Systemic Inflammatory Response to Cardiopulmonary Bypass in Pediatric Patients and Related Strategies for Prevention

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Tara Karamlou and Ross M. Ungerleider

Abstract

Cardiopulmonary bypass in pediatric patients is associated with generalized activation of both innate and acquired immunity. The systemic inflammatory response occurs in response to multiple nonphysiologic stimuli. Activation of the inflammatory response involves an intricate cascade which results in pronounced amplification that affects nearly every end-organ system. These processes have a direct role in commonly encountered postoperative complications and can lead to significant morbidity following repair of congenital heart defects. This chapter will discuss the systemic inflammatory response related to cardiopulmonary bypass and measures that attempt to modulate this phenomenon.

Introduction

Cardiopulmonary bypass (CPB) in pediatric patients is associated with generalized activation of both innate and acquired immunity [1–7], and this phenomenon is exaggerated at the extremes of age [3]. The systemic inflammatory response to CPB occurs in response to multiple nonphysiologic stimuli, including exposure of blood elements to foreign surfaces, nonpulsatile perfusion, periods of relative hypoperfusion, alterations in temperature (especially hypothermia), and ischemia-reperfusion injury.

Defining the "systemic inflammatory response" within the context of pediatric CPB is challenging given that consensus guidelines published by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) in 1992 described a final common pathway in adults, elucidated by a variety of insults [8]. According to these guidelines, two of the following manifestations must be fulfilled for the diagnosis: (1) body temperature higher than 38 °C or lower than 36 °C, (2) heart rate more than 90 beats per minute, (3) respiratory rate more than 20/min or $PaCO_2$ less than 32 mmHg, and (4) leukocyte count more than 12,000 cells/mm^3 or less than 4,000 cells/mm^3, or the presence of more than 10 % neutrophils. Owing to the difficulties extrapolating this initial

T. Karamlou (✉)
Division of Pediatric Cardiac Surgery, UCSF School of Medicine, Benioff Children's Hospital, San Francisco, CA, USA
e-mail: tara.karamlou@ucsfmedctr.org

R.M. Ungerleider
Pediatric Cardiac Surgery, Wake Forest University, Winston-Salem, NC, USA
e-mail: rungerle@wfubmc.edu; rungerle@wakehealth.edu

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definition to particular subsets of patients, a more recent iteration was proposed [9]. The 2001 definition [9] is a hierarchical model, termed *PIRO*, that stratifies patients according to their ***p***redisposing conditions, the nature and extent of the ***i***nsult, the nature and magnitude of the host ***r***esponse, and the degree of concomitant ***o***rgan dysfunction.

Activation of the inflammatory response involves an intricate cascade which results in pronounced amplification that affects nearly every end-organ system. Neutrophils, which are the primary effector cells, become primed; complement and kallikrein-kinin systems are subsequently and systematically stimulated; inflammatory (and anti-inflammatory) cytokines are generated; and platelets are activated, subsequently covering the surface of the extracorporeal circuit resulting in microembolic events, further coagulation disturbances, and thrombocytopenia[2–17]. These processes have a direct role in commonly encountered postoperative complications and can lead to significant morbidity following repair of congenital heart defects. Multiple studies [2–6, 12–21] have demonstrated elevation of inflammatory mediators, myocardial dysfunction, capillary leak syndrome, acute lung injury, coagulopathies, and multiorgan failure[2–6, 12–21]. However, the precise contribution of CPB to these deleterious sequelae is more difficult to ascertain. Patients and procedural factors might play a variable role in inciting the post-CPB inflammatory response, and neither the occurrence nor the degree of postoperative sequelae is uniform [22]. Furthermore, recent evidence suggests that ischemia-reperfusion may play an increased role in the inflammatory cascade, especially concerning the cerebral and myocardial microcirculations. Caputo and colleagues [18] have published data suggesting that oxygen-mediated injury is implicit in myocardial injury (especially in cyanotic neonates) and also contributes to hepatic and neuronal injury.

Despite the multifactorial nature of the systemic inflammatory response following cardiac surgery in pediatric patients, developing techniques to ameliorate post-CPB injury are of considerable interest. Specific strategies aimed at reducing the deleterious systemic effects of CPB discussed in this chapter include pharmacologic agents (steroids), circuit coating, temperature modification, and use of ultrafiltration. The chapter will conclude with substantial discussion of a promising avenue of research and development pursued in our laboratory using circuit miniaturization and avoidance of allogeneic blood transfusion to improve post-CPB outcomes.

The Systemic Inflammatory Cascade

The inflammatory response to CPB has been extensively characterized elsewhere [1–22]. It is complex, incited by the exposure of blood to foreign surfaces, wide fluctuations in temperature, and ischemia-reperfusion injury. Though the majority of "contact activation" is attributed to the extracorporeal circuit interface with blood components, other commonly used adjuncts also contribute to post-CPB inflammation, including the use of cardiotomy suction and intracardiac venting. Patient-dependent factors including extremes of age and the presence of certain congenital defects further contribute to the wide range of systemic effects manifest in pediatric patients following CPB. In general though, several broad pathophysiologic categories can be defined as follows: (1) complement activation; (2) initiation of coagulation, fibrinolytic, and kallikrein cascades; (3) neutrophil activation with degranulation and proteolytic enzyme release; (4) oxygen-derived free radical production; (5) endotoxin and cytokine release; and (6) nitric oxide (NO), endothelin-1 (ET-1), and platelet-activating factor (PAF) production by "primed" endothelial cells [23–37] (Fig. 44.1). The sequential activation of these cascades coupled with extensive interactions result in a sustained and amplified systemic inflammatory response syndrome (SIRS) [21, 29–32].

Currently Used Strategies to Reduce Inflammation

Steroids

Glucocorticoids blunt neutrophil upregulation; inhibit the expression of adhesion molecules produced by the activated endothelial cells,

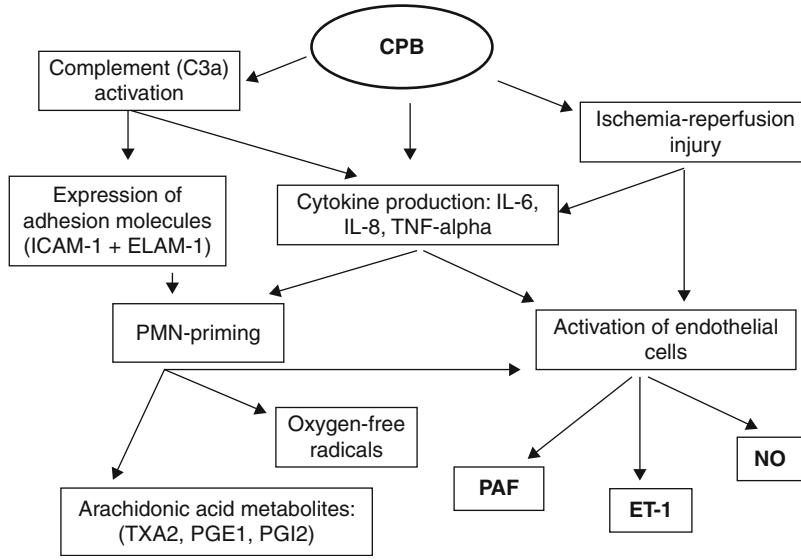

Fig. 44.1 Schematic representation of the biologic mechanisms responsible for the inflammatory response to cardiopulmonary bypass. The cascades are shown in sequential order, but significant redundancy and interactions exist between each arm. The cumulative result of these events is tissue injury and organ dysfunction. *CPB* cardiopulmonary bypass, *ICAM-1* intracellular adhesion molecule-1, *ELAM-1* endothelial-leukocyte adhesion molecule-1, *PMN* polymorphonuclear leukocyte, *TXA2* thromboxane A2, PGE_1 prostaglandin E1, PGI_2 prostacyclin, *PAF* platelet-activating factor, *ET-1* endothelin-1, *NO* nitric oxide, *IL* interleukin, *TNF* tumor necrosis factor

including endothelial-leukocyte adhesion molecule-1 (ELAM-1) and intercellular adhesion molecule-1 (ICAM-1); and therefore reduce diapedesis of leukocytes into injured areas [34–37]. In keeping with their pharmacologic mechanisms of action, steroid administration did appear to have salutary effects on post-CPB outcomes in earlier studies. Ungerleider's group [38, 39] has extensively studied the timing of steroid administration and found that premedication with methylprednisolone (Solumedrol®) 30 mg/kg 12 h preoperatively is beneficial relative to isolated administration in the pump prime. Bronicki and colleagues [40] demonstrated that preoperative administration of dexamethasone (1 mg/kg) intravenously 1 h before the pump run in children produced an eightfold decrease in interleukin-6 and a threefold decrease in tumor necrosis factor-alpha (TNF-α), which improved convalescence. However, more recent studies, including a randomized controlled trial in 76 neonates, have not shown corticosteroids to be beneficial in improving clinical metrics [35, 40–42]. Pasquali and colleagues [19] used a national database to study 46,730 patients aged 0–18 years undergoing congenital heart surgery, 54 % of whom received corticosteroids. These authors found that steroid administration did not reduce neither mortality nor length of mechanical ventilation. Patients receiving steroids had longer hospital length of stay, a greater prevalence of infection and need for insulin use, than nonsteroid recipients. Similarly, a recent meta-analysis [42] also failed to demonstrate any benefit in clinical outcomes with glucocorticoid use. Critics of these negative studies point out that steroid administration protocols were not standardized or even known (as in the study by Pasquali et al.) and therefore may have missed a true effect. It is also possible that changes in circuitry (with biologic coating, oxygenator miniaturization, smaller surface area from decreased circuit size, to cite a few examples) may have an influence in the manifestations of systemic inflammation in the more current era. However, the effect of steroids provided in large doses at least several hours prior to exposure to

the extracorporeal circuit has been shown to reduce the expression of inflammatory mediators, and anecdotal experience by several experts suggests that they remain an important consideration for neonatal and infant CPB.

Ultrafiltration and Leukocyte Reduction

Leukocyte filtration during CPB was initially tested in animals in the early 1990s and subsequently used in humans undergoing cardiac surgery [43]. Ultrafiltration can be broadly classified into two types: conventional ultrafiltration, which is carried out during the entire period of CPB (whether dilutional in which volume is added to the CPB circuit to permit greater levels of ultrafiltration, or otherwise), and modified ultrafiltration (MUF), which is conducted at the termination of CPB. Ultrafiltration of a blood prime prior to the institution of CPB (pre-bypass ultrafiltration, or BUF) is commonly performed at many centers as well. Whether performed in combination or alone, these ultrafiltration methods have been found to lower postoperative morbidity following pediatric CPB [44–48]. In particular, ultrafiltration lowers serum levels of pro-inflammatory cytokines, reduces the rise in total body and lung water following CPB in pediatric patients, and shortens the duration of mechanical ventilation relative to unfiltered control CPB [22]. However, the optimum ultrafiltration method is still debated for several reasons: (1) there is wide variation in the performance of ultrafiltration (type, endpoints, volume of ultrafiltrate); (2) patient characteristics (age, diagnosis, cyanotic or acyanotic lesions) and procedural characteristics (use of deep hypothermic circulatory arrest, temperature, myocardial protection, operative time) are heterogeneous; (3) easily measureable parameters such as cytokines have not consistently translated into linear improvements in durable clinical outcomes; (4) ischemia-reperfusion injury can be mediated initially by other effector cells, and thus occur independent of neutrophil participation [18, 20, 32]; and (5) the removal of certain anti-inflammatory cytokines, such as interleukin-10, may actually produce deleterious effects [18, 22, 49]. Furthermore, each method has unique benefits and drawbacks which complicate decision-making. MUF produces greater levels of hemoconcentration but requires additional exposure to the extracorporeal circuit. In contrast, conventional ultrafiltration does not lengthen the duration of CPB but can only moderately hemoconcentrate [50, 51]. A recent randomized trial of 60 infants undergoing biventricular repair by Williams et al. [22] reported no difference in clinical outcomes among infants receiving either MUF, dilutional conventional ultrafiltration, or both methods. Two recent reviews of ultrafiltration following cardiac surgery concluded that the results of published studies are conflicting and further investigations are necessary to delineate the best method in pediatric patients [22, 33, 50]. Not surprisingly, greater volumes of ultrafiltrate (greater than 104 ml/kg in neonates) appear to improve efficacy, and accordingly, the adequacy of ultrafiltration strategies should be assessed based on a meaningful increase in both hematocrit and arterial blood pressure [51–53]. Some studies may have demonstrated a negative or inconsequential effect of MUF simply because the MUF was not adequately performed.

Biocompatible Coated Circuitry

Heparin-coated circuits and more recently poly-2-methoxyethyl-acrylate (PMEA) coating may attenuate inflammation following infant CPB. Jensen and colleagues showed that the use of a heparin-coated perfusion system reduced fibrinolytic activity following bypass in a prospective randomized trial of 40 children [54]. A similar reduction in C-reactive protein and complement levels with PMEA-coated circuitry was demonstrated by Ueyama et al [55]. in a prospective randomized study comparing heparin-coated, PMEA-coated, and conventional circuits.

Despite the use of these strategies, organ dysfunction remains a significant problem in infants after the use of hypothermic low-flow CPB or deep hypothermic circulatory arrest [16, 30, 31].

Modification of Perfusion Temperature

Hypothermia has been widely used to provide end-organ protection during periods of ischemia [56–58]. The main rationale for body cooling is to reduce metabolic rate sufficiently to allow greater matching between oxygen consumption and delivery. Early studies in pediatric patients demonstrated a systemic anti-inflammatory benefit with lower perfusion temperatures, though salutary effects were been elucidated in the brain parenchyma, where increased white cell activation within the cerebral microcirculation, both histologically and in serum, correlated in linear fashion with increased CPB temperature [56, 59]. Based on studies in adult patients undergoing coronary artery bypass graft operations that demonstrated improved neurologic and myocardial function with normothermic CPB, however, attention was refocused on investigation of the impact of perfusion temperature [18, 56]. Several recent studies have reported either small improvements in measured outcomes [18] or no impact of perfusion temperature on outcomes following pediatric CPB [56, 60]. Caputo and colleagues [18] performed a randomized trial of 59 children undergoing correction of simple congenital heart disease into either a hypothermic (28 °C) strategy or a normothermic strategy (37 °C). Though inflammatory mediators increased in both groups, normothermic CPB produced less myocardial oxidative stress, as measured by troponin I and 8-isoprostane release, compared to hypothermic CPB. Unfortunately, the reduced levels of apparent myocardial injury in this study did not translate into measureable clinical benefits. Stocker and colleagues [56] similarly found that systemic cooling to moderate hypothermia (24 °C) produced no benefit in either short-term clinical outcomes (duration of mechanical ventilation, ICU or hospital length of stay) or serum markers of acute inflammation.

Miniaturized Circuitry and a Bloodless Prime

The deleterious effects of allogeneic blood transfusions are well characterized and include transmission of blood-borne diseases, immunomodulation in cancer patients, and the risk of alloimmunization precluding organ transplantation [20, 21, 32, 61, 62]. Recently, though, the potent pro-inflammatory effects of blood usage have been elucidated [20, 21, 32, 61–63]. Silliman and colleagues have shown that blood transfusion is a major risk factor for postinjury multiorgan system failure, especially in certain susceptible patients, including trauma patients, infants, and those exposed to cardiopulmonary bypass [64, 65]. Silliman et al [65]. have also shown that the risk of transfusion related morbidity is highly correlated with the duration of blood storage.

The neutrophil has been implicated as a primary effector cell in the pathogenesis of transfusion-mediated hyperinflammation [63–67]. The plasma from stored red blood cells directly primes PMNs for cytotoxicity, prompting the release of lytic enzymes (sPLA2, superoxide (O_2-), and elastase) [32, 63–67]. Additionally, recent studies have documented delayed apoptosis of neutrophils in patients receiving blood transfusions [47, 68–71]. Unfavorable sequelae may be further magnified by current treatment paradigms used in congenital heart surgery. Fresh whole blood, often used in the conduct of infant CPB, was associated with increased fluid overload and longer ICU length of stay in a recent randomized study of 200 pediatric patients [72]. In addition, the general reticence to accept a hematocrit <30 % despite evidence that a hematocrit of 25 % is adequate leads to unnecessary transfusion [20, 21, 32].

In addition to the contribution of homologous blood products, inflammation has also been associated with the use of large prime volumes and circuit surface area in animal models [20, 21, 32, 73–75]. Wabeke and colleagues [74] employed vacuum-assisted venous drainage in a rabbit model of CPB and showed that the use of a smaller prime (90 vs. 330 ml) normalized resistance in the peripheral microcirculation. Hanley's group [75] also showed improved

placental hemodynamics and decreased C3a and lactoferrin levels with the use of a miniaturized bypass circuit in an ovine fetal model.

Although small feasibility studies in neonatal piglets have shown that avoidance of blood can be achieved in infant CPB by a sufficient reduction in circuit size [20, 21, 32], few clinical studies have been reported. Fukumura and colleagues [76] used a low-volume prime in conjunction with dilutional ultrafiltration in 19 neonates with transposition of the great arteries undergoing arterial switch operation. The miniaturized circuit reduced postoperative water gain, improved systolic blood pressure, and reduced ventilatory time. Koster and colleagues [77] used a miniaturized circuit of 110 ml for repair of congenital heart defects in 13 consecutive neonates (weight 1.7–4.1 kg), demonstrating that their circuit allowed asanguineous priming in 6 patients. Reduction in inflammatory mediators was similarly shown by Fromes et al [78]. who incorporated biocompatible components into a minimal extracorporeal circuit in adult patients.

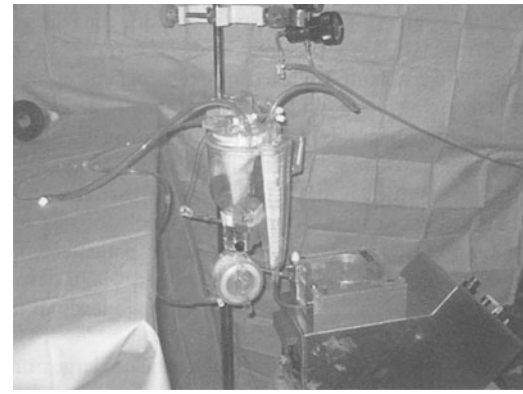

Fig. 44.2 Photograph of the miniaturized cardiopulmonary bypass circuit. A single-roller pump head is stationed immediately adjacent to the operating table to minimize tubing lengths. To improve venous drainage, an additional roller head (out of picture) is used in conjunction with the pictured regulator to provide vacuum-assisted drainage at -20 mmHg. A left ventricular vent drains into the reservoir to prevent left ventricular distension in the presence of aortic insufficiency, sometimes experiences when using the low-flow strategy. The oxygenator has a prime volume of 47 ml, the smallest commercially available. For an asanguineous prime, heparin, sodium bicarbonate, fentanyl, and albumin to a total volume of 50 ml are used to prime the oxygenator only. Immediately on cannulation the circuit and reservoir are retrograde primed and bypass initiated

Reducing Systemic Inflammation with a Miniaturized Circuit

This author's group developed a miniaturized circuit with a total priming volume of 109 ml to determine whether reduction in circuit size and avoidance of blood reduces inflammation following hypothermic low-flow CPB in a neonatal piglet model [20, 21, 32]. The circuit devised for this experiment consisted of a reconfigured pump console that was placed immediately adjacent to the experimental subject, a Polystan infant oxygenator requiring a 52 cc prime, and 3/16' tubing throughout (Fig. 44.2). Vacuum-assisted venous drainage was employed to augment venous return, and there was no arterial filter. Sixteen neonatal piglets (3–5 kg) were divided into three groups based upon the prime constituents: group 1 ($n = 5$) underwent CPB using a conventional circuit (175 ml) primed with fresh blood, group 2 ($n = 5$) underwent CPB using a conventional circuit (175 ml) primed with blood harvested 6 days prior to use, and group 3 ($n = 6$) underwent CPB using a miniaturized circuit (109 ml) to achieve an asanguineous prime. The blood was harvested from donor swine using sterile technique and stored in CPD bags at 4 °C. The piglets were placed on CPB (100 ml/kg/min), cooled to 18 °C and then underwent continuous CPB (50 cc/kg/min) for 30 min. The piglets were then rewarmed to normothermia and weaned from CPB. Serum TNF-α and right ventricular and pulmonary function parameters were measured before and after CPB. Neutrophil priming activity in the fresh and aged donor blood was also assessed.

The results are summarized in Table 44.1. In addition, TNF-α was lower in the miniaturized circuit group (group III) (1465 ± 397 pg/ml) than in the groups receiving blood (3940 ± 77 pg/ml), $P = 0.004$. Neutrophil priming activity, measured by superoxide production, was significantly

Table 44.1 Post-cardiopulmonary bypass (CPB) parameters ($n = 16$). Group I animals received a conventional circuit primed with fresh blood. Group II received a conventional circuit primed with stored blood. Group III animals received a miniaturized circuit and crystalloid prime

Post-CPB Parameters: ** = $P < 0.05$							
	% Increase body weight	% Decrease in Cdyn	RV cardiac index (ml^2 min-1 kg-1)	RV work index ($mmHg^2$mlmin-1 kg-1)	% Increase lung weight	Base deficit (mmol/L)	PVRI ($dynes^2$ml-1 min-1 kg-1)
Group I	7.48±1.3	38.1±4.3	18.8±4.8	421±107.6	84.6±0.6	−1.6±1.2	1168.5±408.5
Group II	9.7±1.9	42.2±4.9	21.5±6.2	511.4±147.9	83.4±0.5	−8.2±2.9	1610.4±485.5
Group III	4.4±0.6**	18.0±5.7**	81.2±11.4**	1355.8±241.8**	81.1±0.6**	−1.3±1.0**	214.4±63.4**

Cdyn dynamic pulmonary compliance, *RV* right ventricular, *PVRI* pulmonary vascular resistance index
**Denotes $P < 0.05$ by repeated measures analysis of variance

higher in aged blood (3.71 ±.55 nmol/min) than in fresh blood (1.89 ± 0.15 nmol/min), $P = 0.02$.

In summary, in a neonatal swine model, the use of a miniaturized circuit and an asanguineous prime reduced TNF-α, improved right ventricular and pulmonary function, and reduced fluid sequestration. Our findings may be partly explained by increased neutrophil priming activity, which is related to the duration of blood storage.

Conclusions

CPB in pediatric patients incites a robust systemic inflammatory response, which contributes to important postoperative morbidity following repair of congenital heart defects. The inflammatory response is a multifactorial and complex cascade that begins with activation of vascular endothelium in response to contact of blood elements with foreign surfaces. The cascade is initiated primarily by neutrophils and involves both the complement and coagulation cascades. End-organ function is impacted in an unpredictable manner, but certain patient subsets (cyanotic lesions) and organs (brain, myocardium) appear to be at increased risk. Strategies to reduce the post-CPB inflammatory response are numerous and include pharmacologic, mechanical, and physiologic manipulation instituted during all phases of perioperative care.

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