Endotoxin release in cardiac surgery with cardiopulmonary bypass: pathophysiology and possible therapeutic strategies. An update

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Summary

Cardiac surgery with cardiopulmonary bypass provokes a systemic inflammatory response syndrome caused by the surgical trauma itself, blood contact with the non-physiological surfaces of the extracorporeal circuit, endotoxemia, and ischemia. The role of endotoxin in the inflammatory response syndrome has been well investigated. In this report, we reviewed recent advances in the understanding of the pathophysiology of the endotoxin release during cardiopulmonary bypass and the possible therapeutic strategies aimed to reduce the endotoxin release or to counteract the inflammatory effects of endotoxin. Although many different strategies to detoxify endotoxins were evaluated, none of them were able to show statistically significant differences in clinical outcome.

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1. Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) provokes a systemic inflammatory response syndrome caused by the surgical trauma itself, blood contact with the non-physiological surfaces of the extracorporeal circuit, endotoxemia, and ischemia. Thus, both material-dependent and material-independent factors contribute to the inflammatory response. This inflammatory reaction may contribute to the development of postoperative complications, including myocardial dysfunction, respiratory failure, renal and neurological dysfunction, bleeding disorders, altered liver function, and multi-organ failure [1]. Over the years, many different strategies, including new pharmacological agents, CPB circuits and components, and surgical techniques have been employed to minimize the inflammatory response post-CPB.

The role of endotoxin in the inflammatory response syndrome has been well investigated. The release of endotoxin first in the portal and later on in the systemic circulation initiates alternative complement pathway activation and has been shown to cause both direct myocardial dysfunction and pulmonary capillary damage [2]. This report will review recent advances in the understanding of the pathophysiology of the endotoxin release during CPB and the possible therapeutic strategies aimed to reduce the endotoxin release, or its effects.

2. Endotoxin

2.1. Endotoxin structure and activity

Bacteria are surrounded by a cell wall that guarantees the shape and the integrity of the microbial body. In Gram-negative bacteria, this envelope represents the outer membrane, in which lipopolysaccharides or endotoxins are the main constituents and essential for bacterial growth and viability [3]. An endotoxin molecule consists of four different parts: a lipid-A moiety, an inner core, an outer core, and an O-antigen. The lipid-A moiety of the endotoxin molecule is composed of two phosphorylated glucosamine saccharides. The two phosphate groups attached to the saccharides are essential for the toxic activity of lipid A (Fig. 1). Lipid A containing only one phosphate group, monophosphoryl lipid A (MPLA), is nontoxic and able to attenuate the lethal effects of endotoxins [4].

Endotoxin is produced by intestinal flora and is normally confined to the lumen of the intestine by a barrier of endothelial cells. When entering the circulation, endotoxins bind to the lipopolysaccharide-binding protein (LBP), which
interacts with various receptors, such as Toll-like receptor-4 (TLR-4) and leads to cytokine production [5] and thus to an inflammatory response.

2.2. Endotoxin and CPB

The release of endotoxins during CPB has been studied widely in the 1990s. The mechanism of endotoxin release in cardiac surgery is reported differently among different authors. Andersen et al. [6] report that the endotoxins registered during CPB are mainly derived from environmental endotoxins. In 10 patients undergoing elective coronary artery bypass grafting (CABG), endotoxin samples were taken from the arterial outlet of the oxygenator, the pulmonary artery, the cardiac suction lines, and the radial artery intra-operatively. Furthermore, fluid samples for endotoxin levels were taken from the cardioplegic fluid, the priming fluid, the blood transfusions, and the ice used for external cooling of the heart. They reported the presence of endotoxins in the priming fluid of the CPB circuit and in the cardioplegic solution. Other authors also reported contamination with endotoxins by the extracorporeal setup, infusion solutions, drugs, and surgical materials, such as instruments and gloves [7].

Rocke et al. [8] stated that, during CPB, hypoperfusion of the gut exists, which leads to increased intestinal permeability, allowing endotoxins to enter the portal circulation. In 1993, Ohri et al. [9] reported on increased gut permeability during CPB in 41 patients undergoing elective CABG, a valve operation, or both. They measured alterations in gastric mucosal blood flow using a laser Doppler probe placed on the mucosa of the body of the stomach in 10 patients. Furthermore, they did small intestinal saccharide studies to assess active carrier-mediated, passive carrier-mediated, transcellular, and paracellular transport, respectively. They found a markedly increased lactulose/L-rhamnose gut permeability ratio after CPB ($p = 0.018$). A 48.7% reduction in gastric mucosal Doppler was found 30 min after the institution of CPB ($p = 0.0001$). In 1994, the same group [10] reported on an animal study in 11 dogs where they did Doppler flow measurements, intramucosal pH by tonometry, and oxygen utilization in a model of hypothermic CPB. In that study, they confirmed their previous findings on decreased laser Doppler flow during CPB. They also demonstrated mucosal acidosis and villus tip ischemia as a sign of metabolic derangement. In 1996, Riddington et al. [11] studied intestinal hyperpermeability in 50 patients undergoing elective CABG or valve replacement. Patients received chromium 51-labeled ethylenediaminetetraacetic acid ($^{51}$Cr-EDTA) as a marker of intestinal permeability, a technique that had been validated in patients with inflammatory bowel disease [12]. They showed a large and varied increase in intestinal permeability to $^{51}$Cr-EDTA, which starts during CPB and is sustained for more than 24 h, postoperatively. In 1997, increased gut permeability during cardiac operations with the use of CPB was confirmed by Oudemans-van Straaten et al. [13,14] To determine whether intestinal permeability increases during cardiac operations and whether the amount of endotoxin release is related to this increased hyperpermeability, they measured in 23 patients undergoing elective CABG the urinary excretion of L-rhamnose and cellobiose, which was administered orally just before surgery and on the fifth postoperative day. They measured an increased level of cellobiose in urine during CPB and a significantly related increased level of endotoxin in the blood as a result of increased intestinal permeability ($p < 0.01$). This increase in cellobiose was also significantly related to hypovolemia and the use of ephedrine during CPB. Ephedrine possibly leads to decreased splanchnic blood flow due to vasoconstriction.

Normally, systemic endotoxins are cleared from the circulation by Kupffer cells of the liver. During CPB, however, Kupffer cell function can be suppressed by an overloading of the reticuloendothelial cells by cellular debris and aggregated proteins [15]. Moreover, during CPB, a down-regulation of surface monocyte lipopolysaccharide-receptor CD-14, identified as the main endotoxin receptor on leucocytes occurs, which might lead to an increase in circulating endotoxin [16].

During cardiac surgery with the use of CPB, pericardial pooled blood is returned to the CPB by cardiotomy suction catheters. In 18 patients undergoing elective CABG, Spanier et al. [17] investigated the levels of endotoxin in pericardial shed blood, which was pooled in the pericardial space for 45 min after placing of the aortic cross-clamp and then returned to the cardiotomy reservoir. Blood samples were taken from the pericardial shed blood and the arterial line at the same time, and before and after reinfusion of the
pericardial shed blood in the CPB circuit. They found a significantly higher amount of endotoxin in the pericardial shed blood as compared with the blood from the arterial line, both before and after reinfusion of the pericardial shed blood to the CPB circuit ($p < 0.05$).

Endotoxin levels can be measured by the Limulus amebocyte lysate (LAL) test described by Baek [18]. Different modifications of this test have been used in the various studies described in this review. Partly due to nonstandardized tests, different amounts of endotoxin are reported, which hampers comparison between study protocols. Jansen et al. [15] described three peaks in endotoxin levels during cardiac surgery. The endotoxin levels were higher after induction of anesthesia, immediately after the start of CPB and after release of the cross-clamp. Other authors also reported a peak level of endotoxin after release of the cross-clamp, during reperfusion [19]. During reperfusion, the flow through the splanchnic bed increases, leading to an extra washout of endotoxins.

Videm et al. [20] described differences in endotoxemia among various cardiac operations. In 136 (CABG $n = 79$, valve $n = 19$, CABG + valve $n = 30$, CABG + carotid artery surgery $n = 8$) patients, endotoxia levels were determined. The endotoxin concentrations in the isolated valve-replacement group were significantly lower than in any of the other three groups ($p < 0.05$). Using multivariate regression analysis, they demonstrated a significant correlation between the number of grafts and the amount of endotoxin measured. Furthermore, they did not find a difference in endotoxin concentrations between the patients, who developed complications and those who recovered uneventfully ($p = 0.62$). From these findings, Videm et al. concluded that there might be a correlation between the amount of atherosclerosis and the endotoxia level. In this study, CPB duration and aortic occlusion time were not significantly related to endotoxin levels. In contrast with Videm et al. [20], Rocke et al. demonstrated a strong correlation between the change in endotoxin levels and the duration of cross-clamping and also the CPB time [8]. In nine patients undergoing cardiac operations requiring a prolonged period of CPB (mitral valve replacement (MVR) combined with aortic valve replacement (AVR), MVR alone, MVR combined with tricuspid valve repair, or redo-CABG), endotoxin levels were determined. They found no correlation between the change in endotoxin concentration and intra-operative mean perfusion pressure, mean bypass flow rate, calculated systemic resistance, nasopharyngeal and rectal temperatures, and arterial blood gas status. However, a strong correlation between endotoxin concentrations and CPB time, and also aortic cross-clamping time ($p < 0.005$) was found.

In all the above-mentioned studies, probably due to small sample sizes, it has not been possible to find a correlation between endotoxin levels and postoperative morbidity.

### 3. Humoral factors in endotoxin detoxification

#### 3.1. Anti-inflammatory cytokines

As a potent trigger of inflammatory and immunological reactions, endotoxin activates humoral- and cellular mediator-producing systems, including cytokine generation. The appearance of cytokines follows a characteristic pattern beginning with tumor necrosis factor-alpha (TNF-$\alpha$) activity. The peak of TNF-$\alpha$ activity is followed by the appearance of other pro-inflammatory cytokines such as interleukin IL-6 and IL-8. Endotoxemia elicits systemic counter-regulatory mechanisms, ranging from neuroendocrine responses to cellular and soluble antagonists of pro-inflammatory activity [21]. Thus, the presence of endotoxins is identified by numerous receptors of innate immunity. Of these receptors, LBP, CD-14 and TLR-4 play a crucial role in the identification of endotoxins. LBP and CD-14 are recognizing and binding endotoxins, thus enhancing the activation of the immune system [22]. LBP is recognized as a typical acute-phase protein principally synthesized by hepatocytes, while CD-14 molecules are either produced de novo as acute-phase protein or are released into body fluids by shedding from cell surfaces. In 40 patients, Kudlova et al. [22] followed LBP and CD-14 levels in CABG surgery either with or without CPB. A significant increase of LBP concentration was found at the first postoperative day in both groups, reaching maximum levels at the third postoperative day. In the on-pump group, the maximum CD-14 level was reached the first postoperative day, while, in the off-pump group, the maximum CD-14 level was reached on the third postoperative day. Comparing CD-14 and LBP levels to known acute-phase proteins such as C-reactive protein and long pentraxin showed no evidence for CD-14 and LBP serving as one of the acute-phase proteins.

Grundmann et al. [23] investigated in 10 patients undergoing elective CABG the role of humoral factors for attenuation of the pro-inflammatory cytokine response to endotoxin stimulation during CPB. They found that during CPB a spontaneous production of anti-inflammatory cytokines such as IL-10 and IL-1 was induced, whereas only small amounts of the prototypical pro-inflammatory cytokines TNF-$\alpha$ and IL-1$\beta$ were measured. This anti-inflammatory plasma activity seemed to result partially from high circulating catecholamines and could contribute to the attenuation of the systemic inflammatory response to CPB.

Tolerance to endotoxin, with an important contribution of macrophages, has been defined in terms of reduced fever in experimental models after repeated injections of endotoxin. In vitro tolerance to endotoxin was described by Fitting et al. [24]. Tolerance to endotoxin was evidenced by a decreased capacity of different cells to respond to in vitro challenge with endotoxin. They found in mice injected intravenously with endotoxin that tolerance to endotoxin is compartmentalized and that bronchoalveolar cells are less likely than, for example, splenocytes and peritoneal cells to develop tolerance to endotoxin, which might be an explanation for the fact that the lungs are a major place of inflammation during infection.

#### 3.2. Anti-endotoxin antibodies (EndoCab)

From early fetal life, each individual has a certain amount of endogenous endotoxin immunity by maternal transfer during pregnancy. The amount of endotoxin immunity is enhanced by subsequent exposure to endotoxin [25]. Antibodies against the inner core region of endotoxins, respectively, immunoglobulin G (IgG) EndoCab and IgM
EndoCab, can be measured by an enzyme-linked immuno-sorbent assay (ELISA) [26]. Bennett-Guerrero et al. were the first to perform a large descriptive trial in 301 patients undergoing CABG and/or valvular heart surgery, evaluating the association between preoperative anti-endotoxin immune status and morbidity following cardiac surgery [27]. Major complications were defined as in-hospital death or length of hospital stay greater than 10 days. Lower serum IgM EndoCab independently predicted an increased risk of major complications ($p = 0.002$). By contrast, IgG EndoCab and total IgM levels did not predict outcome. Low preoperative IgM EndoCab may account for the significant proportion of the variability in outcome seen among patients with identical preoperative risk scores. Hamilton-Davies et al. [28] also demonstrated that low preoperative EndoCab levels were related to poor outcome in valve-replacement surgery. In an observational study among 59 consecutive patients undergoing cardiac valve replacement, they measured preoperative median IgG and IgM EndoCab levels as well as direct postoperative, and at 4 and 24 h postoperative levels. Of the 59 patients, 12 developed at least one complication. Of these 12, all had preoperative significantly lower IgM EndoCab levels as compared with the patients, who recovered uneventfully ($p < 0.025$). Mathew et al. [29] demonstrated in 460 patients undergoing elective CABG, an association between low preoperative EndoCab levels and increased cognitive dysfunction postoperatively, especially in patients over 60 years. Rothenburger et al. [30] investigated the relationship between IgG and IgM EndoCab levels and cytokine release and ventilation time in 100 patients undergoing elective CABG. They demonstrated significantly lower preoperative EndoCab levels in 15 patients, who needed prolonged ventilation ($p < 0.001$) with increased endotoxin and IL-8 levels direct postoperatively, and increased IL-6 levels 3 h postoperatively ($p < 0.001$). Moreover, Moretti et al. [31] demonstrated in 474 patients undergoing CABG that lower preoperative serum IgM EndoCab level is a significant predictor of long-term mortality, independent of other risk factors (hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.53–0.99; $p = 0.04$). Kaplan–Meier 5-year survival curves illustrated significantly lower survival for the group with low EndoCab levels. More recently, Down et al. [32] showed, in a retrospective study, different levels of EndoCab in different populations and different countries, reflecting genetic and environmental variability between patient groups.

4. Pharmacological strategies to reduce endotoxin-mediated inflammation

4.1. Corticosteroids

The influence of prophylactic corticosteroid infusion during CPB, on the inflammatory response and on the postoperative course, is controversial. Some authors have demonstrated that treatment of patients with a large dose of corticosteroids attenuates the CPB-induced systemic inflammatory reaction in patients undergoing cardiac surgery. Thus, corticosteroids can reduce the complement-mediated activation of neutrophils and inhibit the secretion of pro-inflammatory cytokines, including TNF$\alpha$ and IL-6 [33,34]. Bourbon et al. demonstrated that low dose methylprednisolone also reduces the inflammatory reaction after CPB, by inhibition of pro-inflammatory cytokines [35]. A total of 36 patients undergoing elective CABG were divided into three groups: a control group, a group receiving 5 mg kg$^{-1}$ methylprednisolone, and a group receiving 10 mg kg$^{-1}$ methylprednisolone just at the start of CPB. Plasma levels of IL-6 and TNF$\alpha$ were determined before, during, and after CPB as well as oxygen free radical (OFR) production. They found a significant increase in cytokine release and OFR after CPB. Cytokine release was significantly reduced with 5 mg kg$^{-1}$ methylprednisolone ($p < 0.05$). Moreover, OFR release was significantly reduced with a greater dose of methylprednisolone (10 mg kg$^{-1}$). However, Chaney et al. [36] investigated high-dose methylprednisolone in 30 patients undergoing elective CABG. They administered 30 mg kg$^{-1}$ methylprednisolone during sternotomy and 30 mg kg$^{-1}$ methylprednisolone during the initiation of CPB. They measured alveolar–arterial oxygen gradient, lung compliance, shunt, and dead space at four timepoints perioperatively. Postoperative tracheal extubation was performed at the earliest appropriate time. They found that high-dose methylprednisolone during CPB was associated with a significant increase in postoperative alveolar–arterial oxygen gradient and shunt and a prolonged time of tracheal intubation as compared with 30 patients in the control group receiving no methylprednisolone ($p = 0.05$). Karlstad et al. [37] investigated the influence of methylprednisolone on the endotoxin release during CPB. They measured endotoxin release in 13 patients undergoing CABG at different time points and randomized between methylprednisolone infusion (1 g per patient) at induction and no methylprednisolone. They found a significant rise in plasma endotoxin levels following the initiation of CPB and at removal of the aortic cross-clamp ($p < 0.05$), but they showed no differences in endotoxin release in the methylprednisolone-treated group as compared with the control group ($p = 0.68$). However, Wan et al. demonstrated that, in patients undergoing CABG, methylprednisolone might reduce the endotoxin release [38]. They randomized 20 patients undergoing elective CABG to receive either 30 mg kg$^{-1}$ methylprednisolone or matching placebo. They measured endotoxin levels in the superior vena cava and in the inferior vena cava at different time points. They found higher levels of endotoxin in the inferior vena cava as compared with the superior vena cava and a reduced level of endotoxin level in the inferior vena cava in the methylprednisolone-treated group ($p < 0.01$). In both studies, the small number of patients was a limiting factor.

4.2. Ketanserin

The role of ketanserin, an inhibitor of serotonin-induced vasoconstriction and a weak $\alpha_1$ sympathetic blocker, in the reduction of endotoxemia during CPB was investigated by Oudemans-van Straaten et al. [39] In 29 patients undergoing elective CABG, either 0.1 mg kg$^{-1}$ h$^{-1}$ ketanserin intravenously for 4 h, starting at the induction of anesthesia, or matching placebo, was administered. To limit the hypertensive effect of ketanserin, the dose was reduced to 0.05 mg kg$^{-1}$ h$^{-1}$ after 4 h. Circulating endotoxin was lower in patients treated with ketanserin ($p > 0.05$). They found
that ketanserin administration during cardiac surgery might reduce but not abolish the release of endotoxin. Ketanserin appeared to be more protective at the onset of CPB than at the end. The most plausible reason for this phenomenon might be vasoconstriction leading to improved splanchnic microcirculation.

4.3. Taurolidine

Taurolidine is a tauramide derivate. The active metabolite of taurolidine is taurine, which has been identified as a ‘balancing factor’ in the glutamate system to modulate and stabilize calcium homeostasis [40]. Doddakula et al. [41] reported on taurolidine, which was intravenously administered at the time of aortic clamping and at 12 and 24 h after unclamping. A total of 60 patients undergoing elective CABG were randomized in four different groups. Thirty patients received 250 ml 2% taurolidine intravenously, 15 with crystalloid cardioplegia, and 15 received blood cardioplegia. Thirty patients received matching placebo. Pro- and anti-inflammatory cytokines IL-6 and IL-10 were determined at several time points as well as the occurrence of arrhythmias, postoperatively. Administration of taurolidine in crystalloid cardioplegia patients resulted in a significant decrease in serum IL-6 and an increase in serum IL-10 at 24 h post-unclamping compared with placebo (p < 0.0001). In addition, in the blood cardioplegia group, there was a trend in decrease of IL-6 (p = 0.068). Further, postoperative arrhythmias were significantly reduced in the crystalloid cardioplegia with taurolidine group as compared with the placebo group (p < 0.003). In the blood cardioplegia with taurolidine group, there was no significant decrease in arrhythmias, although there was a trend towards a decrease (p = 0.583). In this study, clinical significance could not be demonstrated.

4.4. Selective digestive decontamination

Selective digestive decontamination (SDD) by pharyngeal and gastric application of nonabsorbable antibiotics aims to act against Gram-negative aerobic bacteria, while leaving indigenous anaerobic microflora intact. Although the role of SDD in standard intensive care unit (ICU) patients remains controversial, a recent study of de Smet et al. [42] showed that mortality rates in standard ICU patients were reduced by 3.5% when SDD was applied as compared with standard care (p = 0.02). The underlying theory for the use of SDD in cardiac surgery lies in the diminishing of the number of Gram-negative microorganisms in the gut, leading to less ischemia-associated translocation of these bacteria and thus leading to a reduction in endotoxin release. In 1993, Martinez-Pelus et al. [43] were the first to investigate the role of SDD in reduction of endotoxemia during CPB. In a multicenter study among 80 patients undergoing either CABG or valvular surgery, patients received oral nonabsorbable antibiotics every 6 h from admission until their surgery or did not receive this treatment. The antibiotics consisted of a mixture of amphotericin B, polymyxin E, and tobramycin in sterilized water. Assessment of decontamination was performed by rectal swabs along with the measurement of circulating endotoxins, TNFα, and IL-6. They found significantly lower values of endotoxin in the SDD-treated group (p = 0.01). Nonsignificant differences were found in TNFα levels. In fully decontaminated patients, IL-6 levels were significantly lower after reperfusion (p < 0.05). However, they found no differences in clinical outcome, defined as postoperative fever, length of stay, and in-hospital mortality, between the two groups. In contrast with these findings, Bouter et al. [44] found no reduction in perioperative endotoxemia and cytokine activation when SDD was used. A total of 44 patients undergoing cardiac surgery (CABG, valve, CABG + - valve, or other) were randomized to preoperative administration for 5–7 days of oral nonabsorbable antibiotics (polymyxin B and neomycin) or placebo. They also did rectal swabs and measurement of endotoxin and cytokines TNFα, IL-10, and IL-6. SDD significantly reduced the number of rectal swabs that grew aerobic Gram-negative bacteria (p < 0.001). SDD did not affect the occurrence of perioperative endotoxemia, nor did it reduce TNFα, IL-10, or IL-6 levels (p > 0.20). They also did not find any difference in clinical outcome, defined as length of stay and in-hospital mortality, when SDD was used.

The use of a laxant to clear the bowel from bacterial load was investigated by Taggart et al. [45]. In this study, 60 patients were divided into four groups: preoperative laxative with pulsatile, or nonpulsatile flow during CPB, or no laxative with pulsatile, or nonpulsatile flow during CPB. The laxative Picolax consisted of cathartic sodium picosulfate and an osmotic laxative, magnesium citrate. They found a gradual increase in endotoxin concentration during CPB as compared with baseline levels (p < 0.001), independently of the laxative used or different flow modes.

4.5. Inhibition of TLR-4 signaling

The main toxic part of endotoxins is the lipid-A part in which the two phosphate groups are essential for many biological activities (Fig. 1). By contrast MPLA is not toxic and is even capable of inducing tolerance to subsequent endotoxin exposure. An IL-1-like receptor called TLR-4 is the transmembrane protein receptor for endotoxins that mediates cellular activation.

4.5.1. Eritoran, a lipid-A antagonist

Eritoran was intended to be an endotoxin antagonist and it has been shown to inhibit TLR-4-mediated cell stimulation and to be an effective inhibitor of the toxic effects of endotoxins in animal models [46]. Bennett-Guerrero et al. [47] investigated in a double-blind, placebo-controlled study in 152 patients undergoing elective CABG with or without valve surgery with an ascending dose of Eritoran, its effect on endotoxin-induced systemic inflammation. They found no statistically significant differences in most variables related to systemic inflammation or organic dysfunction. Hence, they concluded that blocking lipid A with Eritoran did not appear to confer any clear benefit to elective cardiac surgical patients.

4.5.2. Alkaline phosphatase

A physiological role for alkaline phosphatase was proposed in 1997 by Poelstra et al. [48] Alkaline phosphatase dephosphorylates and thereby detoxifies endotoxins (lipopolysaccharides) at physiological pH levels.
The phosphorylated lipid-A moiety of endotoxin is a substrate for alkaline phosphatase, which enzymatically dephosphorylates the toxic lipid-A part into monophosphoryl lipid A [49]. In the intestine, alkaline phosphatase detoxifies endotoxins and prevents inflammation in response to gut microbiota [50]. Bovine intestinal alkaline phosphatase (bIAP) has been used in an animal model in sepsis and inflammatory bowel disease [51]. A randomized, double-blind, placebo-controlled study with bIAP in CABG surgery was performed by our group in 2006 [52]. In that study, we found a significant TNFα response only in the placebo-treated group. In this group, next to TNFα, IL-6 and IL-8 were also increased. Such a TNFα response was not observed in the bIAP group, suggesting that there might be a role for bIAP in the attenuation of the inflammatory reaction post-CPB. We did not find any significant differences in clinical outcome, defined as postoperative complications and in-hospital mortality between the two groups.

5. Endotoxin adsorbers

5.1. Alteco® LPS adsorber

In 2009, Blomquist et al. [53] reported on a new endotoxin adsorber device called the Alteco® LPS adsorber. The adsorber consisted of porous polyethylene disks to which a specific polypeptide is bound that bind to the A moiety of endotoxin. The adsorber was included in the bypass circuit between the arterial filter and the venous reservoir. The study was performed in 15 patients undergoing either elective CABG and/or valvular surgery with the use of CPB. In nine of these patients, the LPS adsorber was included in the circuit. At several time points, blood samples were taken for endotoxin and different cytokines such as TNFα, IL-6, and IL-1β. Endotoxin was found only in two patients (one in each group), with long cross-clamp times. There were no significant differences in cytokine levels between both groups; therefore, the authors concluded that this adsorber device can be used safely in the bypass circuit, but that the intended effects of the adsorber could not be demonstrated. Recently, the same adsorber has been used in a study performed by De Silva et al. [54] In a prospective randomized controlled pilot trial, 17 patients were included with an expected CPB time of over 60 min. No significant differences were seen in endotoxin levels or cytokine levels between the adsorber and the control group.

5.2. Polymyxin B-immobilized hemoperfusion cartridge

Polymyxin B has both bacterial and anti-endotoxin capabilities. It can destroy bacterial outer membranes and bind endotoxin, thereby neutralizing its toxic effects [55]. Cartridges containing polymyxin B-immobilized fibers (Tormyixin PMX-F) are used in extracorporeal hemoperfusion to remove circulating endotoxin in patients with severe sepsis, with promising results [56]. In 2007, Ohki et al. [57] reported on an animal study in pigs. Ten pigs were divided into control and PMX groups undergoing normothermic CPB. The IL-8 level 2 h post-CPB was significantly lower in the PMX-treated group (p < 0.05). Cardiac and pulmonary functions, determined by measurement of cardiac output, left ventricular pressure and end-systolic pressure—volume ratio, were well preserved.

6. CPB-related factors

6.1. Off-pump versus on-pump

In a review article by Raja and Berg [58], 19 randomized controlled trials comparing off-pump versus on-pump technique are described, focused on the systemic inflammatory response. They concluded that although off-pump CABG reduces the systemic inflammatory response, it does not abolish it completely. The inflammatory response during off-pump CABG is the result of the response to the surgical trauma, manipulation of the heart, pericardial suction, and other factors such as anesthesia. In 2002, Aydin et al. compared the on- and off-pump technique focusing on endotoxemia [59]. In 30 patients randomized between the on- and off-pump technique, they demonstrated significantly lower endotoxin and lactate levels in the off-pump group and they concluded that this might lead to an improved recovery after off-pump CABG.

6.2. Pulsatile versus nonpulsatile flow

Watarida et al. [60] showed significantly lower levels of endotoxin during CPB using pulsatile flow as compared with nonpulsatile flow. An explanation for this might be the better splanchnic circulation during pulsatile flow leading to a decreased ischemia-induced translocation of bacteria in the portal circulation. Neuhof et al. [61] published similar results in 2001. In 48 patients randomized between pulsatile and nonpulsatile flow, they also demonstrated a significantly lower level of endotoxin when pulsatile flow was used during CPB. Both studies, however, did not show any differences in clinical outcome.

6.3. Hypothermia versus normothermia

In 2007, Rasmussen et al. [62] performed a randomized clinical study comparing the release of systemic mediators in normothermic and hypothermic (32 °C) CABG. They found no differences in mediator release between the two groups. Study limitations were, however, the small group size (n = 30) and low-risk patients, which may have affected study outcome. In 1997, Gercelkoglu et al. [63] studied endotoxin release during hypothermia. In 20 patients, who underwent elective CABG, they compared the endotoxin release between mild (32–24 °C) versus deep (24–28 °C) hypothermia. They found significantly higher endotoxin levels in the group that underwent CABG with deep hypothermia as compared with the group in mild hypothermia. An explanation for this might be that hypothermia causes mucosal ischemia, and that during hypothermia, the immune system and enzyme activities are depressed so that endotoxins are less efficiently detoxified by Kupffer cells. However, both above-mentioned studies showed no difference in clinical outcome between the different groups.
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