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Review Article

Cardiopulmonary Bypass induced Fever and Systemic inflammatory response syndrome in Paediatric patients: Management Strategy

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Abstract

Cardiopulmonary bypass is considered to be the common culprit for the occurrence of fever in the immediate post-operative period i.e, within 24 hours in pediatric patients. Other common causes contributing to fever are anaesthetic drugs, blood transfusions & pain. This early fever usually manifests as tachy-arrthymias in recovery room requiring interventions. This review intends to know the pathophysiology of fever and systemic inflammatory response syndrome after bypass (SIRAB) onset, preventive aspects and better management of the fever in the post-operative period.

Keywords: Fever, SIRAB, CPB

1. Introduction

The therapeutic role of hypothermia in cardiac surgeries is known since decades. Bigelow, Lewis and Gibbon realized the limitations of therapeutic role of hypothermia and inflow occlusion alone in early 1950s. Further in 1954, Lillehei tried the technique of controlled cross circulation, where the lungs of parents functioned as the extracorporeal oxygenator. The evolution of extracorporeal perfusion circuits have come a long way: from monkey lungs, film and bubble oxygenators, to modern miniature membrane oxygenators with centrifugal pumps, vacuum-assisted venous drainage and in-line gas monitoring. Development of mechanical cardiopulmonary bypass circuits in the late 1950s began the era of advanced congenital cardiac surgery[1-3]. Cardiopulmonary bypass circuits set profound systemic inflammatory response leading to elevated body temperature[4,5]. Studies have shown the growing evidence against elevated temperatures in both animals and humans [6,7]. Potential complications can be avoided by understanding the principles of temperature management.

1.1 Physiology of Hypothermia

Humans have very effective temperature regulating homeostatic mechanisms, which maintains the body temperature near 37°C regardless of variations in environmental temperatures. Thermoreceptors in the skin on exposure to cold activate the hypothalamus to discharge a strong sympathetic nervous system response, resulting in vasoconstriction of skin vessels, thereby reducing convective heat loss. This simultaneously leads to vasodilatation of the skeletal muscle vascular beds, enhancing muscular activity which produces heat by tensing and involuntary contractions. The endocrine hormones, oxygen consumption, heart rate, cardiac output, and blood pressure are all exaggerated. Complexity of the above said interactions makes it difficult to understand the physiological response in pediatric patients [8].

1.2 Pathophysiology of Fever

Fever is defined as an increase in body temperature with functioning thermoregulatory mechanisms acting to produce and sustain an elevated body temperature or setpoint[9]. Different groups of cytokines set fever onset in response to exogenous pyrogenic substances such as CPB circuits & micro emboli. The principal mediators of fever are interleukin-1, tumor necrosis factor and interleukin-6. Cytokines interact with receptors in the preoptic anterior hypothalamic thermoregulatory area, causing synthesis and release of prostaglandins, chiefly prostaglandin E_2 which raise the body temperature by initiating local cyclic adenosine monophosphate production, resetting the thermoregulatory set point of the hypothalamus, and by coordination of other adaptive responses such as shivering and peripheral vasoconstriction[10,11]. Fever results from a new set point of body temperature and is not related with alterations of either thermo sensory or thermoeffector mechanisms; attempts to reduce body temperature by simple external cooling are resisted physiologically and can be distressing to the patient [9].

1.3 The Rationale for and Practice of Systemic Hypothermia for Cardiac Surgery [12]

	Possible mechanisms underlying protective effects of hypothermia
1	Prevention of apoptosis
2	Reduced mitochondrial dysfunction,improved energy homeostasis*
3	Reduction of excessive free radical Production*
4	Mitigation of reperfusion injury*
5	Reduced permeability of the blood–brain barrier and the vascular wall; reduced edema formation
6	Reduced permeability of cellular membranes (including membranes of the cell nucleus)*
7	Improved ion homeostasis
8	Reduction of metabolism
9	Depression of the immune response and various potentially harmful pro inflammatory reactions
10	Reduction in cerebral thermopooling
11	Anticoagulant effects
12	Suppression of epileptic activity and Seizures

* Animal studies only.

1.4 Cardiopulmonary bypass machine settings of Pediatric patients[13]

Parameters	Settings
Estimated blood volume	<10 kg:85 ml/kg (285 ml for 3kg)
Dilution effects on blood volume	100-200%
Addition of whole blood or packed red blood cells to prime	Usually
Oxygen consumption	6-8 ml/kg/min
Full CPB flow at 370C	150-200 ml/kg/min for <3 kg
Minimum CPB temperature	Commonly 15-200C
Use of total circulatory arrest or regional low flow perfusion	Common
Perfusion pressure	20-50 mmHg
Acid-base management	Alpha-stat and/or pH-stat
Measured PaCO2	20-80 mmHg
Glucose regulation: hypoglycemia, hyperglycemia	Common; reduced stores Less common; risk for rebound hypoglycemia

1.5 Initiation of Systemic Inflammatory Response after Bypass

SIRAB is initiated by both cellular and noncellular (humoral) elements of blood. As a result there is generation of microemboli, disruption of hemostasis, and generalized whole-body inflammatory response. This sets a sequence of cytokine-mediated events activating vascular endothelium with further neutrophil-mediated inflammatory injury. Contact of blood with the foreign surface of the extracorporeal circuit sets the damaging effects of CPB. Other aggravating factors include altered arterial blood flow patterns, shear stress generated by blood pumps, cardiotomy suction devices, tissue ischemia and reperfusion, hypothermia, relative anemia, and the anticoagulation agents[14]. This continued response in post-operative period can manifest as a wide range of adverse clinical outcomes [5], depending on the intensity of the inflammatory response[12]. The adverse sequel of SIRAB account for significant morbidity in pediatric surgery, in the aged or moribund, and in patients undergoing long, complex surgical procedures[15,16].

2. Management of fever

Early post-operative fever <24hrs (Absence of Pneumonia & Endocarditis)



CPB , Surgical trauma , Blood tranfusion, drug related and altered thermoregulatory mechanisms



Symptomatic treatment
1. Tepid Sponging
2. Antipyretics
3. Cold Saline with gastric lavage
4. Cortiosteroids

3. Management of SIRAB

Complement pathway is complex and an agent yet to be found which can completely inhibit complement system after bypass. Some of agents which are commonly used to attenuate SIRAB include corticosteroids, aprotinin, monoclonal antibodies and cyclooxgenase inhibitors.

4. Pharmacologic approach

4.1 Corticosteroids

Steroids work by the virtue of their anti-inflammatory properties and influence the water/electrolyte balance and the metabolism of carbohydrate, protein, and lipid. Corticosteroids also inhibit leukocyte recruitment, formation of the enzyme required for converting plasminogen into plasmin, and phospholipase A2, thereby decreasing the formation of proinflammatory leukotrienes and prostaglandins [17]. Though corticosteroids alter the inflammatory process associated with CPB when given as large bolus or short course but offer no clinical benefit as per trials. Steroids fail to prevent decrease in the postoperative pulmonary compliance and may delay early extubation; in addition, they enhance the susceptibility to infection by promoting an immunocompromised state[18,19].

4.2 Aprotinin

It is a polypeptide isolated from bovine lung that is a broadly reactive serine protease inhibitor with antifibrinolytic and platelet-sparing activity. It inhibits activation of the kallikrein and complement pathways, albeit at fairly high plasma concentrations, also may decrease generation of fibrin degradation products, which are proinflammatory. Recently it has gained the established role in terms of limiting the systemic inflammatory response to CPB in both infants and adults [20-23]. Oxygenation index and duration of mechanical ventilation also were improved by aprotinin in one recent study [24]. Though there are no established contraindications to aprotinin use in neonates & infants, concern remains regarding the potential to favor clot formation, especially in low-flow or DHCA circumstances and certain surgical situations (e.g., low-flow pathways such as Glenn and Fontan connections, Fontan fenestrations, and coronary anastomoses).

4.3 Neutrophil Activation Remodeling

Leukocytes play a major role in the inflammatory response post CPB, the prevention of their activation would help in preventing many problems associated with CPB. Several techniques currently using monoclonal antibodies are used to block the neutrophil recruitement [25,26]. Studies in their earlier stages have shown promising results in remodeling the inflammatory process by using gene based therapies to modulate or attenuate SIRAB[27].

5. Mechanical approach

5.1 Modified Ultrafiltration

Acts by reversing hemodilution, decreases tissue edema and circulating inflammatory mediators, leading to early recovery. Leukocyte-depleting filters reduce circulating leukocytes, an another effective way to modify the inflammatory process[28].

5.2 Modified circuits

Per-operative pulsatile perfusion has shown improved clinical outcome with respect to hemodynamics, microcirculation and organ dysfunction, compared with nonpulsatile flow[29]. Membrane oxygenator provide better oxygenation and produces less hemolysis and reduces microembolisation when compared with bubble oxygenators[30,31]. Other efforts to attenuate the SIRS include heparin & poly-2-methoxyethylacrylate (PMEA) coating of CPB apparatus. Surface-modifying additives (SMA) technology is another alternative surface coating (family of polysiloxane-containing copolymers) which can be either blended with base polymer resins before processing or coated to blood-contacting surfaces, are in their initial stages of studies[32-40].

6. Conclusion

The most susceptible population to the effect of SIRAB are infants and children. SIRAB is associated with increased morbidity and mortality. CPB is an unavoidable option at present. Ideal CPB circuit yet to be developed to provide utmost care to the pediatric patients with acceptable clinical outcomes. Combined strategy including pharmacological and mechanical manipulation might help in preventing the pediatric patients from the adverse events. Also CPB induced inflammatory response in the form of fever is to be distinguished from post-operative sepsis in this susceptible population by subjecting them to clinical scrutiny.

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