The inflammatory response and its modification

Emad B. Mossad
Elumalai Appachi

Nature’s reaction to every injury, whether physical, chemical, or bacterial, is inflammation, or in other words, congestion with its resulting benefits.

(E.H. Beckman, MD, Southern Minnesota Medical Association, Saint Mary’s Hospital, Mayo Clinic, August 1907).

Introduction

The normal human response to an abnormal allergen or environment is the triggering of a defense mechanism, mediated through a humoral or cellular immune response. This is no more obvious than the response of the body to cardiopulmonary bypass (CPB) and the abnormal environment of extracorporeal circulation (ECC).1

Despite significant advances in cardiac surgery in the past 50 years, and major strides in improving the outcome of congenital cardiac defect repair, CPB remains an integral part of most operations. Cardiac surgery continues to carry an inherent risk of triggering a cascade of reactions leading to the systemic inflammatory response syndrome (SIRS), and manifested as multisystem organ failure (MSOF), especially in small infants and children.2,3

Clinically, the inflammatory response is manifested as reduced pulmonary function, with decreased compliance, worsening oxygenation, and prolonged need for postoperative mechanical ventilation. Cardiovascular dysfunction, requiring inotropic support, and occasionally the use of mechanical assist devices, occurs in more than 50% of children following cardiac surgery. In addition, 3–7% of children experience renal and hepatic dysfunction; in some series neurologic morbidity occurs in up to 30% of patients; and a high percentage have significant tissue edema and weight gain.4

Mechanisms of activation

The inflammatory response is triggered with the initiation of CPB, from contact of blood with the non-endothelial surface of ECC, activating the coagulation and complement cascades. Other triggers of inflammation include bowel hypoperfusion with endotoxemia, and organ ischemia and reperfusion injury with release of the aortic cross-clamp and termination of bypass. Multiple triggers, mediators, and effectors interact to initiate, propagate, and maintain the inflammatory response and produce end-organ damage (Table 6.1).

Blood contact with the artificial surface activates the intrinsic coagulation pathway (increased factor XIIa), as well as the extrinsic pathway (factor VII contact with tissue factor). Despite the use of high dose systemic heparin, and maintaining an adequate activated clotting time (ACT > 480 seconds), markers of thrombin generation (prothrombin F 1+2, fibrinopeptide A) increase with the progression of bypass. The fibrinolytic system is also activated, with increased kallikrein, bradykinin, and tissue plasminogen activator (tPA).5

The complement system is a series of 19 functionally linked plasma proteins which, once activated, interact to effect humoral immunity and inflammatory response. The complement proteins generally are inactive until activated by the antigen–antibody complex (classic pathway) or by infectious

Table 6.1 Inflammatory triggers and mediators during cardiopulmonary bypass.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement</td>
<td>C3a, C5a, C5b-9</td>
</tr>
<tr>
<td>Leukocyte and adhesion molecules</td>
<td>CD11b/CD18, E-selectin, ICAM-1, integrins</td>
</tr>
<tr>
<td>Arachidonic acid metabolites</td>
<td>Thromboxane A2, prostaglandins</td>
</tr>
<tr>
<td>Endotoxin</td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>TNF-α, IL-6, IL-8, IL-10</td>
</tr>
<tr>
<td>PAF</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Endothelins</td>
<td>Endothelin-1</td>
</tr>
<tr>
<td>Oxygen free radicals</td>
<td>Superoxide anion, singlet oxygen, hydroxyl radicals, hydrogen peroxide</td>
</tr>
</tbody>
</table>

ICAM-1, intercellular adhesion molecule-1; IL, interleukin; NO, nitric oxide; PAF, platelet-activating factor; TNF-α, tumor necrosis factor-α.
Pathophysiology of the inflammatory response

Following activation by surface contact, complement, organisms (alternate pathway). The main event in complement activation is the generation of C3a and C3b from C3 by the action of C3 convertases, and increased C5a (neutrophil attractant) at the onset of bypass. The classic pathway is activated at the end of bypass by the protamine–heparin complex and increased C4a concentration. The end result is release of activated anaphylotoxins (C3a, C4a, and C5a) that in turn cause histamine release, increased vascular permeability, and neutrophil activation. C5a is the most potent of the anaphylotoxins, and acts directly on the endothelial cells, stimulating contraction, vascular leak, and exocytosis. The combined effect of actions of C5a, C3a, and C4a on mast cells, endothelial cells, and neutrophils determines the inflammatory response at the site of complement activation, and thus the degree of organ damage. In a group of 29 children undergoing cardiac surgery, Seghaye et al. showed a significant increase in C3a and C5a at the initiation of CPB, significant transpulmonary neutropenia, and correlation between the degree of complement activation with postoperative morbidity. The elevation of C3a and C5a is proportional to the duration of CPB and the increasing age of patients. Infants have a more pronounced increase in C3a and C5a when compared to neonates.

The initiation of CPB is associated with decreased gastric mucosal pH, intestinal hypoperfusion, and increased permeability. The absorption of ingested monosaccharides (l-rhamnose), dependent on transcellular transport, is decreased during and following CPB, due to intestinal cellular edema. Meanwhile, paracellular transport and urinary excretion of disaccharides (cellobiose) is increased up to the third postoperative day.

Levels of circulating endotoxin and the need for inotropic support correlate with increased intestinal mucosal permeability. The severity of necrotizing enterocolitis (NEC) in newborns correlates with the amount of endotoxin and mediators of inflammation (proinflammatory interleukins [IL] IL-1β and IL-8) in the circulation. The lipopolysaccharide (LPS) bacterial outer membrane of Gram-negative organisms, and circulating endotoxin, bind to macrophages and monocytes, initiating release of mediators of inflammation.

The final trigger to the inflammatory cascade is the ischemia-reperfusion injury that occurs with unclamping the aorta, discontinuing CPB, and resuming pulsatile perfusion. Both in clinical observations and experimental models of ischemia and reperfusion, there is significant increase in neutrophil count, plasma granulocyte elastase, serum IL-6 and IL-8, associated with pulmonary leukocyte sequestration, myocardial and cerebral neutrophil infiltration, and organ dysfunction.

endotoxemia, and reperfusion, the inflammatory response is mediated by expression and secretion of tumor necrosis factor-α (TNF-α), various cytokines and arachidonic acid metabolites.

Macrophages and monocytes, which are already primed by C5a, release TNF-α (also known as cachexin due to its prominent presence in cachexia of chronic illness) in response to stimulation by endotoxin. Plasma levels of TNF-α have been shown to increase during and after CPB with a bimodal peak at 2 and 18–24 hours postoperatively. Tumor necrosis factor-α release is the initial event in the release of further pro- and anti-inflammatory cytokines (Fig. 6.1). Tumor necrosis factor-α acts on mononuclear phagocytes, and on the vascular endothelium, to stimulate secretion of a cascade of pro- and anti-inflammatory cytokines that share many biologic activities.

Cytokines are polypeptide or glycopeptide hormones of low molecular weight (5–28 kDa) that are produced by various cell types. They mediate and regulate the immune and inflammatory response to external stimuli, and facilitate the communication between leukocytes (hence the name “interleukins” or IL). The cell types producing cytokines include macrophages, monocytes, lymphocytes, and endothelial cells. Cytokines are not stored as pre-formed molecules, and their synthesis is initiated by new gene transcription. Once synthesized, cytokines are rapidly secreted, resulting in a burst of serum cytokine release. Cytokines often influence the synthesis and release of other cytokines, leading to a cascade-like increase of their plasma concentrations in a series of successive waves. Positive and negative regulatory mechanisms mediate the biologic effects and concentration of the various cytokines. The wave of release begins with an increase in serum TNF-α, followed by release of several proinflammatory cytokines.
interleukins (IL-1β, IL-6, and IL-8) and anti-inflammatory (IL-10) cytokines.

Tumor necrosis factor-α, C3a, and C5a stimulate macrophage and monocyte IL-1β production and release. Interleukin-1β levels have been shown to increase after CPB and to reach its peak levels at 24 hours postoperatively. Interleukin-1β also activates neutrophils and endothelial cells to cause adhesion between them. Interleukin-1β stimulates the production of IL-6 and IL-8 and thus plays a central role in the inflammatory process. It has been shown to cause decreased myocardial β-adrenergic receptor (BAR) response to catecholamine stimulation. It also causes fever by the production of prostaglandin E2 in the hypothalamus, thus known as the endogenous pyrogen.

Interleukin-6 is produced by various cell types, including macrophages, monocytes, endothelial cells, lymphocytes, and fibroblasts in response to TNF-α. It is known as the acute phase interleukin. The acute phase response consists of fever, leukocytosis, altered vascular permeability, decreased synthesis of albumin, and increased synthesis of acute phase proteins, like C-reactive protein (CRP) by the liver. Interleukin-6 levels peak 3–6 hours after CPB and correlate with postoperative organ dysfunction. In one study, plasma IL-6 levels in children undergoing ventricular septal defect repair (105 ± 12 pg/mL) were significantly lower than levels in patients who underwent complex surgical repairs (220 ± 25 pg/mL). Elevated levels of IL-6 after bypass may be related to the severity of the preoperative condition, the duration of CPB, or myocardial compromise postoperatively. Interleukin-6 seems to be the best indicator of outcome after sepsis or CPB-induced multi-organ failure.

Interleukin-8 is the chemokine that attracts neutrophils to the site of inflammation. The same cell types that produce other cytokines also produce IL-8, through stimulation by endotoxin and TNF-α. Levels of IL-8 begin to rise at rewarming, and peak at 1–3 hours after CPB, and are present after 24 hours. Interleukin-8 attracts neutrophils to the site of inflammation and causes upregulation of adhesion molecules necessary for neutrophil adhesion to endothelial cells. It also stimulates neutrophils to release oxygen free radicals and proteolytic enzymes which enhance endothelial damage. Another group of proinflammatory cytokines, the β-chemokines monocyte chemotactant protein (MCP-1), are significantly increased following CPB, and correlate with duration of bypass, longer surgical time, and increased need for inotropes.

Interleukin-10 is an anti-inflammatory cytokine as opposed to IL-6 and IL-8, which are proinflammatory cytokines. Interleukin-10 levels also increase and peak around 3 hours after CPB (Fig. 6.1). Interestingly IL-6 stimulates the release of IL-10 by macrophages, endothelial cells, and monocytes. Interaction between pro- and anti-inflammatory cytokines likely determines the severity of the inflammatory response and multi-organ dysfunction following CPB in children.

There are conflicting reports regarding the time of release, the degree of increase in plasma levels, and the relative ratio between pro- and anti-inflammatory cytokines in the literature. These discrepancies may stem from the source of sampling (arterial or venous blood), the timing of when blood is sampled, and the various measurement techniques (enzyme-linked immunosorbent assay, radioimmunoassay, or in vitro cell cytotoxicity assay). However, it is clear that the initial response is a release of TNF-α with an early and late peak, followed by a series of waves of interleukin release.

Other important mediators of inflammation are the leukotrienes, arachidonic acid metabolites, endothelin, and oxygen free radicals. The leukotrienes and arachidonic acid metabolites are humoral inflammatory mediators produced by macrophages, neutrophils, and monocytes after stimulation by C5a and IL-8. Leukotriene B4 causes chemotaxis, release of proteolytic enzymes and generation of oxygen free radicals from neutrophils. Other leukotrienes cause arteriolar constriction and induce a profound increase in vascular permeability. Thromboxane A2 and prostaglandins are arachidonic acid metabolites. Thromboxane A2 has strong vasoconstrictor and platelet-aggregating properties. Thromboxane A2 has been shown to cause myocardial dysfunction and pulmonary hypertension after CPB in animal models. Prostaglandins (PGE1, prostacyclin) on the other hand have vasodilating and antiplatelet-aggregating properties, and therefore counter balance the effect of thromboxane A2.

Endothelin is released from the endothelial cells, and is a potent vasoconstrictor. It thus regulates arterial blood pressure and influences cardiac output. Increased levels of endothelin have been demonstrated in patients who develop pulmonary hypertension. Elevated levels of endothelin occur after CPB and correlate with postoperative renal dysfunction. Endothelin release after CPB may also cause myocardial ischemia and the development of pulmonary edema.

These mediators of the inflammatory response (TNF-α, interleukins IL-1β, IL-6 and IL-8, and arachidonic acid metabolites), modulate the response of the body to the inflammatory trigger of bypass through neutrophil-endothelial adhesion, BAR downregulation, and inducible nitric oxide synthase (iNOS) production.

Once activated, neutrophils adhere to endothelial cells, and eventually migrate out of the vessel wall into the tissues (Fig. 6.2). There are specific adhesion molecules on the surface of neutrophils and endothelial cells. These molecules include selectins (present on leukocytes, L-selectin, endothelial cell, E-selectin, and platelets, P-selectin), integrins (neutrophil only), and the immunoglobulin superfamily (endothelial cells only). One study found that atrial and skeletal muscle E-selectin mRNA levels increase significantly following CPB in children. ELAM-1 (endothelial leukocyte adhesion molecule-1) presents on the endothelial surface after stimulation of TNF-α or IL-1, and plays a key role in the binding of neutrophils to endothelium.
CHAPTER 6 The inflammatory response and its modification

The released elastase causes damage to endothelial cells, underlying basement membrane, subendothelial matrix, and parenchyma of various organs, and plasma levels are significantly elevated after CPB.

Platelets become activated during CPB from the action of C5a and also by platelet-activating factor (PAF) secreted by endothelial cells, which leads to the expression of platelet P-selectin. Platelets attached to the vascular endothelium play an important role in neutrophil adhesion and transmigration by attracting more neutrophils to the endothelium from the expression of P-selectin.23

Endothelial cells are responsible for the permeability barrier through which the exchange of substances takes place by transcytosis. The endothelium also promotes structural changes of the blood vessel in response to a local change in environment. The vascular endothelium is exposed to various inflammatory stimuli including endotoxin, cytokines, and the physical injury of surgical trauma. These stimuli may cause a disruption of the barrier function, vasoconstriction, abnormal coagulation, leukocyte adhesion, smooth muscle proliferation, and they release of more mediators of inflammation, like cytokines released from the cytoplasmic vacuoles called Weibel–Palade bodies.

Another mechanism by which the inflammatory response is mediated is through BAR downregulation. Discontinuation of CPB is a critical event, often associated with transient myocardial dysfunction, requiring increasing inotropic support. Canine transmyocardial left ventricular biopsies reveal the density of BAR to be significantly decreased following bypass.24 The response of BAR in the myocardium or bronchial smooth muscles to non-selective β-agonists (isoproterenol), or selective β2-agonists (zinterol), is impaired following CPB. The decreased density, and desensitization of BAR, is reproducible with TNF-α exposure, and correlates with the post-CPB increase in serum cytokines.25

The endothelium-derived relaxing factor, nitric oxide (NO), is a natural regulator of vasomotor tone and blood flow to organs. Under normal conditions, picomolar concentrations of NO are formed in the circulation, by the effect of constitutive nitric oxide synthase (cNOS). However, at the start of CPB, hemodilution, non-pulsatile flow, and circuit contact activate endothelial inducible nitric oxide synthase (iNOS), to produce excessive (nanomolar) concentrations of NO. Nitric oxide will modulate vasodilation, neutrophil adhesion, and tissue injury by TNF-α, cytokines, and other mediators of inflammation.26

The negative inotropic effect of TNF-α on isolated papillary muscle contraction, was blocked in the presence of N-monomethyl-l-arginine (l-NMMA), a specific NOS inhibitor. The concentration-dependent, reversible myocardial depression of TNF-α reappears with the addition of l-arginine.27 Neuronal apoptosis following hypothermic circulatory arrest, especially in the hippocampus and neocortex, is significantly reduced by neuronal NOS inhibition.28 Nitric oxide regulates...
Clinical effects of the inflammatory response

Complications following CPB due to the systemic inflammatory response remain common and obvious, despite significant improvement in equipment, material, and the conduct of surgery. Following prolonged surgery, children may present to the intensive care unit with marked whole-body edema and multiple organ failure, especially those patients who require greater pharmacologic and mechanical support (Fig. 6.3).

High fever, thrombocytopenia, cardiorespiratory insufficiency, and failure of one or more vital organ systems, occur in more than 3.5% of children after open heart surgery.30

One study found 13/24 neonates developed capillary leak syndrome (CLS), which was associated with higher complement (C5a) and cytokine (TNF-α) levels postoperatively (Fig. 6.4). Plasma albumin fell significantly, and histamine release during CPB was more pronounced in patients with CLS.31

There is a strong association between triggering the inflammatory response and the development of coagulopathy following bypass. An inverse correlation is present between in vitro platelet aggregation and plasma IL-1β or IL-6 levels. Cytokines are important mediators of disseminated intravascular coagulopathy, fibrinolysis, and bleeding associated with CPB and sepsis.32 Cardiac surgery still consumes more than 20% of the nation’s blood supply, and almost 80% of all transfusions are used in only 15% of patients, who commonly show other signs of MSOF and systemic inflammatory response.

Myocardial dysfunction requiring inotropic support is common in the immediate postoperative period. The severity of cardiac depression appears to be associated with the extent of stimulation of the inflammatory response. In adults presenting for myocardial revascularization on CPB, a bimodal increase in TNF-α and IL-6 is noted postoperatively that is proportional to the duration of cross-clamp. Left ventricular wall motion abnormalities, episodes of myocardial ischemia, and inotropic requirements, correlated with cytokine expression.33 Cardiac index and systemic vascular resistance are

Fig. 6.3 Systemic inflammatory response syndrome following extracorporeal circulation, leading to multisystem organ failure in a neonate with congenital heart disease.

Fig. 6.4 Course of tumor necrosis factor-α (TNF-α) before, during and after cardiopulmonary bypass (CPB) in neonates with (black), and without (white) capillary leak syndrome (CLS). CCA, complete circulatory arrest; PO, postoperatively (*P < 0.05). Adapted from Seghaye MC, Grabitz RG, Duchateau J et al. Inflammatory reaction and capillary leak syndrome related to cardiopulmonary bypass in neonates undergoing cardiac operations. J Thorac Cardiovasc Surg 1996; 112: 687–97, with permission from Elsevier.
inversely related, while pulmonary capillary wedge pressure was directly related to IL-6 increase postoperatively. Preoperative depression of cardiac function appears to pre-dispose the patient to develop an accentuated inflammatory response, with a significant increase in post-pump cytokines in patients with an ejection fraction of less than 0.45 preoperatively, compared to those with normal cardiac function.

Myocardial damage appears to occur up to the fourth post-operative day in children following repair of congenital heart defects, and the changes in serum troponin, creatine kinase, and procalcitonin correlate with the increases in markers of inflammation.

The pulmonary injury following CPB is one of the major causes of morbidity after cardiac surgery in children, and is known as “pump-lung”. Pulmonary edema, microatelectasis, increased alveolar–arterial oxygen gradient (A–aO₂ gradient), and increased pulmonary vascular resistance, are common postoperatively. Duration of CPB in children correlates with decreases in surfactant, transpulmonary neutropenia, and neutrophil-lung sequestration. Granulocyte adhesion molecule expression (CD11b/CD18, MCP-1), and increase in serum IL-8, correlate with a deterioration in oxygenation in children after surgery. Serum and alveolar epithelial IL-6 increase significantly following CPB in children, and correlated with intraoperative blood transfusion, fluid gain, Pediatric Risk of Mortality Score (PRISM), and survival (Fig. 6.5).

Neurologic injury occurs frequently in children following repair of congenital heart disease (CHD), with gross deficits (strokes, seizures) found in 3%, and psychomotor and neuro-developmental dysfunction found in 30% of children. Despite a relation between adhesion molecules, TNF-α, and cognitive dysfunction in other disease states, these markers of systemic inflammatory response showed no relationship with neurologic outcome at 5-day and 3-month performance tests.

The risk of acute renal failure (2.7%) and gastrointestinal complications (1%) in children following CPB is associated with triggering the inflammatory response. In patients with severe end-stage cardiomyopathy, five out of 16 developed fulminant hepatic failure despite adequate hemodynamic support by a left ventricular assist device. Markers of inflammation (CRP, IL-6, and IL-8) were significantly increased in patients who developed hepatic dysfunction.

**Modification of the inflammatory response**

Multiple treatment modalities and interventions are used in an attempt to limit the generation and extent of inflammation after bypass and avoid organ dysfunction. One obvious method to decrease the triggering of inflammation is to avoid CPB, and currently over 16% of coronary artery bypass graft surgeries are performed without bypass. However, the use of ECC remains essential for all intracardiac repairs of congenital heart defects. Thus the interventions needed to limit the inflammatory response to CPB include: (i) preoperative therapies (intestinal decontamination, pre-surgical inotropes, and anesthetics); (ii) modifications of circuit biocompatability (heparin-coating, pulsatile flow, prime solution); (iii) changes in CPB conduct (temperature, leukocyte depletion, hemofiltration); and (iv) pharmacologic interventions (steroids, aprotinin, monoclonal antibodies). The treatment modalities and therapies are used in concert to treat the multifaceted inflammatory response to bypass (Fig. 6.6).

**Digestive decontamination**

Endotoxemia in children with CHD is present in 40% of patients preoperatively, and 96% following CPB. Plasma levels of IL-6, unstable hemodynamics, and mortality are higher in children with more significant endotoxemia. The use of selective digestive decontamination (polymyxin E, tobramycin, and amphotericin B) for 72 hours preoperatively reduces gut content of enterobacteria, and lowers endotoxin and cytokine concentrations post-bypass.

**Inotropic support**

Perioperative administration of low dose milrinone improves splanchic perfusion on CPB, thus limiting intestinal mucosal ischemia and injury, thereby decreasing translocation of intestinal flora and endotoxia. The use of milrinone 0.5 µg/kg/minute improves gastric intramucosal acidosis, reduces hepatic venous congestion, and reduces postoperative IL-6.

**Prime solution and blood transfusion**

The use of plasma expanders and the maintenance of colloidal osmotic pressure in prime solution limits activation of the alternative and common complement pathways.
PART 1 History, education, and science

**Temperature control**

The use of hypothermic CPB appears to offer a protective effect from the inflammatory response. One study compared maintaining a core temperature of 28°C vs. 36°C, and found markers of inflammation to be significantly reduced. In an *in vitro* pediatric CPB circuit preparation, neutrophil activation and upregulation of adhesion molecules was significantly increased on normothermic (35°C) compared to hypothermic (17°C) bypass.55 Even though a predominance of literature supports the concept that moderate or deep hypothermic bypass attenuates the inflammatory response and decreases histologic organ damage, some investigators have shown no difference in those markers with changing temperature.57,58

**Heparin-coated circuits**

The use of a heparin-coated (HC) or bonded extracorporeal circuit reduces heparin requirements during cardiac operations, and improves oxygen tension (HC 597.2 ± 31.2 vs. control 220.5 ± 42.3 mmHg), and pulmonary vascular resistance (HC 408.6 ± 69.4 vs. control 1159.8 ± 202.4 dyne · s · cm⁻⁵) 2 hours after CPB.59 Heparin bonding of the entire circuit, or the oxygenator (which forms > 80% of the circuit surface area in children), significantly reduces postoperative central hyperthermia and respiratory index. Plasma levels of terminal complement complexes, and expression of neutrophil adhesion molecules and serum cytokines are markedly reduced in children managed with HC circuits.60–62 Two different processes of coating circuits with heparin have been described. The Carmeda process (Medtronic, Inc., Minneapolis, MN) deposits a polymer coating on the circuit surface, followed by covalently bonding heparin fragments to that coating. The Duraflo II process (Baxter Healthcare Corp., Irvine, CA) modifies the physicochemical properties of unfractionated heparin with a binding agent, giving it a high affinity for synthetic surfaces.63 Although the Carmeda equipment appears more effective in reducing complement activation, both methods were similar in blunting the expression of cytokines and the inflammatory response.

**Leukocyte depletion**

The use of a blood cell separator can limit the triggering of the inflammatory response and its deleterious effects. Leukocyte and platelet depletion (LPD) decrease leukocyte and platelet counts; and serum elastase, thromboxane, and thrombin–antithrombin III (TAT) complex are also lowered. This therapy leads to higher arterial oxygen tension and a lower

---

Despite allogeneic blood transfusion causing more immunosuppression than autologous blood, exposure to any transfusion, especially platelet concentrates, leads to a significant increase in markers of inflammation (C3a, C5a, TNF-α, and IL-6). The magnitude of the interleukin response to CPB correlates with blood transfusion and duration of bypass.49

**Oxygenators and perfusion mechanics**

Compared to bubble oxygenators, the use of membrane oxygenators in pediatric cardiac surgery is associated with better cardiac performance, better postoperative pulmonary compliance, and decreased shunt fraction, free hemoglobin, blood loss, postoperative pyrexia, and length of hospitalization. When extracorporeal perfusion lasts more than 2 hours, membrane oxygenators reduce the release of granulocyte adhesion molecules, lactoferrin, myeloperoxide, and pro-inflammatory cytokines.50,51

The use of non-pulsatile flow is associated with a progressive increase in systemic vascular resistance, decreased tissue oxygen consumption, metabolic acidosis, and the expression of inflammatory markers. Pulsatile perfusion (although less popular) and non-occlusive centrifugal pumps can be used during pediatric CPB, and may limit complement activation and reduce the inflammatory response.52,53

---

**Fig. 6.6** Treatment options of the inflammatory response to cardiopulmonary bypass (CPB). MSOF, multisystem organ failure; TNF-α, tumor necrosis factor-α.
and use of lower catecholamine doses.⁶⁴,⁶⁵

Conventional and modified ultrafiltration

The hemodilutional effects of CPB are pronounced in children due to the disproportionately large priming volume and surface area of the circuit. Hemoconcentration applies a hydrostatic pressure gradient to a semipermeable membrane, removing excess water, low-molecular-weight substances, and inflammatory mediators. The filter can be used during rewarming, and placed between the oxygenator and the venous reservoir (in conventional ultrafiltration [CUF]), or after CPB, and placed between the arterial cannula and the right atrium (in modified ultrafiltration [MUF]). The suction pressure should not exceed 200 mmHg, removing fluid at a rate less than 50 mL/kg/minute. Both methods are effective in reducing proinflammatory cytokines, complement activation (C3a, C5a), and weight gain.⁶⁶,⁶⁷

Cytokine removal strategies using CUF or MUF are limited to the intraoperative period and are unable to limit the inflammatory response due to reperfusion injury in the postoperative period. The use of a Tenckhoff catheter for removal of peritoneal fluid was shown to remove significant amounts of IL-6 and IL-8, and may be beneficial in improving the pro- to anti-inflammatory (IL-6/IL-10) serum cytokine balance.⁶⁸

Intravenous anesthetics

The use of intravenous anesthetics to modulate the inflammatory response to CPB is an interesting and evolving area of investigation. The effect of pharmacologic concentrations of intravenous anesthetics on the expression of leukocyte adhesion molecules and release of cytokines has been studied in a cultured whole blood sample incubated with LPS endotoxin.⁶⁹ Compared to control, the LPS-stimulated TNF-α response was inhibited by thiopentone (12.8%) and ketamine (46.4%), augmented by propofol (172.3%), and unchanged with midazolam or fentanyl.

Aprotinin

Aprotinin reduces endotoxin activation of the plasma kallikrein–kinin and complement system.⁷⁰ Aprotinin is a serine protease inhibitor commonly used in adult and pediatric cardiac surgery to decrease blood loss and transfusion requirements. Aprotinin shortens sternal closure times, decreases 24-hour chest tube drainage, transfusion of packed red blood cells and platelets, and overall hospital expense in children with cyanotic heart disease.⁷¹,⁷² Aprotinin is an expensive medication, with known risk of anaphylaxis. Exposure to topical aprotinin in fibrin sealant resulted in developing aprotinin-specific immunoglobulins E and G in 8–39% of children.⁷³ However, only aprotinin blocks kallikrein and plasmin, thus preventing contact activation, the release of cytokines, and the inflammatory response to CPB. In a bronchial epithelial cell line, aprotinin blocks the expression of iNOS and the production of injurious concentrations of NO in response to cell stimulation with TNF-α and other cytokines.⁷⁴,⁷⁵

Corticosteroids

The beneficial effects of steroid administration before CPB to attenuate the “post-pump syndrome” have long been investigated. Earlier studies focused on the hemodynamic effects of methylprednisolone (MPSS at 10–30 mg/kg) or dexamethasone (DXM at 1–6 mg/kg). Both glucocorticoids increased cardiac index, reduced peripheral vascular resistance, and improved microcirculation and visceral perfusion.⁷⁶ Steroid use has an equal and even a synergistic effect with other agents, such as aprotinin, in blunting the inflammatory response. Methylprednisolone improved oxygenation, cardiac index, and cytokine balance following CPB, when added to high dose aprotinin.⁷⁷,⁷⁸

Several investigations have shown that steroid pretreatment modulates different aspects of the inflammatory response, and the most recent studies are summarized in Table 6.2.⁷⁹–⁹⁰ Steroids blunt the endotoxin-mediated increases in CD11b/CD18, and neutrophil surface adhesion-receptor expression.⁷⁷ They reduce the expression of proinflammatory cytokines, and LPS-stimulated production of IL-1β and TNF-α by macrophages. Methylprednisolone has been shown to block the upregulation of neutrophil integrin adhesion receptors, and preserve chemotactic properties, as well as attenuate complement activation with protamine administration.⁸² Dexamethasone decreases proinflammatory cytokines, and the expression of ELAM-1 (endothelial leukocyte adhesion molecule-1) and ICAM-1 adhesion receptors.⁸⁶ The net results of steroid pretreatment appear to include improvement in hemodynamics, pulmonary mechanics, and recovery of cerebral perfusion and metabolism following deep hypothermic circulatory arrest.⁸⁰,⁸⁶,⁸⁸ Steroids cause attenuation of capillary leak and weight gain, and reduce postoperative pyrexia through limiting the inflammatory response.

The type, timing, and dose of steroid used are controversial, and may explain the discrepancy in outcome of some studies.⁹⁰ Administration of steroids 1–8 hours prior to incision appears to have a stronger impact on cytokines and acute phase-reactants (CRP), than does the same dosage used in the pump prime.⁷⁹,⁸⁴ The administration of MPSS 20–30 mg/kg/pump prior to surgical incision significantly improved the anti- to proinflammatory cytokine balance, and maintained a favorable postoperative clinical outcome (Fig. 6.7).⁸⁷

Anticytokine and monoclonal antibodies

Experimental studies have shown a benefit for strategies to block cytokines in sepsis-like syndromes using soluble
The inflammatory response to CPB is a cascade of events, with multiple triggers, mediators, and modulators, culminating in end-organ injury and poor outcome. The treatment modalities to this inflammatory response need to be preemptive, multifaceted, and used in combination to prevent the response, blunt its degree of expression, or limit the severity of organ dysfunction.77,96 In one study, the use of four anti-inflammatory strategies (methylprednisolone, aprotinin, TNF-α receptors and neutralizing factors, and IL-1β-receptor antagonists.91 Inhibition of neutrophil adhesion using monoclonal antibodies and anti-selectins leads to improved recovery of ventricular function, myocardial oxygen consumption, and attenuates myocardial neutrophil proliferation following cold cardioplegic ischemia.92-94 Clinical studies have shown the safety and efficacy of a humanized, recombinant, single chain antibody specific for human C5 in limiting the inflammatory response to bypass. Patients receiving 1–2 mg/kg i.v. of the complement inhibitor preoperatively had effective inhibition of the proinflammatory complement by-products (sC5b-9) and reduced surface adhesion molecules (CD11b/CD18).95 Those patients had a 40% reduction in myocardial injury, improved scores on a mini-mental state examination, and a significant reduction in blood loss. There is ongoing investigation in this area, especially in children, to identify anti-adhesion molecules and cytokine inhibitors that limit the response of the body to the stress of bypass.

The inflammatory response to CPB is a cascade of events, with multiple triggers, mediators, and modulators, culminating in end-organ injury and poor outcome. The treatment modalities to this inflammatory response need to be preemptive, multifaceted, and used in combination to prevent the response, blunt its degree of expression, or limit the severity of organ dysfunction.77,96 In one study, the use of four anti-inflammatory strategies (methylprednisolone, aprotinin, TNF-α receptors and neutralizing factors, and IL-1β-receptor antagonists.91 Inhibition of neutrophil adhesion using monoclonal antibodies and anti-selectins leads to improved recovery of ventricular function, myocardial oxygen consumption, and attenuates myocardial neutrophil proliferation following cold cardioplegic ischemia.92-94 Clinical studies have shown the safety and efficacy of a humanized, recombinant, single chain antibody specific for human C5 in limiting the inflammatory response to bypass. Patients receiving 1–2 mg/kg i.v. of the complement inhibitor preoperatively had effective inhibition of the proinflammatory complement by-products (sC5b-9) and reduced surface adhesion molecules (CD11b/CD18).95 Those patients had a 40% reduction in myocardial injury, improved scores on a mini-mental state examination, and a significant reduction in blood loss. There is ongoing investigation in this area, especially in children, to identify anti-adhesion molecules and cytokine inhibitors that limit the response of the body to the stress of bypass.

**Table 6.2** Recent randomized evaluations of steroid effect on inflammatory response to cardiopulmonary bypass.79-90

<table>
<thead>
<tr>
<th>Study</th>
<th>Steroid use: type, dose, and time</th>
<th>Subjects</th>
<th>Biochemical markers</th>
<th>Clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wan et al.79 (1996)</td>
<td>MPSS 500 mg preop. (GP-I) or 1.5 h post-clamp (GP-II)</td>
<td>20 adult transplants</td>
<td>↓ TNF &amp; IL-8 ↑ IL-10 (GP-I)</td>
<td>↓ Postop. fever</td>
</tr>
<tr>
<td>Butler et al.80 (1996)</td>
<td>MPSS 10 mg/kg Pump prime</td>
<td>24 children</td>
<td>↓ IL-6, CRP</td>
<td>No difference between MPSS and DXM</td>
</tr>
<tr>
<td>Tabardel et al.81 (1996)</td>
<td>MPSS 30 mg/kg vs DXM 1 mg/kg 4 h pre-CPB</td>
<td>22 adults</td>
<td>↓ IL-8, TNF-α ↑ IL-10</td>
<td>No difference between MPSS and DXM</td>
</tr>
<tr>
<td>Loubser82 (1997)</td>
<td>MPSS 30 mg/kg pre-CPB</td>
<td>16 adults</td>
<td>↓ C3a, C4a after protamine</td>
<td></td>
</tr>
<tr>
<td>Mayumi et al.83 (1997)</td>
<td>MPSS 20 mg/kg pre- and post-CPB</td>
<td>24 adults</td>
<td>↓ IL-2, CRP, T &amp; B cells</td>
<td></td>
</tr>
<tr>
<td>Lodge et al.84 (1999)</td>
<td>MPSS 30 mg/kg 8 h &amp; 1.5 h preop. vs pump prime</td>
<td>18 neonatal piglets</td>
<td>↑ Compliance ↓ A-a gradient, PVR, fluid gain</td>
<td></td>
</tr>
<tr>
<td>Dernek et al.85 (1999)</td>
<td>MPSS 30 mg/kg preop.</td>
<td>50 adults</td>
<td>↓ Complement ↓ Ig activation ↓ Pulmonary neutrophil sequestration</td>
<td></td>
</tr>
<tr>
<td>Bronicki et al.86 (2000)</td>
<td>DXM 1 mg/kg 1 h prior to CPB</td>
<td>29 children</td>
<td>↓ IL-6, TNF-α ↔ C3a, neutrophil count ↓ Rectal temp. ↓ A-a gradient ↓ Mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Mossad et al.87 (2000)</td>
<td>MPSS 20 or 30 mg/kg prior to incision</td>
<td>47 infants</td>
<td>↓ IL-6, IL-8 ↑ IL-10 ↓ PD drainage</td>
<td></td>
</tr>
<tr>
<td>Langley et al.88 (2000)</td>
<td>MPSS 30 mg/kg i.m. 2 h preop.</td>
<td>16 neonatal piglets on DHCA</td>
<td>↑ Recovery of regional &amp; global CBF &amp; CMRO₂</td>
<td></td>
</tr>
<tr>
<td>Volk et al.89 (2001)</td>
<td>MPSS 15 mg/kg preop.</td>
<td>39 adults</td>
<td>↓ IL-1β, IL-6, IL-8, TNF-α response to LPS ↑ IL-10</td>
<td></td>
</tr>
<tr>
<td>Mott et al.90 (2001)</td>
<td>MPSS 1 mg/kg x 4 doses preop. &amp; 24 h postop.</td>
<td>246 children</td>
<td>↑ Risk of PPS</td>
<td></td>
</tr>
</tbody>
</table>

A-a gradient, alveolar-to-arterial oxygen gradient; CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate for oxygen; CPB, cardiopulmonary bypass; CRP, C-reactive protein; DHCA, deep hypothermic circulatory arrest; DXM, dexamethasone; GP-I, Group I; GP-II, Group II; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharide; MPSS, methylprednisolone sodium succinate; PD, peritoneal dialysis; PPS, post-pericardiotomy syndrome; PVR, pulmonary vascular resistance; TNF, tumor necrosis factor.
The inflammatory response and its modification

and adhesion molecule expression, in response to the same triggers. The patient’s preoperative cardiac function appears to contribute to the extent of inflammatory response. Patients with severe end-stage heart failure have elevated serum TNF-α levels, which correlates with their New York Heart Association Status and degree of ventricular dysfunction. The proinflammatory cytokines play an important role in the pathogenesis of heart failure, but may also be triggered and released in the circulation from poor visceral perfusion.99 The increase in serum IL-6 and TNF-α was more pronounced in patients with depressed preoperative cardiac function and lower ejection fraction.34

Similar to other disease states, the inflammatory response may have a spectrum of genetic expression responsible for the variability in response to the stimulus of CPB.100 The expression of adhesion molecules in response to transient cerebral ischemia can be genetically modulated, and this presents a new target site for therapy of post-ischemic reperfusion injury.101

Treatment modalities to the inflammatory response may have side effects that supercede their benefits. Glucocorticoids cause postoperative hyperglycemia, and may aggravate ischemic neuronal damage. Despite effective suppression of the complement and interleukin response, DXM increased the size of cerebral infarct by 10-fold using a middle cerebral artery occlusion model.102 There is evidence that steroids may worsen neurological outcomes in neonatal patients following a 42-day tapering course of steroids in ventilator-dependent low-birth-weight infants. One-year follow-up showed a significant increase in intracranial abnormalities, and a greater risk of developing cerebral palsy.103

The synergistic immunosuppression caused by high-dose MPSS and CPB (suppression of IL-2 helper T-cell function, and increased natural killer cells) may be detrimental.83 The use of preoperative digestive decontamination, leukocyte depletion, and steroids may also increase the risk for post-operative infection.

Finally, stimulation of the inflammatory response is a complex process necessary for wound healing and immune defense. Therefore the goal of any therapy must not be the complete suppression of the inflammatory response to CPB. In fact, despite an abolished complement and adhesion-molecule response to CPB in a complement-deficient animal model, bypass-associated lung injury still occurs.104 Patients with leukocyte adhesion deficiency syndrome (LADS I and II), manifest absence of cell surface expression adhesion molecules, and have a significant risk of recurrent bacterial infections, skin lesions with impaired pus formation, and delayed wound healing. Replacement therapy with granulocyte–macrophage colony-stimulating factor increases cytokine and integrin expression, and improves their clinical condition.105

The inflammatory response is a natural defense mechanism which protects the body from foreign antigens and

---

Unanswered questions

Although the etiology of the systemic inflammatory response in cardiac surgery appears to be related to the contact-activation and exposure to the extracorporeal circuit, markers of inflammation have been detected in operations done without bypass. The combined stress of surgical trauma, vascular injury, and anesthesia may contribute significantly to the CPB-induced inflammatory response. In children operated upon with and without CPB, the activation of the alternate complement pathway, cytokines, and adhesion molecule expression were seen in both groups (C3d: 8.16 ± 3.6 vs. 4.12 ± 1.43 mg/L, peak IL-6: 164.4 vs. 277.8 pg/mL, ICAM-1: 241 ± 35 vs. 325 ± 29 pg/mL, E-selectin: 56.1 ± 32.8 vs. 42.4 ± 17.7 pg/mL, CPB vs. no CPB respectively).37 Avoiding bypass will not completely eliminate the risk of triggering the inflammatory response to surgical stress.98

The response to surgical stress and CPB varies significantly between patients, with a wide range of cytokine release and leukocyte depletion, or HC circuit) effectively attenuated markers of the inflammatory response to ECC, and decreased mortality to 2.3%, compared to a 5.7% risk stratification predicted mortality of the population studied.96

Fig. 6.7 Serum interleukin-6 (IL-6) (a) and IL-10 (b) concentrations before and after cardiopulmonary bypass (CPB) (*P < 0.05). Control, no steroids; MP 20, methylprednisolone 20 mg/kg; MP 30, methylprednisolone 30 mg/kg. Reproduced with permission from Mossad E, Appachi E, Kapural M et al. Effects of methylprednisolone on the inflammatory response to cardiopulmonary bypass in children. Anesth Analg 2000; 90: SCA 28.
limits their injury to a local site. However, when the stimulus is excessive, the response becomes exaggerated and harmful, and requires multimodal therapy to limit end-organ injury, but not to abolish it completely.

References

CHAPTER 6 The inflammatory response and its modification


67 Hennein HA, Kiziltepe U, Barst S et al. Venovenous modified ultrafiltration after cardiopulmonary bypass in children: A
History, education, and science


102 Tsubota S, Adachi N, Chen J et al. Dexamethasone changes brain