Systemic Inflammatory Response and Cardiopulmonary Bypass

3

Ahmet Rüçhan Akar, Bahadır İnan, Karan P. Punjabi, and Sadettin Dernek

Abbreviations

ACT:	activated clotting time
CABG:	coronary artery bypass grafting
CPB:	cardiopulmonary bypass
CRRT:	continuous renal replacement therapy
DAMP:	damage associated molecular pattern
DIC:	disseminated intravascular coagulation
ET:	endothelin
FDPs:	fibrin degradation products
HBC:	heparin bonded circuits
HPA:	hypothalamic-pituitary-adrenal
IL:	interleukin
MECC:	minimized extracorporeal circulation
NO:	nitric oxide
PAMP:	pathogen associated molecular pattern
PGI_2:	prostacyclin
ROS:	reactive oxygen species
SDD:	selective decontamination of the digestive tract
SIRS:	systemic inflammatory response syndrome
TXA_2:	thromboxane

Learning Objectives

- Understand the etiopathogenesis of SIRS
- Understand the complexity of the CPB-associated SIRS
- Understand the results from a multitude of humoral, cellular, metabolic and endocrine mechanisms
- Understand the different treatment strategies to manage SIRS
- Understand the haemodynamic consequences of SIRS

Major surgery, trauma, sepsis, ischemia-reperfusion injury, or cardiac surgery with cardiopulmonary bypass (CPB) provoke a "*whole-body inflammatory response*" or "*systemic inflammatory response syndrome*" (SIRS) [1, 2]. SIRS is an exaggerated, nonspecific defense response of the body to a noxious stressor [3]. The etiopathogenesis of SIRS broadly divides into the damage-associated molecular pattern (DAMP) and pathogen-associated molecular pattern (PAMP) [3].

Currently, it is estimated that more than one million cardiac operations are performed each

A. R. Akar (✉) · B. İnan
Department of Cardiovascular Surgery, Ankara University School of Medicine, Ankara, Turkey

K. P. Punjabi
School of Medicine, St. George's University of London, London, UK

S. Dernek
Department of Cardiovascular Surgery, Osmangazi University, Ankara, Turkey

P. P. Punjabi, P. G. Kyriazis (eds.), *Essentials of Operative Cardiac Surgery*,
https://doi.org/10.1007/978-3-031-14557-5_3

year worldwide with CPB support using a heart-lung machine [4]. In CPB related SIRS early potential triggers are; (1) surgical trauma, (2) contact between heparinized blood components with the artificial surface of the CPB circuit, (3) nonendothelial cell surfaces in the mediastinum, (4) blood-air interface, (5) non-pulsatile blood-flow patterns, (6) ischemia and reperfusion injury, (7) endotoxemia [1, 5–10].

CPB associated SIRS is a complex process involving multiple humoral, cellular, and metabolic pathways involving autonomic, endocrine, hematological, and immunological alterations [3, 10]. Amplified inflammatory cascade and dysregulated cytokine storm may exacerbate multiple organ dysfunction [3, 11, 12]. Clinical manifestations may involve pyrexia or hypothermia, increase in oxygen consumption, impaired hemodynamics, systolic and diastolic myocardial dysfunction, vasodilation, and increased capillary permeability, coagulopathy, neurocognitive defects, acute renal insufficiency, increased pulmonary reactivity, acute respiratory distress syndrome, increased gut permeability and increased susceptibility to infection both in adults and pediatric population [4, 5, 10, 11, 13–16].

SIRS is characterized by the activation of the endothelium, complement system, neutrophils, monocytes, platelets, kallikrein–bradykinin and fibrinolytic systems, cytokines, and coagulation pathways. SIRS may also cause disseminated intravascular coagulation (DIC) by aggravating the consumption of coagulation factors. Post-CPB SIRS is defined by the satisfaction of any two of the criteria below:

1. temperature > 38 °C or < 36 °C;
2. heart rate > 90 beats per minute,
3. respiratory rate > 20 act per minute; or, PaCO2 < 32 mmHg,
4. leukocyte count >12,000/mm^3; or, leukocyte count <4000/mm^3; or, over 10% immature forms or bands. However, some investigators suggest redefining the current definition of CPB-related SIRS by the leading societies of cardiothoracic surgery, anesthesia, and perfusion [17].

MacCallum NS et al. [18] showed that nearly all patients (96.2%) undergoing cardiac surgery fulfilled the standard two criterion definition within 24 hours of ICU admission. The investigators suggested that meeting at least three defining criteria for SIRS, or requiring that at least two criteria are met for six consecutive hours, would be more discriminatory in defining a cohort of patients with adverse clinical outcomes [18]. Recently, Squiccimarro E et al. [19] reported a 28.3% incidence of SIRS within 24 hours from cardiac surgery. Data from 28,763 patients from 20 centers in Australia and New Zealand who underwent coronary artery bypass grafting (CABG) and valve surgery demonstrated that increased patient age was strongly associated with reduced acute immune response and postoperative SIRS prevalence due to immunosenescence [20].

SIRS is also a frequent complication in the pediatric population after congenital heart surgery, which affects nearly one-third of children [13]. The investigators showed that the duration of CPB and the amount of fresh frozen plasma given were identified as significant risk factors for CPB-related SIRS [13]. Other investigators reported further independent risk factors for SIRS development in the pediatric population, including bodyweight below 10 kg and preoperative diagnosis of right to left shunt congenital heart disease [21].

SIRS is incited by some factors, including the interaction of blood with the foreign surfaces of the CPB circuit (i.e., contact activation), altered blood flow patterns (i.e., non-pulsatile flow), ischemia-reperfusion injury, and endotoxins (Fig. 3.1). Interaction between activated endothelial cells, leukocytes, and platelets, is mediated through the expression of three main groups of adhesion molecules: the selectins, the integrins, and the immunoglobulin superfamily [22].

Initiation results from a multitude of humoral, cellular, and metabolic processes:

1. **Humoral Response**
   - Kinin system and Hageman factor activation

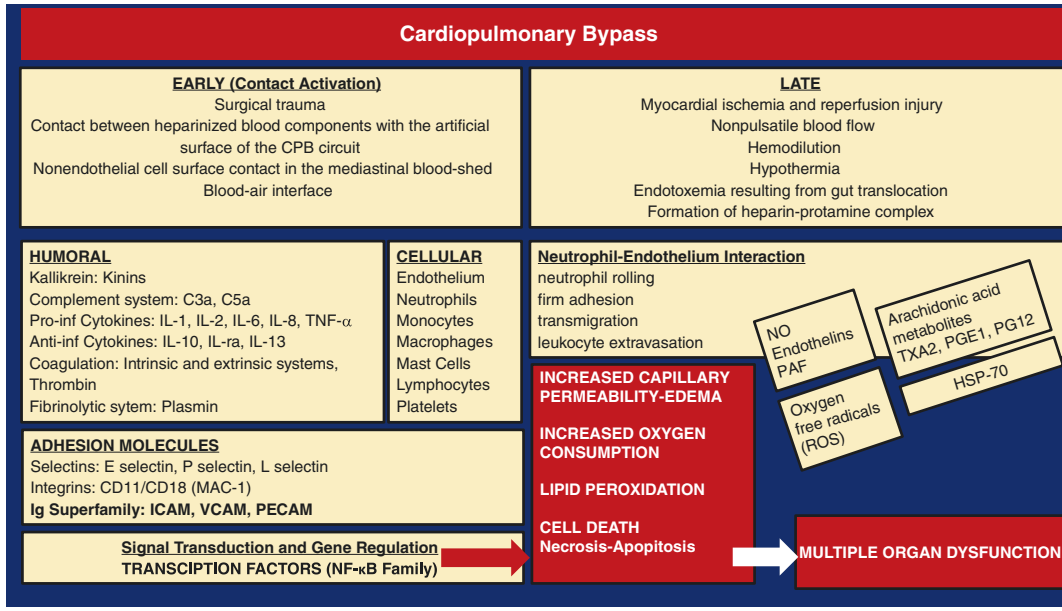

Fig. 3.1 Inflammatory response pathways in cardiopulmonary bypass-related SIRS

- Complement system activation
- Fibrinolytic system activation
- Synthesis of pro-inflammatory and anti-inflammatory cytokines

2. **Cellular Response**
   - Endothelium activation
   - Neutrophil activation
   - Platelet activation

3. **Metabolic and Endocrine Response**
   - Sympathetic nervous system and catecholamine response
   - Endocrine response

Humoral Response

Kinin System Activation and Hageman Factor

Exposure of blood to the extracorporeal circuit activates the contact system. Surface activation of the Hageman factor (Factor XII) may be the first critical event in the activation of other cascades. Activation of Hageman factor converts prekallikrein to kallikrein. Kallikrein has six main actions; a) activation of plasma prekallikrein via a positive feedback loop, b) cleavage of HMWK to release bradykinin which is a potent vasodilator that increases vascular permeability, c) activation of complement system (C3 and C5), d) activation of the fibrinolytic pathway by stimulating tissue plasminogen activator, e) activation of the sympathetic nervous system and f) initiates the intrinsic coagulation cascade that leads to the formation of thrombin [2].

Thrombin plays a pivotal role in signaling inflammatory processes that directly activates complement factor 5 (C5) and neutrophils and also activates the endothelium [10]. Tissue factor and thrombin generation activation can also occur after ischemia-reperfusion injury [23].

The Complement System

The complement system consists of over 30 plasma proteins that are involved in chemoattraction, activation, opsonization, and cell lysis. Three major complement activation pathways have been described: the classical pathway, triggered by immune complexes; the mannose-binding lectin pathway, triggered when lectin

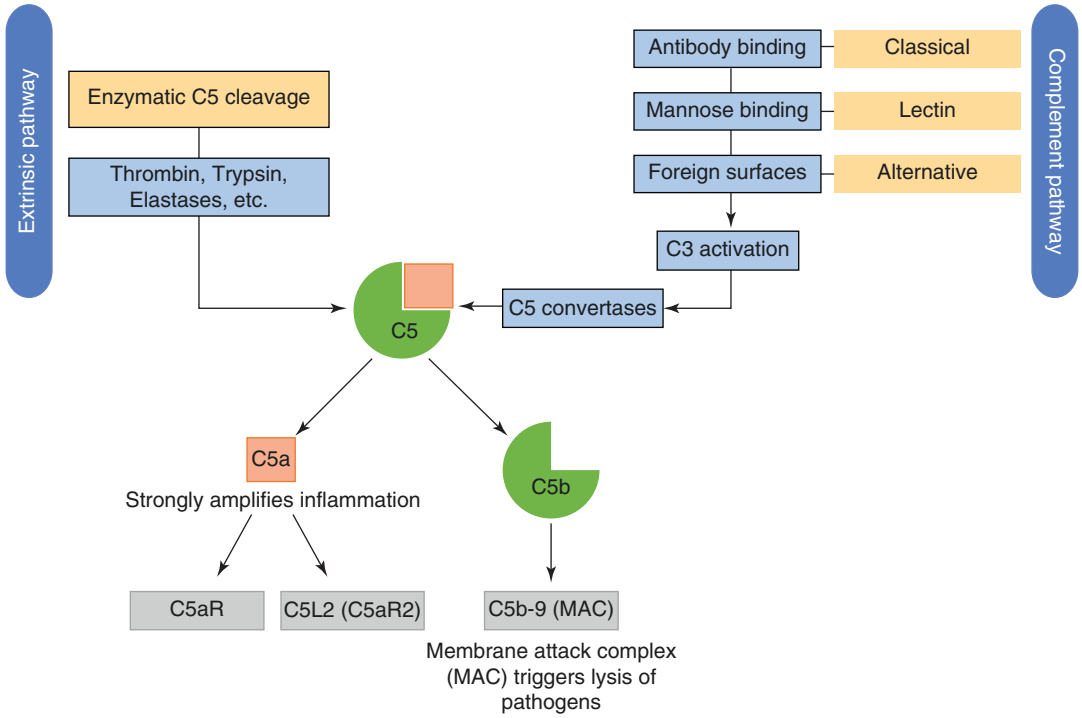

Fig. 3.2 Complement activation in response to cardiopulmonary bypass

binds mannose groups in bacteria; and the alternative or properdin pathway, triggered by contact with various viruses, bacteria, fungi, and tumor cells [24].

During CPB, the complement system is activated at three different times; a) blood contact with nonendothelial cell surfaces, b) after protamine administration, and formation of the protamine-heparin complex, c) during reperfusion of ischemic arrested heart [7, 25].

Contact with the CPB circuit provokes the formation of anaphylatoxins C3a and C5a soon after the institution of CPB (Fig. 3.2) [7, 25]. Activated complement products promote vasodilation, increased vascular permeability, leukocyte activation, leukocyte mobilization, chemotaxis and adhesion and phagocytosis of organisms by neutrophils and macrophages.

The classical pathway involves the activation of C1 by an antibody-antigen complex. The alternative pathway does not require an antibody for its activation: C3 fragments free-floating in serum attach directly to antigens, endotoxins, or foreign surfaces (otherwise known as contact activation). The standard step linking both pathways is the cleavage of C3. Cleavage of C3 to its activated form C3a stimulates the release of histamine and other inflammatory mediators from mast cells, eosinophils, and basophils, which results in smooth muscle constriction and an increase in vascular permeability. C5a is a potent chemotactic factor for neutrophils as it promotes its aggregation, adhesion, and activation. C3b and C5b interact on cell membranes with components C6–C9 to form a "membrane attack complex," which activates platelets and "punches" holes in cell membranes. This process is rapid: plasma levels of activated complement factors rise within 2 min of the onset of the bypass, and a second rise can be detected after the release of the aortic cross-clamp and rewarming. Levels decline postoperatively and generally return to average 18–48 hours postoperatively.

Fibrinolytic System Activation

Exposure of blood to the artificial surface of the CPB circuit, temperature changes, medications, mechanical trauma, or blood products trigger fibrin clot formation, resulting in activation of the fibrinolytic system. The fibrin clots are continuously proteolytically digested into fibrin degradation products (FDPs) by plasmin. Plasmin production is upregulated via two pathways:

(a) Bradykinin upregulates tissue plasminogen activator (tPA), which in turn converts plasminogen to plasmin. tPA levels peak with 30 minutes of CPB and return to baseline within 24 hours.
(b) Kallikrein and HMWK upregulate urokinase, which activates urokinase plasminogen activator (uPA), which in turn converts plasminogen to plasmin. Intravascular fibrin clots lead to impaired microcirculation and hypoxic cellular damage. FDPs compete with thrombin and slow down clotting by inhibiting the conversion of fibrinogen to fibrin. The net effect is endothelial and platelet dysfunction.

Synthesis of pro-Inflammatory and Anti-Inflammatory Cytokines

Cytokines are critical regulatory messengers released in response to local injury that generally acts in a paracrine fashion. They are secreted by immune cells, namely lymphocytes and macrophages, endothelial cells, neurons, glial cells, and other types of cells. Cytokines play a critical role in the pathophysiology of CPB-related SIRS.

Release of pro-inflammatory cytokines; interleukin-1 (IL1) and TNF-alpha results in dissociation of nuclear factor-kB (NF-kB) from its inhibitor [3]. NF-kB is thus able to induce the mass release of other pro-inflammatory cytokines, including IL-6, IL-8, and Interferon-gamma [3]. IL-6 induces the release of acute-phase reactants, including procalcitonin and C reactive protein. The compensatory anti-inflammatory response is also elevated and mediated by Interleukins IL-4 and IL-10, which tend to inhibit the production of TNF-alpha, IL-1, IL-6, and IL-8 [3]. These inflammatory mediators generally reach peak levels 2–4 h after termination of CPB [5, 26]. However, the balance among these cytokines is essential in determining the level of the inflammatory response following CPB [2]. Serum IL-19 and IL-22 were also induced during CPB concomitant with induction of IL-6 and TNF-alpha [27]. Excessive levels of cytokines lead to uncontrolled systemic inflammation causing tissue damage and acute kidney injury [3, 15]. Besides, they stimulate further expression of procoagulant and fibrinolytic enzymes.

Using coronary sinus blood sampling, Wan S. et al. [28] reported that myocardium is a significant source of pro-inflammatory cytokines in patients undergoing CPB. Another clinical study showed that CPB provokes a more significant pulmonary than systemic inflammatory response [29]. The investigators demonstrated that the production of all cytokines was 1.5–3 times higher in alveolar macrophages obtained at the end of surgery than in plasma monocytes obtained simultaneously in patients who underwent CPB [29].

Cellular Response

The Endothelium

The endothelium is an organ system [30], lines the interior surface of the vascular tree and lymphatic vessels. The endothelium is a genuinely pervasive cell layer, weighing 1 kg and covering a total surface area of 4000–7000 m^2 [31]. Physiologically, the endothelium is highly metabolically active organ sensing changes in the extracellular compartment and responding in ways that are beneficial or, at times, harmful to the host [30, 32]. In brief, endothelium not only functions as a barrier but also controls vascular tone and permeability, regulates coagulation, has the capacity for repair and regeneration.

Four key mediators mainly regulate vascular tone, namely nitric oxide (NO), prostacyclin PGI_2, thromboxane (TXA_2), and endothelin (ET).

Local vasodilation is mediated through nitric oxide and prostacyclin [33]. Nitric oxide (NO), corresponding to the endothelium-derived relaxing factor, is a significant regulator of vasomotor tone and blood flow. Extremely potent and long-lasting vasoconstriction is mediated by endothelin-1, which is a peptide with 21 amino acid residues, also released from the endothelium. A significant release of endothelin-1 after CPB has been shown in patients undergoing CABG.

Furthermore, the endothelium has the capacity for secreting anticoagulants such as tissue plasminogen activator (tPA), thrombomodulin, and heparin-like substances. The principal agonists for endothelial cell activation during CPB are thrombin, C5a, and the cytokines IL-1β and TNF-α, which bind to specific receptors on the endothelium.

Neutrophil Activation

Leucocytes play a fundamental role in the pathophysiology of CPB related inflammation [34]. Neutrophil-endothelium interaction via the expression of selectins is central to the development of the inflammatory process during CPB [4].

Activated endothelial cells, express on the cell (luminal) surface the adhesion molecule ligands corresponding to those being expressed in the activated neutrophil. The adhesion molecules family includes selectins (E selectin, L selectin, P selectin), integrins (CD11/CD18 (MAC-1)), and immunoglobulin superfamily (ICAM, VCAM, PECAM). The expression of integrin receptors results in tighter binding to the endothelial cells. The increased adhesive capability of activated circulating neutrophils flowing over activated vascular endothelial cells results in a step-wise interaction comprising three distinctive steps: neutrophil rolling, firm adhesion, and transmigration causing leukocyte extravasation [4]. Neutrophils and macrophages release reactive oxygen species (ROS) synthesized via the NADPH oxidase pathway with the stimuli of cytokines. Increased capillary permeability can lead to cell edema and cell necrosis or apoptosis.

Platelet Activation

Platelet dysfunction following CPB has been consistently demonstrated in several studies [35–38]. Platelet activation, degranulation, and adherence to vascular endothelium during CPB is evident by thrombin with the resultant clinical effects [38, 39]. Platelet aggregation stimulates serotonin (5-HT) release, which further enhances the interaction of platelets with circulating tissue factor-rich microvesicles [40]. Activated platelets also play an essential role in neutrophil adhesion and transmigration.

Metabolic and Endocrine Response

The extracellular fluid volume increases while body temperature decreases during CPB. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and catecholamine release is evident with the unset of CPB [41]. Plasma epinephrine concentrations may increase up to ten-fold over the pre-bypass concentrations; norepinephrine levels typically increase to a lesser extent. Clinical studies showed that plasma cortisol, adrenocorticotropic hormones, and vasopressin or antidiuretic hormone (ADH) markedly increase during CPB [42, 43], which leads to peripheral vasoconstriction and shifts to visceral blood flow.

Genetic Predisposition

The interleukin 6–174 G/C polymorphism was demonstrated to have a role in the modulation of postoperative interleukin-6 levels and was associated with postoperative renal and pulmonary dysfunction [44]. Grunenfelder J. et al. [45] showed that the apolipoprotein E and the tumor necrosis factor-beta polymorphisms are associated with increased releases of interleukin-8 and

tumor necrosis factor-alpha during CPB and risk factors for CPB-related SIRS.

Treatment Strategies for Sirs

Modulation of the inflammatory response in CPB can be broadly categorized into three groups, mainly pharmacological therapies, technical strategies, and endotoxemia-reducing strategies [2, 46].

Pharmacological Therapies

Corticosteroids

Preoperative use or the addition of methylprednisolone to the CPB circuit prime reduced the inflammatory response in experimental models [47]. Steroids suppress uncontrolled complement-mediated activation of neutrophils and lower pro-inflammatory cytokines TNFα, IL-6, IL-8, and E-selectin levels and increase IL-10 and IL-1ra. However, methylprednisolone has no measurable effect on recovery and increase anesthetic complications and impaired glucose tolerance in patients with SIRS. However, dexamethasone use during induction of anesthesia reduced gut permeability in pediatric patients undergoing cardiac surgery [48].

In a multicenter, randomized, double-blind, placebo-controlled trial (the DECS trial) of 4494 adult patients in the Netherlands enrolled between 2006 and 2011 patients were randomly assigned to receive a single intraoperative dose of 1 mg/kg dexamethasone (n = 2239) or placebo (n = 2255) [49]. The primary outcome measures of the study were the composite of death, myocardial infarction, stroke, renal failure, or respiratory failure within 30 days of randomization. However, the use of intraoperative dexamethasone did not reduce the 30-day incidence of major adverse events compared with placebo [49]. In another recent double-blind, randomized, controlled trial performed between 2007–2013 entitled The Steroids In caRdiac Surgery (SIRS) study [50], 7507 patients were randomly assigned to methylprednisolone (n = 3755) and placebo (n = 3752). The investigators reported that methylprednisolone did not have a significant effect on mortality or significant morbidity after cardiac surgery [50].

In neonatal cardiac surgery, intravenous 30 mg/kg methylprednisolone administered before CPB resulted in a decreased systemic inflammatory response. However, the investigators could not demonstrate any cardioprotective effects of this strategy or effects on clinical outcomes [51].

Serine Protease Inhibitors (Aprotinin)

Aprotinin is a nonspecific serine protease inhibitor that was discovered in 1930 by a research group at the University of Munich. The research group isolated an inhibitor of kallikrein from bovine lung and pancreas tissues. The drug also binds directly to the fibrinolytic plasmin. Aprotinin inhibits platelet glycoprotein loss (GpIb and GpIIb/IIIa receptors) associated with CPB.

Royston et al. [52] randomized 22 patients undergoing repeat open-heart surgery to receive the serine proteinase inhibitor aprotinin (700 mg intravenously from the start of anesthesia to the end of the operation). Blood transfusion requirements were eightfold higher in the control group than in the aprotinin group [52]. Aprotinin also confers significant protection against platelet dysfunction and activation of the systemic inflammatory response [53].

Nitric Oxide

Nitric oxide (NO) is a soluble, non-flammable, free-radical gas reacts rapidly with oxygen to form nitrogen oxides. Primary functions of NO are vasodilation and antagonist properties for platelet activation and leukocyte recruitment [54–56]. In a prospective, randomized, blinded, placebo-controlled study, children were undergoing repair of tetralogy of Fallot enrolled to either 20 ppm of gaseous nitric oxide or placebo

delivered to the membrane oxygenator during CPB [56]. Nitric oxide group resulted in better myocardial protection, improved fluid balance, and an improved postoperative intensive care unit course [56].

Antioxidants

During CPB, endogenous oxygen free radical scavengers like Vitamin E (alpha-tocopherol) and Vitamin C (ascorbic acid) diminish, which results in increased production of oxygen free radicals from neutrophils, leading severe endothelial damage. Although several randomized studies performed with the exogenous replacement of Vit C and D, none of these studies resulted in significant advantages affecting immune response after CPB [57–59].

In SIRS, due to other causes such as sepsis, use of Selenium, Glutamine, and Eicos-pentanoic acid as antioxidants are shown to be effective in reducing bowel permeability and reducing endotoxemia [60, 61].

Complement Inhibitors

Attempts to efficiently to control complement system in systemic inflammation include the application of endogenous soluble complement inhibitors (C1-inhibitor, recombinant soluble complement receptor 1- rsCR1), the administration of antibodies, either blocking critical proteins of the cascade reaction (e.g., C3, C5), neutralizing the action of the complement-derived anaphylatoxin C5a, or interfering with complement receptor 3 (CR3, CD18/11b)-mediated adhesion of inflammatory cells to the vascular endothelium [62].

The complement inhibitor that has achieved the most widespread attention as a therapeutic agent is a monoclonal antibody to C5. The advantage of this strategy is that it prevents the generation of C5a, the most potent of the anaphylatoxins.

Pexelizumab, a C5 complement inhibitor, was evaluated in a randomized, double-blind, placebo-controlled trial, including 3099 adult patients undergoing CABG with or without valve surgery at 205 hospitals in North America and Western Europe from 2002 to 2003 [63]. However, compared with placebo, pexelizumab was not sufficient for improving clinical outcomes [63]. A recent study in the pediatric cardiac surgical population, C1 esterase inhibitor given intravenously 60 min after CPB, was effective in reducing the inflammatory activation [64].

Phosphodiesterase Inhibitors

Phosphodiesterases are a class of enzymes that catalyze the hydrolysis of cAMP and cGMP into AMP and GMP. Phosphodiesterase inhibitors like milrinone, vesnarinone, and amrinone, inhibit the action of cyclic adenosine monophosphate (cAMP) phosphodiesterase. Specific inhibition results in an increased level of cAMP and also calcium levels causing positive myocardial inotropy [65].

cAMP and cGMP have an essential role in endothelial cells to maintain capillary endothelial barrier properties in acute inflammation. In a severe lipopolysaccharide (LPS)-induced systemic inflammation model in rats, Phosphodiesterase-4-inhibitors (PD-4-Is) rolipram or roflumilast increased endothelial cAMP, which reduces capillary permeability and breakdown of microcirculatory flow [66].

The phosphodiesterase inhibitors also directly affect interleukin production and release; vesnarinone and amrinone reduce endotoxin-induced IL- 1b, TNF-a, and iNO releases [67], milrinone, reduces IL-6 and IL-1b production [68].

Cyclooxygenase Inhibitors

Leukotrienes, prostaglandins, and thromboxane are the products of cyclooxygenase (COX) and lipooxygenase pathways of arachidonic acid. They play an essential role in systemic inflammatory response; they decrease systemic vascular resistance, augment platelet aggregation, start membrane lysis, and increase capillary permea-

bility. Most of the main events taking place during SIRS. Drugs that restrain or inhibit these pathways have been studied to treat SIRS.

Ibuprofen has been tested in a randomized trial in 455 patients with sepsis, reducing prostaglandin I2 and thromboxane levels, but there was no decrease in mortality [69]. However, in another study, ibuprofen administration decreased mortality in patients with sepsis and hypothermia [70].

Pentoxyphyline, as a COX inhibitor, increases thromboxane, and tissue plasminogen activator prevents endothelial cell dysfunction and suppresses of TNF-α, IL-1, and IL-10. A study by Otani et al. shows that preoperative daily administration of 900 mg/day Pentoxyphyline attenuates SIRS due to cardiopulmonary bypass and has a beneficial effect on the postoperative course after cardiovascular surgery [71]. Pentoxyphyline improves scores of organ dysfunction in a randomized, double-blind, placebo-controlled study [72], and reduces all-cause mortality in neonatal studies [73, 74].

Technical Strategies

Evolving technical strategies include reducing surgical tissue trauma by minimally invasive approaches, avoiding CPB altogether such as off-pump CABG or minimally invasive cardiac operations, inhibition of neutrophil and platelet activation, inhibition of complement activation, and leucocyte depletion [4, 46].

Minimized Extracorporeal Circulation System

Minimized extracorporeal circulation (MECC) system has been introduced to reduce surface area and the priming volume, coatings to improve the biocompatibility of extracorporeal surfaces, and optimization of suction blood management [75]. Koster A. et al., showed that avoidance of aspiration of blood via the cardiotomy suction line significantly reduces hemostatic activation during on-pump CABG [76]. Fromes Y. et al. randomly randomized sixty consecutive patients undergoing CABG assigned to either standard normothermic CPB (n = 30) or the MECC system (n = 30). The investigators demonstrated a milder inflammatory reaction when compared to standard CPB. In another small randomized trial, Bical O. et al. also demonstrated the lesser inflammatory response of a miniaturized CPB compared to a standard CPB in patients undergoing aortic valve replacement.

Heparin Bonded Circuits (HBC) and Biocompatibility

In vitro and in vivo experimental studies in the 1960s showed that a colloidal graphite surface was capable of bonding heparin [77]. Subsequently, improved heparin coatings have been developed for bonding to various biomedical devices, including bileaflet valves, circuits, and oxygenators [78]. In addition to the antithrombotic property of heparin, potential biocompatibility properties include inhibition of contact and complement activation and adsorb lipoproteins, which may create a surface that can potentially stimulate cell membranes, and reduce the pro-inflammatory aspects of CPB. A meta-analysis of 41-randomized trials demonstrated a reduction in the incidence of blood transfusion required, decreased re-sternotomy rates, ICU length of stay, and hospital stays [79]. However, investigators showed only marginal differences for other outcomes [79].

Heparin Management

Heparin management may have an impact on hemostatic activation and inflammatory response during CPB. Koster A. et al., [80] compared heparin concentration-based anticoagulation management with activated clotting time (ACT)-based heparin management and showed that heparin concentration-based anticoagulation management during CPB leads to a significant reduction of thrombin generation, fibrinolysis, and neutrophil activation [80].

Leucofiltration and Leukocyte Depletion

The clinical benefit of white cell filters designed to remove polymorphonuclear cells (PMNs) and soluble mediators in patients who developed SIRS after CPB is still debatable [34, 81]. Several investigators support the cardioplegic leucocyte depletion strategy as the optimal method for attenuating neutrophil activation and myocardial ischemia-reperfusion injury [34].

Hemofiltration, Ultrafiltration and Hemoadsorption

Non-physiologic conditions during CPB, such as hypothermia, hemodilution, non-pulsatile flow, anticoagulation, and circulation of blood out of the body in non-endothelialized surfaces, are the leading causes of systemic inflammatory response. Hemodilution increases SIRS, and SIRS increases total body water, which results in hemodilution. Thus, the use of hemofiltration, hemodialysis, or ultrafiltration for the removal of cytokines has essential roles in preventing or treating SIRS [82].

The use of ultrafiltration during pediatric open-heart surgery has beneficial effects in reducing complement activation and pro-inflammatory cytokine release, together with hemodynamic, pulmonary, and hemostatic improvements [83–85]. In adults, ultrafiltration also reduces cytokines and adhesion molecules during and after CPB; however, this has not been associated with any clinical advantage [86].

In a retrospective case series study (n = 16), treatment of patients with a cytokine adsorber device (CytoSorb; CytoSorbents) combined with continuous renal replacement therapy (CRRT) who present with severe post-CPB SIRS resulted in a reduction of elevated cytokine levels and improved organ function [87].

Centrifugal Pumps

A comparison of the two pumps used in cardiopulmonary bypass systems is still controversial [88]. Some studies mention that Centrifugal pumps are superior to roller pumps because of less blood trauma, reduced activation of the coagulation cascade, and improved biocompatibility [89, 90]. However, in other studies, both show similarities in terms of platelet damage [91], and immune response [92]. Additionally, recent studies showed increased inflammatory response during CPB with a centrifugal pump [93, 94].

Not only pump type, but pulsatility is also a significant concern during cardiopulmonary bypass, some studies show reduced amounts of endotoxins and other mediators [95, 96] with pulsatility whereas others [97] do not have such results.

Cardiopulmonary Bypass Temperature

Bigelow described hypothermia as the most critical part of myocardial protection [98]. Although hypothermia significantly decreases cardiac metabolism, significant disadvantages were also reported [99–101].

There are several studies in the literature comparing hypothermia with normothermia, the main issue here is some authors mention 33–34 C as normothermic, while for others 36–37 C is normothermic. Most of these studies do not report any differences between normothermia and hypothermia. Menasche et al. have concluded that hypothermia delays but do not entirely prevent the expression of inflammatory mediators. They have found an increase in adhesion molecules and leukocyte proteolytic enzymes in normothermia [102–104] In another study, it has shown that during normothermia Nitric Oxide (NO) production is increased resulting in diminished systemic vascular resistance which limits the inflammatory response [105].

Endotoxemia Reducing Strategies

Selective Decontamination of the Digestive Tract

Selective decontamination of the digestive tract (SDD) is a strategy to prevent the colonization of the gut. Numerous randomized controlled trials have shown that SDD reduces the incidence of pneumonia and mortality in ICU patients [106, 107]. Martinez-Pellus et al., randomized one hundred consecutive patients undergoing CPB, allocated to two groups; gut decontamination (n = 50) who received oral non-absorbable antibiotics (polymyxin E, tobramycin and amphotericin B) and controls (n = 50). The investigators showed that SDD reduced the gut content of enterobacteria associated with the lower endotoxin and cytokine levels detected in SDD patients. A meta-analysis by Nathens AB. et al., demonstrated that SDD reduced mortality in critically ill surgical patients in whom rates of nosocomial infection are high and in whom infection contributes notably to adverse outcomes [108].

Disclosures The authors have no financial disclosures that would be a potential conflict of interest with the current manuscript.

Key Pearls and Pitfalls

SIRS is likely to have several causes. CPB produces multiple noxious stimuli which aggravate systemic inflammatory response in a unique fashion. The pathogenesis of CPB-associated SIRS is linked to surgical trauma, contact between heparinized blood components with the artificial surface of the CPB circuit, nonendothelial cell surfaces in the mediastinum, blood-air interface, non-pulsatile blood-flow patterns, ischemia and reperfusion injury, and endotoxemia. CPB associated uncontrolled inflammatory response is often a complex process involving humoral, cellular, and metabolic pathways.

Furthermore, the inflammatory response is modified by patient-specific factors. Novel pharmacological agents and technical strategies are under intense investigation for anti-inflammatory protection to improve patient outcomes. Several critical issues should be considered together to produce efficient prophylactic strategies to minimize SIRS.

Comprehension Questions

1. Which of the listed is <u>not</u> one of the primary triggers of CPB-related SIRS?
   (a) myocardium
   (b) ischemia-reperfusion injury
   (c) immunomodulation
   (d) endotoxemia
   (e) contact between heparinized blood components with the artificial surface of the CPB circuit
2. Which one is the time where the complement system is mostly activated during CPB?
   (a) cross-clamping
   (b) after protamine administration, and formation of the protamine-heparin complex
   (c) weaning of CPB
   (d) anesthesia induction
   (e) hypothermic cardioplegic cardiac arrest
3. Which description is <u>incorrect</u>?
   (a) Post-CPB SIRS is defined by the satisfaction of all of the four criteria.
   (b) Aprotinin, as a serine protease inhibitor, may cause SIRS.
   (c) Phosphodiesterase inhibitors deplete cAMP and cause SIRS.
   (d) The depletion of platelets is the primary mechanism responsible for SIRS during CPB.
   (e) Methylprednisolone lowers cytokines TNFα, IL-6, IL-8, and increases IL-10 and IL-1ra levels and helps to limit the inflammatory response.
4. Which one is <u>not</u> one of the technical strategies that are involved in the modulation of the inflammatory response during CPB?

(a) Hemodilution
(b) Minimized extracorporeal circulation system (MECC)
(c) Leukocyte filtration
(d) Heparin bonded circuits (HBC)
(e) Hemofiltration

Answers.

1 (c), 2 (b), 3 (b), 4 (a).

References

1. Taylor KM. SIRS–the systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg. 1996;61(6):1607–8.
2. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update Eur J Cardiothorac Surg. 2002;21(2):232–44.
3. Chakraborty RK, Burns B. Systemic inflammatory response syndrome. Treasure Island (FL): StatPearls; 2019.
4. Punjabi PP, Taylor KM. The science and practice of cardiopulmonary bypass: from cross circulation to ECMO and SIRS. Glob Cardiol Sci Pract. 2013;2013(3):249–60.
5. Cremer J, Martin M, Redl H, Bahrami S, Abraham C, Graeter T, et al. Systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg. 1996;61(6):1714–20.
6. Lee WH Jr, Krumhaar D, Fonkalsrud EW, Schjeide OA, Maloney JV Jr. Denaturation of plasma proteins as a cause of morbidity and death after intracardiac operations. Surgery. 1961;50:29–39.
7. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med. 1981;304(9):497–503.
8. Wachtfogel YT, Kucich U, Greenplate J, Gluszko P, Abrams W, Weinbaum G, et al. Human neutrophil degranulation during extracorporeal circulation. Blood. 1987;69(1):324–30.
9. Edmunds LH Jr. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg. 1998;66(5 Suppl):S12–6. discussion S25-8
10. Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg. 2003;75(2):S715–20.
11. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology. 2002;97(1):215–52.
12. Day JR, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg. 2005;3(2):129–40.
13. Boehne M, Sasse M, Karch A, Dziuba F, Horke A, Kaussen T, et al. Systemic inflammatory response syndrome after pediatric congenital heart surgery: incidence, risk factors, and clinical outcome. J Card Surg. 2017;32(2):116–25.
14. Fransen E, Maessen J, Dentener M, Senden N, Geskes G, Buurman W. Systemic inflammation present in patients undergoing CABG without extracorporeal circulation. Chest. 1998;113(5):1290–5.
15. Zhang WR, Garg AX, Coca SG, Devereaux PJ, Eikelboom J, Kavsak P, et al. Plasma IL-6 and IL-10 concentrations predict AKI and long-term mortality in adults after cardiac surgery. J Am Soc Nephrol. 2015;26(12):3123–32.
16. Taylor KM. Brain damage during cardiopulmonary bypass. Ann Thorac Surg. 1998;65(4 Suppl):S20–6. discussion S7-8
17. Landis RC. 20 years on: is it time to redefine the systemic inflammatory response to cardiothoracic surgery? J Extra Corpor Technol. 2015;47(1):5–9.
18. MacCallum NS, Finney SJ, Gordon SE, Quinlan GJ, Evans TW. Modified criteria for the systemic inflammatory response syndrome improves their utility following cardiac surgery. Chest. 2014;145(6):1197–203.
19. Squiccimarro E, Labriola C, Malvindi PG, Margari V, Guida P, Visicchio G, et al. Prevalence and clinical impact of systemic inflammatory reaction after cardiac surgery. J Cardiothorac Vasc Anesth. 2019;33(6):1682–90.
20. Dieleman JM, Peelen LM, Coulson TG, Tran L, Reid CM, Smith JA, et al. Age and other perioperative risk factors for postoperative systemic inflammatory response syndrome after cardiac surgery. Br J Anaesth. 2017;119(4):637–44.
21. Guvener M, Korun O, Demirturk OS. Risk factors for systemic inflammatory response after congenital cardiac surgery. J Card Surg. 2015;30(1):92–6.
22. Asimakopoulos G, Taylor KM. Effects of cardiopulmonary bypass on leukocyte and endothelial adhesion molecules. Ann Thorac Surg. 1998;66(6):2135–44.
23. Hammon JW Jr, Vinten-Johansen J. Myocardial protection from surgical ischemic-reperfusion injury. Introduction Ann Thorac Surg. 1999;68(5):1897.
24. Michalski M, Pagowska-Klimek I, Thiel S, Swierzko AS, Hansen AG, Jensenius JC, et al. Factors involved in initiation and regulation of complement lectin pathway influence postoperative outcome after pediatric cardiac surgery involving cardiopulmonary bypass. Sci Rep. 2019;9(1):2930.
25. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1983;86(6):845–57.

26. Struber M, Cremer JT, Gohrbandt B, Hagl C, Jankowski M, Volker B, et al. Human cytokine responses to coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg. 1999;68(4):1330–5.
27. Hsing CH, Hsieh MY, Chen WY, Cheung So E, Cheng BC, Chang MS. Induction of interleukin-19 and interleukin-22 after cardiac surgery with cardiopulmonary bypass. Ann Thorac Surg. 2006;81(6):2196–201.
28. Wan S, DeSmet JM, Barvais L, Goldstein M, Vincent JL, LeClerc JL. Myocardium is a major source of proinflammatory cytokines in patients undergoing cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1996;112(3):806–11.
29. Kotani N, Hashimoto H, Sessler DI, Muraoka M, Wang JS, O'Connor MF, et al. Cardiopulmonary bypass produces greater pulmonary than systemic proinflammatory cytokines. Anesth Analg. 2000;90(5):1039–45.
30. Aird WC. Endothelium as an organ system. Crit Care Med. 2004;32(5 Suppl):S271–9.
31. Wolinsky H. A proposal linking clearance of circulating lipoproteins to tissue metabolic activity as a basis for understanding atherogenesis. Circ Res. 1980;47(3):301–11.
32. Aird WC. Endothelium and haemostasis. Hamostaseologie. 2015;35(1):11–6.
33. Lee WL, Slutsky AS. Sepsis and endothelial permeability. N Engl J Med. 2010;363(7):689–91.
34. Samankatiwat P, Samartzis I, Lertsithichai P, Stefanou D, Punjabi PP, Taylor KM, et al. Leucocyte depletion in cardiopulmonary bypass: a comparison of four strategies. Perfusion. 2003;18(2):95–105.
35. Friedenberg WR, Myers WO, Plotka ED, Beathard JN, Kummer DJ, Gatlin PF, et al. Platelet dysfunction associated with cardiopulmonary bypass. Ann Thorac Surg. 1978;25(4):298–305.
36. Ho LTS, Lenihan M, McVey MJ, Karkouti K. Transfusion avoidance in cardiac surgery study i. the association between platelet dysfunction and adverse outcomes in cardiac surgical patients. Anaesthesia. 2019;74(9):1130–7.
37. Czer LS, Bateman TM, Gray RJ, Raymond M, Stewart ME, Lee S, et al. Treatment of severe platelet dysfunction and hemorrhage after cardiopulmonary bypass: reduction in blood product usage with desmopressin. J Am Coll Cardiol. 1987;9(5):1139–47.
38. Weerasinghe A, Taylor KM. The platelet in cardiopulmonary bypass. Ann Thorac Surg. 1998;66(6):2145–52.
39. Zilla P, Fasol R, Groscurth P, Klepetko W, Reichenspurner H, Wolner E. Blood platelets in cardiopulmonary bypass operations. Recovery occurs after initial stimulation, rather than continual activation. J Thorac Cardiovasc Surg. 1989;97(3):379–88.
40. Lopez-Vilchez I, Diaz-Ricart M, White JG, Escolar G, Galan AM. Serotonin enhances platelet procoagulant properties and their activation induced during platelet tissue factor uptake. Cardiovasc Res. 2009;84(2):309–16.
41. Wallach R, Karp RB, Reves JG, Oparil S, Smith LR, James TN. Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: a study of hemodynamic and humoral factors. Am J Cardiol. 1980;46(4):559–65.
42. Taylor KM, Wright GS, Reid JM, Bain WH, Caves PK, Walker MS, et al. Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary bypass. II. The effects on adrenal secretion of cortisol. J Thorac Cardiovasc Surg. 1978;75(4):574–8.
43. Uozumi T, Manabe H, Kawashima Y, Hamanaka Y, Monden Y. Plasma cortisol, corticosterone and nonprotein-bound cortisol in extra-corporeal circulation. Acta Endocrinol. 1972;69(3):517–25.
44. Gaudino M, Di Castelnuovo A, Zamparelli R, Andreotti F, Burzotta F, Iacoviello L, et al. Genetic control of postoperative systemic inflammatory reaction and pulmonary and renal complications after coronary artery surgery. J Thorac Cardiovasc Surg. 2003;126(4):1107–12.
45. Grunenfelder J, Umbehr M, Plass A, Bestmann L, Maly FE, Zund G, et al. Genetic polymorphisms of apolipoprotein E4 and tumor necrosis factor beta as predisposing factors for increased inflammatory cytokines after cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2004;128(1):92–7.
46. Raja SG, Dreyfus GD. Modulation of systemic inflammatory response after cardiac surgery. Asian Cardiovasc Thorac Ann. 2005;13(4):382–95.
47. Lodge AJ, Chai PJ, Daggett CW, Ungerleider RM, Jaggers J. Methylprednisolone reduces the inflammatory response to cardiopulmonary bypass in neonatal piglets: timing of dose is important. J Thorac Cardiovasc Surg. 1999;117(3):515–22.
48. Malagon I, Onkenhout W, Klok M, Linthorst L, van der Poel PF, Bovill JG, et al. Dexamethasone reduces gut permeability in pediatric cardiac surgery. J Thorac Cardiovasc Surg. 2005;130(2):265–71.
49. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, et al. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA. 2012;308(17):1761–7.
50. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, et al. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386(10000):1243–53.
51. Keski-Nisula J, Pesonen E, Olkkola KT, Peltola K, Neuvonen PJ, Tuominen N, et al. Methylprednisolone in neonatal cardiac surgery: reduced inflammation without improved clinical outcome. Ann Thorac Surg. 2013;95(6):2126–32.
52. Royston D, Bidstrup BP, Taylor KM, Sapsford RN. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet. 1987;2(8571):1289–91.

53. Day JR, Landis RC, Taylor KM. Aprotinin and the protease-activated receptor 1 thrombin receptor: antithrombosis, inflammation, and stroke reduction. Semin Cardiothorac Vasc Anesth. 2006;10(2):132–42.
54. Lowson SM, Hassan HM, Rich GF. The effect of nitric oxide on platelets when delivered to the cardiopulmonary bypass circuit. Anesth Analg. 1999;89(6):1360–5.
55. Mellgren K, Mellgren G, Lundin S, Wennmalm A, Wadenvik H. Effect of nitric oxide gas on platelets during open heart operations. Ann Thorac Surg. 1998;65(5):1335–41.
56. Checchia PA, Bronicki RA, Muenzer JT, Dixon D, Raithel S, Gandhi SK, et al. Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children–a randomized trial. J Thorac Cardiovasc Surg. 2013;146(3):530–6.
57. Westhuyzen J, Cochrane AD, Tesar PJ, Mau T, Cross DB, Frenneaux MP, et al. Effect of preoperative supplementation with alpha-tocopherol and ascorbic acid on myocardial injury in patients undergoing cardiac operations. J Thorac Cardiovasc Surg. 1997;113(5):942–8.
58. Yau TM, Weisel RD, Mickle DA, Burton GW, Ingold KU, Ivanov J, et al. Vitamin E for coronary bypass operations. A prospective, double-blind, randomized trial. J Thorac Cardiovasc Surg. 1994;108(2):302–10.
59. Butterworth J, Legault C, Stump DA, Coker L, Hammon JW Jr, Troost BT, et al. A randomized, blinded trial of the antioxidant pegorgotein: no reduction in neuropsychological deficits, inotropic drug support, or myocardial ischemia after coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 1999;13(6):690–4.
60. Angstwurm MW, Schottdorf J, Schopohl J, Gaertner R. Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. Crit Care Med. 1999;27(9):1807–13.
61. Quan ZF, Yang C, Li N, Li JS. Effect of glutamine on change in early postoperative intestinal permeability and its relation to systemic inflammatory response. World J Gastroenterol. 2004;10(13):1992–4.
62. Kirschfink M. Controlling the complement system in inflammation. Immunopharmacology. 1997;38(1–2):51–62.
63. Verrier ED, Shernan SK, Taylor KM, Van de Werf F, Newman MF, Chen JC, et al. Terminal complement blockade with pexelizumab during coronary artery bypass graft surgery requiring cardiopulmonary bypass: a randomized trial. JAMA. 2004;291(19):2319–27.
64. Miyamoto T, Ozaki S, Inui A, Tanaka Y, Yamada Y, Matsumoto N. C1 esterase inhibitor in pediatric cardiac surgery with cardiopulmonary bypass plays a vital role in activation of the complement system. Heart Vessel. 2019;
65. Rathmell JP, Prielipp RC, Butterworth JF, Williams E, Villamaria F, Testa L, et al. A multicenter, randomized, blind comparison of amrinone with milrinone after elective cardiac surgery. Anesth Analg. 1998;86(4):683–90.
66. Schick MA, Wunder C, Wollborn J, Roewer N, Waschke J, Germer CT, et al. Phosphodiesterase-4 inhibition as a therapeutic approach to treat capillary leakage in systemic inflammation. J Physiol. 2012;590(11):2693–708.
67. Takeuchi K, del Nido PJ, Ibrahim AE, Cao-Danh H, Friehs I, Glynn P, et al. Vesnarinone and amrinone reduce the systemic inflammatory response syndrome. J Thorac Cardiovasc Surg. 1999;117(2):375–82.
68. Hayashida N, Tomoeda H, Oda T, Tayama E, Chihara S, Kawara T, et al. Inhibitory effect of milrinone on cytokine production after cardiopulmonary bypass. Ann Thorac Surg. 1999;68(5):1661–7.
69. Bernard GR, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The ibuprofen in sepsis study group. N Engl J Med. 1997;336(13):912–8.
70. Arons MM, Wheeler AP, Bernard GR, Christman BW, Russell JA, Schein R, et al. Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in sepsis study group. Crit Care Med. 1999;27(4):699–707.
71. Otani S, Kuinose M, Murakami T, Saito S, Iwagaki H, Tanaka N, et al. Preoperative oral administration of pentoxifylline ameliorates respiratory index after cardiopulmonary bypass through decreased production of IL-6. Acta Med Okayama. 2008;62(2):69–74.
72. Staubach KH, Schroder J, Stuber F, Gehrke K, Traumann E, Zabel P. Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study. Arch Surg. 1998;133(1):94–100.
73. Lauterbach R, Pawlik D, Kowalczyk D, Ksycinski W, Helwich E, Zembala M. Effect of the immunomodulating agent, pentoxifylline, in the treatment of sepsis in prematurely delivered infants: a placebo-controlled, double-blind trial. Crit Care Med. 1999;27(4):807–14.
74. Lauterbach R, Zembala M. Pentoxifylline reduces plasma tumour necrosis factor-alpha concentration in premature infants with sepsis. Eur J Pediatr. 1996;155(5):404–9.
75. Starck CT, Bettex D, Felix C, Reser D, Dreizler T, Hasenclever P, et al. Initial results of an optimized perfusion system. Perfusion. 2013;28(4):292–7.
76. Koster A, Bottcher W, Merkel F, Hetzer R, Kuppe H. The more closed the bypass system the better: a pilot study on the effects of reduction of cardiotomy suction and passive venting on hemostatic activation during on-pump coronary artery bypass grafting. Perfusion. 2005;20(5):285–8.

77. Gott VL, Whiffen JD, Dutton RC. Heparin bonding on colloidal graphite surfaces. Science. 1963;142(3597):1297–8.
78. Gott VL, Daggett RL. Serendipity and the development of heparin and carbon surfaces. Ann Thorac Surg. 1999;68(3 Suppl):S19–22.
79. Mangoush O, Purkayastha S, Haj-Yahia S, Kinross J, Hayward M, Bartolozzi F, et al. Heparin-bonded circuits versus nonheparin-bonded circuits: an evaluation of their effect on clinical outcomes. Eur J Cardiothorac Surg. 2007;31(6):1058–69.
80. Koster A, Fischer T, Praus M, Haberzettl H, Kuebler WM, Hetzer R, et al. Hemostatic activation and inflammatory response during cardiopulmonary bypass: impact of heparin management. Anesthesiology. 2002;97(4):837–41.
81. Treacher DF, Sabbato M, Brown KA, Gant V. The effects of leucodepletion in patients who develop the systemic inflammatory response syndrome following cardiopulmonary bypass. Perfusion. 2001;16(Suppl):67–73.
82. Jaffer U, Wade RG, Gourlay T. Cytokines in the systemic inflammatory response syndrome: a review. HSR Proc Intensive Care Cardiovasc Anesth. 2010;2(3):161–75.
83. Naik SK, Knight A, Elliott M. A prospective randomized study of a modified technique of ultrafiltration during pediatric open-heart surgery. Circulation. 1991;84(5 Suppl):III422–31.
84. Journois D, Pouard P, Greeley WJ, Mauriat P, Vouhe P, Safran D. Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery. Effects on hemostasis, cytokines, and complement components. Anesthesiology. 1994;81(5):1181–9. discussion 26A-27A
85. Wang S, Palanzo D, Undar A. Current ultrafiltration techniques before, during and after pediatric cardiopulmonary bypass procedures. Perfusion. 2012;27(5):438–46.
86. Grunenfelder J, Zund G, Schoeberlein A, Maly FE, Schurr U, Guntli S, et al. Modified ultrafiltration lowers adhesion molecule and cytokine levels after cardiopulmonary bypass without clinical relevance in adults. Eur J Cardiothorac Surg. 2000;17(1):77–83.
87. Trager K, Fritzler D, Fischer G, Schroder J, Skrabal C, Liebold A, et al. Treatment of post-cardiopulmonary bypass SIRS by hemoadsorption: a case series. Int J Artif Organs. 2016;39(3):141–6.
88. Parolari A, Alamanni F, Naliato M, Spirito R, Franze V, Pompilio G, et al. Adult cardiac surgery outcomes: role of the pump type. Eur J Cardiothorac Surg. 2000;18(5):575–82.
89. Steinbrueckner BE, Steigerwald U, Keller F, Neukam K, Elert O, Babin-Ebell J. Centrifugal and roller pumps–are there differences in coagulation and fibrinolysis during and after cardiopulmonary bypass? Heart Vessel. 1995;10(1):46–53.
90. Moen O, Fosse E, Dregelid E, Brockmeier V, Andersson C, Hogasen K, et al. Centrifugal pump and heparin coating improves cardiopulmonary bypass biocompatibility. Ann Thorac Surg. 1996;62(4):1134–40.
91. Misoph M, Babin-Ebell J, Schwender S. A comparative evaluation of the effect of pump type and heparin-coated surfaces on platelets during cardiopulmonary bypass. Thorac Cardiovasc Surg. 1997;45(6):302–6.
92. Perttila J, Salo M, Peltola O. Comparison of the effects of centrifugal versus roller pump on the immune response in open-heart surgery. Perfusion. 1995;10(4):249–56.
93. Ashraf S, Butler J, Tian Y, Cowan D, Lintin S, Saunders NR, et al. Inflammatory mediators in adults undergoing cardiopulmonary bypass: comparison of centrifugal and roller pumps. Ann Thorac Surg. 1998;65(2):480–4.
94. Baufreton C, Intrator L, Jansen PG, te Velthuis H, Le Besnerais P, Vonk A, et al. Inflammatory response to cardiopulmonary bypass using roller or centrifugal pumps. Ann Thorac Surg. 1999;67(4):972–7.
95. Orime Y, Shiono M, Hata H, Yagi S, Tsukamoto S, Okumura H, et al. Cytokine and endothelial damage in pulsatile and nonpulsatile cardiopulmonary bypass. Artif Organs. 1999;23(6):508–12.
96. Watarida S, Mori A, Onoe M, Tabata R, Shiraishi S, Sugita T, et al. A clinical study on the effects of pulsatile cardiopulmonary bypass on the blood endotoxin levels. J Thorac Cardiovasc Surg. 1994;108(4):620–5.
97. Taggart DP, Sundaram S, McCartney C, Bowman A, McIntyre H, Courtney JM, et al. Endotoxemia, complement, and white blood cell activation in cardiac surgery: a randomized trial of laxatives and pulsatile perfusion. Ann Thorac Surg. 1994;57(2):376–82.
98. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia; its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. Ann Surg. 1950;132(5):849–66.
99. Martin DR, Scott DF, Downes GL, Belzer FO. Primary cause of unsuccessful liver and heart preservation: cold sensitivity of the ATPase system. Ann Surg. 1972;175(1):111–7.
100. McMurchie EJ, Raison JK, Cairncross KD. Temperature-induced phase changes in membranes of heart: a contrast between the thermal response of poikilotherms and homeotherms. Comp Biochem Physiol B. 1973;44(4):1017–26.
101. Russ C, Lee JC. Effect of hypothermia on myocardial metabolism. Am J Phys. 1965;208:1253–8.
102. Menasche P, Peynet J, Lariviere J, Tronc F, Piwnica A, Bloch G, et al. Does normothermia during cardiopulmonary bypass increase neutrophil-endothelium interactions? Circulation. 1994;90(5 Pt 2):II275–9.
103. Menasche P, Peynet J, Haeffner-Cavaillon N, Carreno MP, de Chaumaray T, Dillisse V, et al. Influence of temperature on neutrophil trafficking during clinical cardiopulmonary bypass. Circulation. 1995;92(9 Suppl):II334–40.

104. Le Deist F, Menasche P, Kucharski C, Bel A, Piwnica A, Bloch G. Hypothermia during cardiopulmonary bypass delays but does not prevent neutrophil-endothelial cell adhesion. A clinical study. Circulation. 1995;92(9 Suppl):II354–8.
105. Ohata T, Sawa Y, Kadoba K, Kagisaki K, Suzuki K, Matsuda H. Role of nitric oxide in a temperature dependent regulation of systemic vascular resistance in cardiopulmonary bypass. Eur J Cardiothorac Surg. 2000;18(3):342–7.
106. Ulrich C, Harinck-de Weerd JE, Bakker NC, Jacz K, Doornbos L, de Ridder VA. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study. Intensive Care Med. 1989;15(7):424–31.
107. Rocha LA, Martin MJ, Pita S, Paz J, Seco C, Margusino L, et al. Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. A randomized, double blind, placebo-controlled study. Intensive Care Med. 1992;18(7):398–404.
108. Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. Arch Surg. 1999;134(2):170–6.