are released by different cell types in response to different stimuli [16]. These mediators activate immune cells and modulate the inflammatory response of the body. CPB induces an altered release of pro- and anti-inflammatory cytokines [17]. Increased levels of the pro-inflammatory cytokines tumour necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-8 were found to be associated with adverse clinical outcomes in patients undergoing cardiac surgery [18]. Furthermore, human myocardial contractile function was profoundly depressed after exposure to TNF-α and IL-1β ('myocardial depressant factor') [19].

Nitric oxide

In response to physiologic stimuli such as pulsatile flow and shear stress, endothelial cells regulate the vascular tone through the release of nitric oxide (NO). The constitutive nitric oxide synthase (cNOS) in endothelial cells produces NO from the amino acid L-arginine in response to calcium signalling. Constitutively released NO decreases smooth muscle contraction, thereby promoting vasodilatation and reducing shear stress [20].

In response to the release of pro-inflammatory cytokines or endotoxins, endothelial cells and smooth muscle cells express an inducible nitric oxide synthase (iNOS), which is independent of calcium signalling [21]. Besides the beneficial role of NO under physiologic conditions, iNOS-derived NO impairs the mitochondrial respiratory chain. NO-mediated inhibition of the cytochrome oxidase increases the production of reactive oxygen species (ROS) [22]. ROS alter intracellular pH levels, reduce adenosine triphosphate (ATP) production and induce cellular damage through lipid peroxidation, oxidation

of DNA and inactivation of specific enzymes [23]. In the presence of NO, ROS may also form highly noxious peroxynitrite [24]. These compounds can lead to the necrosis of endothelial cells, thereby impairing the endothelial barrier function and enabling vascular leakage. Extracellular ROS serve as potent pro-inflammatory stimuli, as they may trigger an up-regulation of cell-surface adhesion molecules and release of cytokines by activated macrophages [25].

Platelets and inflammation

In addition to their coagulation function, platelets contribute to the inflammatory response following EC. Heparinisation, hypothermia and surgical trauma activate platelets. Activated platelets change their shape and release a variety of mediators, including inflammatory cytokines. Platelet granules contain chemokines (chemokine (C–C motif) ligand 3, 5, 7, 17 and chemokine (C-X-C motif) ligand 4, 5, 7, and 8), cytokines (IL-1β, CD 40 ligand and β-thrombomodulin), adhesion factors (P-selectin, GP IIb/IIIa and von Willebrand factor), growth factors (platelet-derived growth factor, transforming growth factor-β, epidermal growth factor and vascular endothelial growth factor) and coagulation factors (factor V, factor XI, plasminogen activator inhibitor-1, plasminogen and protein S) (reviewed in ref. [26]). These mediators act on other platelets, leucocytes and endothelial cells.

Platelets are activated by the CPB system, resulting in the up-regulation of P-selectin on their surface membranes [27]. Platelet P-selectin binds to P-selectin glycoprotein ligand (PSGL)-1 expressed on leucocytes, thus mediating the first cell–cell interaction [28–30]. P-selectin binding to PSGL-1 promotes monocyte activation leading to secretion of cytokines such as IL-1β, IL-8 and monocyte chemoattractant protein (MCP)-1 [31,32]. In the course of the exocytosis of cytokines, activated monocytes present TF on their surface, which initiates the extrinsic coagulation pathway and favours thrombus formation [33].

The initial contact between platelets and leucocytes is further strengthened by integrins [34]. Integrins are a family of transmembrane αβ heterodimeric receptors, which are expressed on almost all cell surfaces [35]. They bind to extracellular matrix as well as immunoglobulin-like adhesion molecules, but a conformational change of the molecules is required before binding to a ligand. The leucocyte integrin $\alpha_M ß_2$ (CD11b/CD18) recognises platelet GP Ib and fibrinogen, which is bound to the platelet GP IIb/IIIa receptor. Platelet intercellular adhesion molecule (ICAM)-2 interacts with the leucocyte integrin $\alpha_L \beta_2$ (CD11a/CD18).

The vascular endothelium presents the adhesion molecule CD40, which is bound by the complementary CD40 ligand (CD40L) on platelets. The transmembrane CD40L is structurally related to TNF-α and promotes the endothelial secretion of pro-inflammatory cytokines (IL-8 and MCP-1). Thus, platelets bound to the endothelium contribute to neutrophil recruitment and activation of monocytes by direct platelet–leucocyte interaction, by release of pro-inflammatory granules or by stimulation of endothelial cells [7,36]. In patients undergoing CPB during cardiac surgery, the level of platelet–leucocyte aggregates was shown to increase [37].

EC activates leucocytes

Following cardiac surgery with CPB, neutrophil recruitment is involved in the pathogenesis of SIRS [38]. Polymorphonuclear neutrophils store intracellular granules containing neutrophil elastase, myeloperoxidase and several lysozymes [39]. After being activated, neutrophils release their granules and undergo a respiratory burst discharging large quantities of superoxide and hydrogen peroxide. Activated neutrophils also release nuclear extracellular traps (NETs), which are potent antibacterial compounds, composed of chromatin fragments, histones and granular proteins [40]. Neutrophil compounds may cause tissue damage and may increase microvascular permeability [4].

During inflammation, cytokines such as TNF-α and IL-1β stimulate endothelial cells, which up-regulate the expression of adhesion molecules [41]. Activated endothelial cells express P-selectin on their cell surface followed by an increased expression of E-selectin, which occurs 2–4 h later [42,43]. These adhesion molecules mediate the initial interaction between leucocytes and activated endothelial cells and they initiate the leucocyte recruitment cascade consisting of capturing, rolling, adhesion, crawling and transmigration.

E- and P-selectins expressed on activated endothelial cells bind PSGL-1 on neutrophils. This cell-to-cell contact induces an intracellular signalling in neutrophils, resulting in integrin activation and in a deceleration of the rolling velocity of leucocytes [34,44]. During rolling, PSGL-1 engagement and the activation of GPCRs by chemokines induce full integrin activation and leucocyte arrest. Neutrophils express the β_2 integrins $\alpha_L\beta_2$ (function-associated antigen (LFA)-1), $\alpha_M\beta_2$ (macrophage-1 antigen (Mac-1)), $\alpha_x\beta_2$ and low levels of $\alpha_4\beta_1$ [45]. LFA-1 is responsible for selectin-mediated slow leucocyte rolling and chemokine-induced arrest, whereas Mac-1 is required for post-adhesion strengthening [39]. After leucocyte adhesion, leucocytes start crawling along the endothelium to find permissive sites for diapedesis.

A recently published study demonstrated that cardiac surgery with CPB abrogates selectin-induced slow leucocyte rolling on E-selectin/ICAM-1 and P-selectin/ICAM-1 [46]. By contrast, chemokine-induced arrest and transmigration was significantly increased. The abolishment of slow leucocyte rolling was mechanistically linked to disturbances in intracellular signalling with reduced phosphorylation of phospholipase C (PLC) γ2, Akt and p38 mitogen-activated protein kinase. Furthermore, CPB induced an elevated transmigration, which was caused by up-regulation of Mac-1 on neutrophils [46].

Ischaemia–reperfusion injury

Reperfusion injury is the tissue damage caused when blood supply returns to the tissue after a period of ischaemia or lack of oxygen [25]. During cardiac surgery with the use of CPB, blood supply to the heart and lungs is temporarily almost completely stopped. The lack of oxygen within these organs promotes cells to accumulate metabolic intermediates such as adenosine monophosphate and hypoxanthine, resulting in ROS production. ROS-mediated cellular damage induces the up-regulation of cell-surface adhesion molecules and expression of pro-inflammatory cytokines [23]. After reperfusion, the tissue injury even increases due to leucocyte recruitment into the inflamed tissue.

Following reperfusion, the recruited neutrophils increase tissue levels of ROS, cytokines and chemoattractants, thereby amplifying the inflammatory response [25,47]. Neutrophils are the major source of ROS production, which may damage cells even in non-hypoxic tissue [48,49]. Recruitment of neutrophils increases vascular permeability [39]. Cellular swelling and damage due to hypoxia or cytotoxic compounds may shift the equilibrium between pro- and anticoagulation factors produced by the endothelium towards thrombus formation. Platelets as well as neutrophils may stick within inflamed capillaries, thereby provoking hypoperfusion of hypoxic tissues, the so-called no-reflow phenomenon [50]. Finally, the devastating neutrophil recruitment during ischaemia–reperfusion contributes to the generation of acute respiratory distress syndrome (ARDS), SIRS and MOF causing high morbidity and mortality [51].

Endotoxaemia

Gram-negative intestinal flora produce lipopolysaccharides and endotoxins as a part of their cell wall. In patients undergoing cardiac surgery, hypoperfusion and hypoxia may impair the intestinal barrier integrity, which is necessary to avoid the transition of endotoxins [52]. Intravascular endotoxins bind to various receptors, such as Toll-like receptors on leucocytes, causing cytokine production and leucocyte activation [53]. Clinical studies investigating endotoxin levels during cardiac surgery demonstrated a reduced inflammatory response in off-pump patients, but these studies failed to show improvements in clinical outcomes (reviewed in ref. [52]).

Inflammatory response and organ dysfunction

Each of the mediators mentioned above may influence patients' inflammatory response during and after CPB. Inappropriate inflammatory response can lead to ARDS, AKI and finally MOF.

The pathogenesis of ARDS depends on a multitude of different factors, among those a number of vasoactive mediators released by activated leucocytes and platelets, which contribute to oedema formation and increased pulmonary vascular resistance [23]. In a rat model, neutropaenia mitigated ischaemia–reperfusion injury of the lung, showing that neutrophils directly contribute to tissue

damage [54]. In a mouse model, blocking of P-selectin inhibited the formation of platelet–neutrophil aggregates, thereby attenuating the severity of ARDS in a model of acid-induced lung injury [55].

Further detailed insights into the pathogenesis and therapeutic options of organ dysfunctions following CBP will be provided by separate reviews by Huffmyer et al. and Landoni et al. within this issue.

Therapeutic options

During CPB, a multitude of stimuli trigger the emergence of an SIRS. Enormous efforts have been made to promote the development of drugs or technical approaches able to ameliorate inflammatory responses (Table 1). Clinical studies to evaluate the effect of single interventions are fundamentally flawed, as multiple factors contribute to the clinical picture of SIRS and to the varying degrees of inflammatory response [16].

Technical approaches to ameliorate the inflammatory response

Several components of the CPB circuit, including type of oxygenator, pulsatile versus non-pulsatile flow, selective leucocyte filters and different priming solutions (reviewed in ref. [56]), were tested with respect to their inflammatory properties. Until now, only few strategies were able to significantly ameliorate the inflammatory response and to improve patients' outcome.

As soon as blood comes into contact with the CBP circuit, a multitude of stimuli contribute to the development of SIRS. Several attempts have been made to improve the biocompatibility of circuit compounds by coating the circuit surfaces with heparin, poly-2-methoxyethylenacrylate, hyaluronan or phosphophorycholine [16]. A recent meta-analysis by Mahmood and colleagues provides evidence that heparin coating does not increase the number of adverse events, but it decreases blood transfusion requirements, re-operation rates, time of mechanical ventilation and length of stay (LOS) in the intensive care unit (ICU) and in hospital [56]. The authors justify the usage of coated CPB circuits with improved clinical outcome. Before heparin-coated circuits are implemented in daily practice, further investigations are warranted.

Mini-extracorporeal circuits (MECCs) provide a small-volume circuit, which consists of a heparin-coated system and a membrane oxygenator but lacks the venous reservoir of a standard CBP circuit

Table 1
List of clinical trials that revealed beneficial effects on outcome of patients after cardiac surgery due to technical or pharmacologic intervention.

	Approach	Targeted mechanism	Clinical effect	Reference
Technical approaches	Coating circuit compounds	Reduce activation of blood coagulation compounds due to contact to nonendothelial surfaces	Blood transfusions ↓ mechanical ventilation time ↓ LOS on ICU ↓	[56]
	Mini-extracorporeal circuits	Reduce haemodilution and associated impairment of oxygen delivery capacity avoid activation of coagulation pathways and cellular activation	Blood transfusions ↓ levels of IL-6 and TNF-α ↓	[59]
Pharmacologic approaches	High-dose versus low-dose propofol	Antioxidant and anti-inflammatory effects	Markers of neuronal injury ↓	[68,69]
	Volatile anaesthetics versus TIVA	Ischaemic preconditioning	Rate of myocardial infarction ↓ mortality ↓	[70,71]
	Statin administration	Pleiotropic effects binding to leucocyte LFA-1 receptor	Rate of new onset of atrial fibrillation ↓ LOS in hospital ↓ myocardial infarction ↓ mortality ↓	[74]
	Glucocorticoid administration	Anti-inflammatory effects	Rate of new onset of atrial fibrillation ↓ incidence of pneumonia ↓	[80,81]

[57]. Standard CPB circuits need large priming volumes, which lead to significant haemodilution associated with reduced blood oxygen transport capacity and impairment of coagulation [58]. Compared to conventional CPB, MECCs lead to significant reduction of haemodilution and red blood transfusion requirements in a study of 199 patients undergoing coronary artery bypass grafting [59]. Moreover, levels of the inflammatory cytokines IL-6 and TNF-α were significantly decreased in patients undergoing CABG with MECCs [60]. A similar effect of MECC on inflammatory cytokines was observed in patients undergoing aortic valve replacement [61]. These results are promising, but pulmonary complications, neurologic events or mortality were not significantly reduced due to usage of MECC [62]. Despite improvements regarding haemodilution and blood transfusion requirements, MECCs still contain a considerable potential to trigger an SIRS [63].

Pharmacologic approaches

Anaesthetic agents

In addition to their anaesthetic effect, the majority of anaesthetic agents used during general or local anaesthesia possess immunomodulatory effects [64]. High-dose opiates are used during cardiac anaesthesia to preserve haemodynamic stability and to attenuate the stress response to surgical stimuli due to their potent analgesic effects [65]. In a small randomised pilot study, remifentanil administration was associated with a shortened length of stay and a reduced level of cytokine signalling [66]. Although remifentanil has a favourable pharmacokinetic property, this substance may have immunomodulatory functions in patients undergoing elective CBP surgery compared to fentanil [66].

Propofol is commonly administered for induction and maintenance of general anaesthesia, which negatively affects haemodynamic parameters. High-dose administration of propofol (200 μg/kg/min) decreased the mean arterial pressure and cardiac index followed by an increased heart rate [67]. This resulted in a decreased myocardial blood flow and myocardial oxygen consumption [67]. In addition, high-dose propofol appears to exert a brain-protective effect due to its antioxidant and anti-inflammatory properties [68,69].

Volatile anaesthetics were shown to decrease levels of the pro-inflammatory cytokines IL-6, IL-8 and TNF-α [64,70]. According to a comparing body of evidence, anaesthetic preconditioning by volatile anaesthetics attenuates the deleterious consequences of ischaemia–reperfusion and protects the heart through a mechanism similar to ischaemic preconditioning [70]. Protective effects on the myocardium were also investigated by randomised controlled trials comparing volatile anaesthetics and total intravenous anaesthesia in patients undergoing cardiac surgery. A meta-analysis by Landoni and colleagues revealed that desflurane and sevoflurane reduced the incidence of myocardial infarction and all-cause mortality [71]. This indicates that the use of volatile anaesthetics for patients undergoing cardiac surgery is associated with a reduction of adverse major events [70].

The application of thoracic epidural anaesthesia (TEA) may offer several benefits including sympathetic block with stable heart rate and decreased myocardial oxygen consumption [65]. One of the main concerns against the application of TEA in this patient population undergoing cardiac surgery is the risk of epidural haematoma, due to heparinisation during CBP. A risk assessment of TEA application for cardiac surgery in 2012 revealed that the risk of epidural haematoma is very low, similar to the general surgery population [72]. Providing TEA in cardiac patients is not unreasonable but it requires protocols to safely manage these patients' coagulation profiles and post-operative anti-platelet therapies [65].

Pleiotropic effects of statins

Inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (statins) are well established in the treatment of hypercholesterolaemia and have beneficial effects on morbidity and mortality due to the prevention of major cardiovascular events [73]. Beyond their lipid-lowering effect, statins were found to have anti-inflammatory properties, the so-called 'pleiotropic effects' [74]. These may particularly be explained by the binding of statins to the leucocyte integrin LFA-1, which is involved in the neutrophil recruitment cascade [75]. Statins counteract pro-inflammatory transcriptional pathways and suppress the activity of pro-oxidant enzymes within endothelial cells [74].

Several randomised controlled trials investigated the effect of perioperative statin treatment in patients undergoing cardiac surgery. A recent review and meta-analysis provided by de Waal and colleagues demonstrated that preoperative initiation of statin administration reduces mortality, myocardial infarction, perioperative new-onset atrial fibrillation and length of hospital stay [76].

Administration of glucocorticoids

The administration of glucocorticoids aims at attenuating the inflammatory response following CBP. The first positive effects of glucocorticoid administration were obtained by Moses et al. as early as 1966. The authors investigated dogs undergoing prolonged CPB [77]. Over decades, several clinical trials scrutinised the anti-inflammatory effect of glucocorticoids on major and minor outcome parameters in human patients. After several promising results in single-centre trials, a thorough meta-analysis revealed that the positive effects of glucocorticoid application were minor than initially thought [78]. There was no difference in major outcome parameters such as major cardiac events, pulmonary complications or mortality after 30 days. Secondary outcomes such as length of stay in ICU and hospital, as well as new-onset atrial fibrillation, showed a slight trend towards steroid administration [79]. Although glucocorticoid administration is believed to raise the incidence of infectious complication, Dieleman and colleagues observed less pneumonia in the dexamethasone group [80]. The Steroids in Cardiac Surgery (SIRS) trial is a large international randomised controlled study that investigates the effects on AKI and other outcome parameters [81]. Nevertheless, until now, there has been no evidence for an effect of glucocorticoid administration on mortality or severe cardiac complications [78].

Conclusion

EC can induce an SIRS response in patients undergoing cardiac surgery. This syndrome is frequently associated with organ injury and MOF. The understanding of the inflammatory processes and the interplay of humoral factors and cellular immune response increased rapidly during the last decade. Multiple anti-inflammatory strategies were applied in the past, which significantly reduced cytokine levels without improving clinical outcome. This implies that the amplitude of inflammatory cytokines does not directly predict patients' outcome. The lack of evidence may also be due to poor study design or large variations in covariants, such as different transfusion regiments, CBP circuits and temperature management. Future studies should aim at maximising the standardisation of peri- and post-operative patient management and addressing multiple targets as anti-inflammatory strategy.

Practice points

- The use of CPB in patients undergoing cardiac surgery is frequently associated with the development of an SIRS. A variety of pro-inflammatory stimuli contributes to the activation of endothelial cells, neutrophil activation and recruitment and production of cytotoxic compounds.
- While there is no doubt that the administration of glucocorticoids and statins is effective in reducing the cytokine levels, improvements in major clinical outcome parameters have not been evidenced.
- Volatile and intravenous anaesthetic agents possess multiple immunomodulatory effects. The choice of anaesthetic agent was shown to have the potential to positively influence the outcome of patients undergoing cardiac surgery with CPB.

Research agenda

- The knowledge of inflammatory processes and the interplay between humoral factors and cellular immune response has been rapidly increasing over the last few decades. Future studies should aim at targeting multiple inflammatory mediators simultaneously to attenuate the evolution of SIRS.

- Early diagnosis of organ dysfunction such as AKI is an indispensable precondition for the early initiation of adequate treatment. Large, randomised controlled trials are needed to provide evidence for pharmaceutical and technical approaches that aim to reduce post-operative complications following cardiac surgery.

Conflict of interest

The authors have no conflicts of interest to declare.

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