Effects of anesthetic choice on inflammatory response in cardiac surgery

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Cardiac surgery is associated with the development of a systemic inflammatory response. The cytokine response in cardiac surgery patients is well explained and is dominated by the pro-inflammatory cytokines tumour necrosis factor (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), and the anti-inflammatory cytokine interleukin-10 (IL-10). The release of these cytokines has been related to the development of complications after cardiopulmonary bypass (CPB). In addition to many factors, choice of anesthetic agents affects immune response in cardiac surgery. This article summarizes recently published literature concerning inflammatory cytokines associated with cardiopulmonary bypass, use of anesthetic management techniques and their effects on inflammatory response in cardiac surgery.

Keywords: anesthesia; cardiac surgery; inflammation

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Introduction

Cardiopulmonary bypass (CPB) conduces to the release of antiinflammatory cytokines that intervene the inflammatory response observed during and after open heart surgery [1].

CPB may especially activate the inflammatory response over at least three different mechanisms. One mechanism includes direct “contact activation” of the immune system following exposure of blood to the foreign surfaces of the CPB circuit. A second mechanism involves ischemia-reperfusion injury to vital organs as a result of aortic cross-clamping. There is a changing in perfusion of a lot of organs such as intestines, kidneys, brain, and myocardium resulting in cellular ischaemia before and after the initiation of CPB. The third mechanism involves systemic endotoxemia resulting from gut translocation of endotoxin across a damaged mucosal barrier compromised following splanchnic hypoperfusion. Endotoxemia may indirectly activate the inflammatory cascade [2, 3].

Actuation of the complement cascade occurs and secretion of interleukin 6 (IL-6), interleukin 8 (IL-8) and tumour necrosis factor (TNF-α) also begins [4]. Due to the inflammatory cascades, severe amplification begins to produce multi-organ system dysfunction such as coagulopathy, respiratory failure, myocardial dysfunction, renal insufficiency, and neurocognitive defects [5].
Although the nature of peroperative cytokine response seems to be specially identified by direct surgical trauma, anesthesia regiments may perform a modifying effect [6,7]. Anesthetic regiments for cardiac surgery have developed over the years, range from primarily volatile inhalation anesthesia to high dose opioid, total intravenous anesthesia. In recent years total intravenous anesthesia with short acting agents and a combination of volatile agents with intravenous anesthesia has become most popular [8].

**Cytokines associated with CPB**

Cytokines are a wide and swiftly growing group of polypeptides manufactured by several diverse cell types and necessary for optimum function of the immune system [9]. TNF-α, IL-6, IL-8, and interleukin-1β (IL-1β) are the major pro-inflammatory cytokines response to cardiac surgery [2, 9, 10]. The proinflammatory cytokine response is balanced by a phased antiinflammatory cytokine response with soluble cytokine receptors, cytokine receptor antagonists, and antiinflammatory cytokines. The prime antiinflammatory cytokines are interleukin-10 (IL-10), interleukin-1 receptor antagonist (IL-1ra), and TNF soluble receptors 1 and 2 (TNFsr 1 and 2) [2].

TNF-α is made by activated monocytes and mononuclear phagocytes, and it has a significant role in inflammation [11]. Plasma levels of TNF-α increase with CPB [12] and increase faster than other cytokines, showing its role as a pioneer in the inflammatory response. It has a big role in rised microvascular permeability [13] and is liable for the post CPB weight gain, worse respiratory index and prolonged hospital stay [14]. TNF-α can engender hypotension, coagulopathy and renal dysfunction and its increased levels are closed with systemic inflammatory response syndrome/multiple organ dysfunction syndrome (SIRS/MODS) [15].

IL-6 is a proinflammatory cytokine and is one of the prime mediators in the acute phase response causing a host of organ involvement, chiefly including the respiratory system and the central nervous system [3]. It is the major predictor within the pro-inflammatory cytokines of LV systolic dysfunction, myocardial ischemic episodes, reduction in systemic vascular resistance, need for vasopressor support, and cardiovascular abnormalities and associated with mortality rates in inflammatory states like sepsis [16, 17]. High levels of IL-6 are also significantly associated with hepatic and renal dysfunction [18].

IL-8 is a proinflammatory cytokine, and its level increases in cardiac surgeries with CPB. Elevated IL-8 levels associated with respiratory dysfunction, length of inotropic support and were inversely related to the ratio of PaO2 to FiO2 [19].

IL-10 is a powerful anti-inflammatory cytokine made by monocytes and macrophages that inhibits production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-8 and IL-1β [20] and also provides protection from ischaemia and reperfusion (I/R) injury [21].

**High dose opioid anesthesia**

Since the 1980s, high-dose opioid methods have been used in cardiac anesthesia due to their good circulatory stability and stress reduction characteristics [22]. However pure high-dose opioid anesthesia (e.g., fentanyl, 50-100 mcg/kg, or sufentanil, 15-25 mcg/kg) performs longer postoperative respiratory depression (12-24 h) and is associated with an unacceptably high incidence of patient awareness during surgery. Also muscle rigidity during induction and prolonged postoperative ileus are undesired effects of this regimen. Moreover, simultaneous administration of benzodiazepines with large doses of opioids can produce hypotension with myocardial depression. When short acting agents, such as sufentanil or remifentanil are used instead of fentanyl, patients generally regain consciousness and can be extubated earlier [8].

Opioids have many effects on the immune system, intervened indirectly over the central nervous system or through direct interactions with the cellular immune system [23, 24]. Fentanyl increases concentrations of IL-1ra in *in vitro* monocyte cultures [25].

Guggenberger and colleagues [26] compared the effects of remifentanil with sufentanil on pulmonary function and showed remifentanil anaesthesia was better in improving pulmonary function in CABG patients. Brix-Christensen et al [27] showed that a high or low dose opioid has similar effects on the perioperative cytokine response to cardiac surgery.

**Total intravenous anesthesia (TIVA)**

The drive for cost containment in cardiac surgery was a major impetus for development of anesthesia techniques with short acting agents. This method utilizes induction with propofol (0.5-1.5mg/kg followed by 25-100 mcg/kg) and small doses of fentanyl (total doses of 5-7 mcg/kg) or remifentanil (1 mcg/kg bolus followed by 0.25-1 mcg/kg/min) [8].

Propofol may boost the antiinflammatory response to surgery by several mechanisms. Propofol may maintain hepatoplaschning blood flow during CPB [28]. It not only changes the balance between proinflammatory and antiinflammatory cytokines, increasing production of the antiinflammatory cytokine IL-10 and IL-1ra [29] while decreasing neutrophil IL-8 [30] secretion, and also cleans reactive oxygen species either [31]. And also propofol with low doses decrease neutrophil uptake in the coronary circulation following myocardial ischemia and reperfusion.
Propofol reduces free-radical-mediated lipid peroxidation and systemic inflammation in patients with impaired myocardial function undergoing CABG [33].

Several studies have investigated the effects of different anaesthetic managements on the immune response during and after cardiac surgery, and have suggested that propofol may have beneficial effects on post-traumatic immune changes [34]. In addition, it has been showed that propofol may alleviate the cytokine response observed during septic shock in rodents [35]. El Azab and colleagues compared the effects of three different anaesthesia regimens on the cytokine response during cardiac surgery [36]. They showed that the cytokine response was similar after volatile anaesthetics, propofol/sufentanil anaesthesia and midazolam/suffentanil anaesthesia [37].

A study comparing desflurane with propofol in patients undergoing off pump CABG surgery showed that postoperative troponin was lower and hemodynamic function was better in patients receiving desflurane [36]. In contrast, a small study that administered high-dose propofol (120 mcg/kg/min), low-dose propofol (60 mcg/kg/min) while on pump or titrated isoflurane throughout surgery improved troponin levels and gave better hemodynamic function in the large-dose propofol group compared to the isoflurane or low-dose propofol group [37]. Baki et al studied the effect of propofol versus desflurane anesthesia on systemic immune modulation and the central nervous system in cardiac surgery patients with CPB. They showed that the immune reaction was less in patients exposed to desflurane anesthesia when compared to propofol anesthesia, as indicated by lower plasma concentrations of IL-8 and IL-6.

Mixed intravenous/Inhalation anesthesia

Renewed interest in volatile agents came about following studies demonstrating the protective effects of volatile agents on ischemic myocardium and an increased emphasis on fast track recovery of cardiac patients. Propofol (0.5-1.5 mg/kg) or etomidate (0.1-0.3 mg/kg) is often used for anesthesia induction. Opioids are given in small doses together with a volatile agent with 0.5-1.5 minimum alveolar concentration (MAC) for maintenance anesthesia. The opioid may be given in small intermittent boluses, by continuous infusion, or both [8]. The most commonly used volatile anaesthetics are isoflurane, sevoflurane and desflurane. Nitrous oxide is generally not used during the time interval between cannulation and decannulation because of its tendency to expand any intravascular air bubbles that may form [8]. Sevoflurane, isoflurane, and enflurane reduce IL-1β, TNF-α release by human peripheral mononuclear cells in vitro [38]. Isoflurane decreases alveolar macrophage phagocytosis and microbicidal function more than propofol [39]. Halothane, isoflurane, and enflurane minimize free radical-mediated myocardial injury [40, 41].

Winterhalter et al compared the effects of continuous infusion of remifentanil with intermittent fentanyl on the endocrine stress response and inflammatory activation during CABG surgery [22]. They used propofol for induction and also maintenance with sevoflurane in their study. They showed that remifentanyl group patients were extubated earlier than the fentanyl patients in their study. Stress hormones (ADH, ACTH, cortisol) and interleukins (TNF-α, IL-6, IL-8) were higher in the fentanyl group compared to the remifentanyl group.

Other techniques

Patients with hemodynamic instability the combination of ketamine with midazolam is a useful technique for induction and maintenance of anesthesia.

Midazolam has little effect on host defense mechanisms and decreases neutrophil IL-8 secretion in response to lipopolysaccaride [30]. Midazolam decreases postsischemic uptake of neutrophils in the coronary circulation following myocardial ischemia and reperfusion [32].

Ketamine decreases the increased levels of IL-6 concentrations during and following CPB [42] and decreases coronary uptake of neutrophils following myocardial ischemia and reperfusion [32]. High concentrations of ketamine affects E.Coli clearance and neutrophil and monocyte phagocytosis in vitro [43]. Ketamine in subanaesthetic doses was shown to have beneficial effects on the immune response during and after surgery [44, 45, 46]. Welters et al [10] investigated the plasma levels of inflammatory markers with an anaesthetic regimen based on ketamine as the sole analgesic. They showed that anaesthesia with ketamine may have beneficial effects in attenuating the CPB-induced systemic inflammatory response.

Conclusions

Cardiac surgery evokes a generalized inflammatory response in all patients, with serious clinical consequences [2]. A better understanding of the inflammatory response to cardiac surgery may be the key to development of successful strategies in pharmacology, perfusion technology, cardiovascular monitoring, and anesthetic and surgical technique in order to minimize patient morbidity.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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