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Review

Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update

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Summary

Cardiac surgery with cardiopulmonary bypass (CPB) induces an acute phase reaction that has been implicated in the pathogenesis of several postoperative complications. Recent data indicate that a complex sequence of events leads to the final activation of leukocytes and endothelial cells (EC), which is responsible for cell dysfunction in different organs. Activation of the contact system, endotoxemia, ischemia and reperfusion injury and surgical trauma are all potential triggers of inflammation following CPB. Different pro- and anti-inflammatory mediators (cytokines, adhesion molecules) are involved and their release is mediated by intracellular transcription factors (nuclear factor-kB, NF-kB). In this review, we examine recent advances in the understanding of the pathophysiology of the CPB-induced acute phase reaction and evaluate the different pharmacological, technical and surgical strategies used to reduce its effects. Emphasis is given to the central role of transcription factor NF-kB in the complex mechanism of the inflammatory reaction and to the effects of compounds such as heparin and glycosaminoglycans, phosphodiesterase inhibitors and protease inhibitors whose role as anti-inflammatory agent has only recently been recognized. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) provokes a systemic inflammatory response syndrome (SIRS). Contact of the blood components with the artificial surface of the bypass circuit, ischemia–reperfusion injury, endotoxemia and operative trauma are all possible causes of SIRS. This inflammatory reaction may contribute to the development of postoperative complications, including myocardial dysfunction, respiratory failure, renal and neurologic dysfunction, bleeding disorders, altered liver function, and ultimately, multiple organ failure (MOF).

A number of different strategies, including new pharmacologic agents, CPB circuits and components, and surgical techniques, have been employed during the last few years in attempts to minimize the impact of SIRS on the outcome of cardiac surgical patients. However, the complex pathophysiology of this problem has not allowed, until now, the use of a single strategy.

This report will review recent advances in the understanding of the pathophysiology of the cardiac surgery-related acute phase reaction and the latest developments in the pharmacological, technical and surgical strategies aimed to reduce it.

2. Acute phase reaction — stimuli and mediators

The activation of the acute phase reaction during CPB is an extremely complex process (Fig. 1). It occurs at different times and has various triggers: the surgical trauma itself [1], blood contact with the non-physiological surfaces of the extracorporeal circuit, endotoxemia and ischemia. Several mediators which are involved, exert synergistic effects, and thereby amplify this process.

2.1. Contact and complement systems

Exposure of blood to the extracorporeal circuit activates the contact system. The active form of factor XII converts prekallikrein to kallikrein and initiates the intrinsic coagulation cascade that leads to the formation of thrombin. The complement system is also activated, mainly through its alternative pathway. The CPB circuit lacks the endothelial

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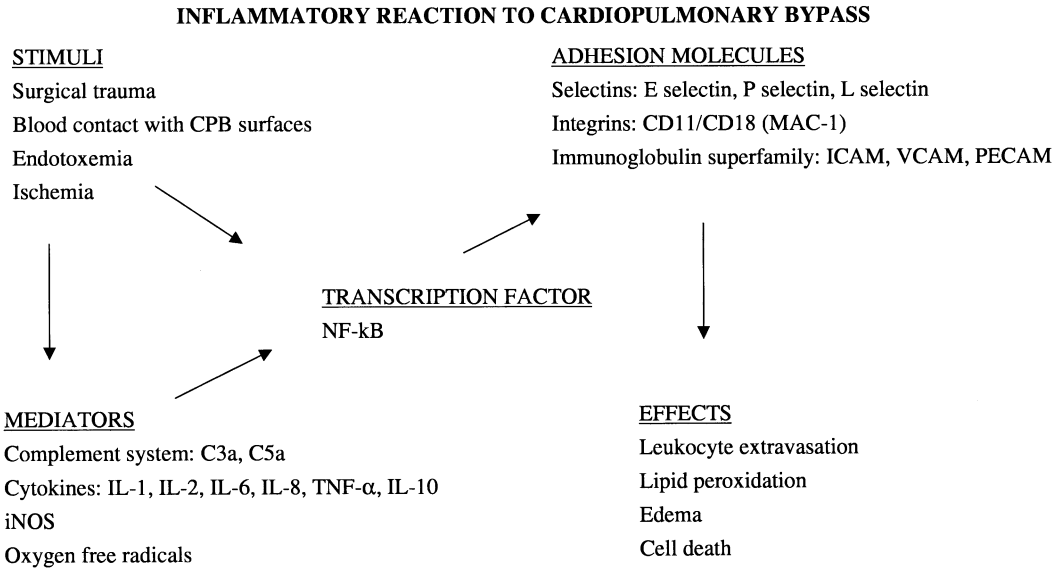

Fig. 1. Schematic of the inflammatory process induced by CPB. The key role of NF-kB leading to the EC and leukocytes activation is highlighted.

cell (EC) surface inhibitors that normally limit cofactor C3 activation, and this contact activation, along with the stimulus of kallikrein, provokes the formation of anaphylotoxins C3a and C5a with anaphylactic and chemotactic activity [2]. The activation of the classic pathway factors C4 and C2 may also occur. However, C4 and C2 are specifically induced by heparin–protamine complexes [3] and their activation is not observed in patients undergoing off pump coronary artery bypass grafting (CABG) without protamine administration [1].

The activity of complement anaphylotoxins is mediated by the complement receptor Type 1 (CR1) which is a transmembrane glycoprotein expressed on leukocytes that regulate complement pro-inflammatory activity and can also exert an important inhibitory role in both the classical and alternative pathways [4].

2.2. Cytokines

Complement factors and their degradation products can exert an immunomodulatory effect, inducing the synthesis of pro-inflammatory cytokines [5,6]. Cytokines are intercellular messengers produced by tissues in response to different stimuli. They have been generally considered to be products of mature leukocytes within the lymphatic system but recent reports show that their secretion may also be modulated by different cell lines such as platelets [7] and EC [8].

The role of cytokines in the pathophysiology of the CPB-related acute phase reaction has been studied extensively [9]. Besides the well-documented increased levels of pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), interlukin-6 (IL-6), IL-8), the role of the anti-inflammatory cytokine (IL-10) and the balance among these cytokines may be important in determining the level of the inflammatory response [10].

Increased levels of pro-inflammatory cytokines have generally been associated with negative outcomes after cardiac surgery. Recent data allow us to better understand these effects. TNF-α and IL-1β synergistically depress human myocardial contractile function through a mechanism mediated by sphingosine [11]. Sphingosine is rapidly released after cardiac myocyte exposure to TNF-α and it exerts a negative inotropic effect impeding Ca^{2+}-induced Ca^{2+}-release from the sarcoplasmic reticulum.

In rats, TNF-α and nitric oxide synthase (iNOS) dramatically increase systemic vascular permeability and induce pulmonary vascular barrier dysfunction with increased lung water content and impaired oxygenation [12]. TNF-α released during CPB also induces glomerular fibrin deposition with cellular infiltration and vasoconstriction, leading to a reduction of the glomerular filtration rate and kidney dysfunction [13].

2.3. Endotoxin

Endotoxemia is another activator of the CPB-related acute phase reaction. Bacterial lipopolysaccharide (LPS) is released by gram-negative bacteria during their growth and replication or after the disruption of bacterial cell membranes consequent to antibiotic administration. In plasma, endotoxin binds to LPS-binding protein, a human serum protein whose concentration rises during the acute phase reaction, forming an endotoxin–LPS-binding protein complex. This complex binds to the macrophage receptor CD14 and considerably enhances macrophage TNF-α production [14]. Bacterial LPS is also able to stimulate EC to produce IL-6 [15]. The presence of endotoxin in patients' blood after CPB has been demonstrated in a number of studies [16,17]. Interestingly, high levels of endotoxin have also been found preoperatively in children

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undergoing complex repair of congenital heart defects; this finding had a negative prognostic significance [18].

2.4. Nitric oxide

Pro-inflammatory cytokines and endotoxin can induce the release of NO by EC and smooth muscle cells through the inducible form of the enzyme NOS (iNOS). Constitutive NO (cNO) is normally produced by EC from the amino acid L-arginine by means of calcium-dependent NOS. NO modulates vasomotor tone in response to physiologic stimuli such as pulsatile flow and shear stress [19]. iNOS produces larger amounts of NO because of the activation of several transcription factors. iNOS derived NO (iNO) is implicated in the pathophysiology of the inflammatory state inducing vasodilation and increased vascular permeability. Several reports now highlight the direct role of iNO in inducing organ dysfunction during SIRS. As already described, TNF-α-induced iNOS production increases lung vascular permeability and selective inhibition of iNOS prevents vascular barrier dysfunction [12]. While iNO has a role in the pathophysiology of myocardial stunning, [20] cNO plays a protective role and its release is impaired after CPB [21,22].

2.5. Ischemia

CPB and aorta cross-clamping induce myocardial hypoxia and ischemia, both of which are pro-inflammatory stimuli. Together with other factors such as complement, histamine, pro-inflammatory cytokines, endotoxin and thrombin, ischemia contributes to the activation of EC and leukocytes, the effectors of inflammatory cytotoxicity. Activated transcription factors transduce the pro-inflammatory stimuli through the cytoplasm of these cells to the nucleus, inducing the transcription, translation and activation of inflammatory mediators involved in the final tissue injury.

3. Acute phase reaction — transcription factor

3.1. Nuclear factor kB

Nuclear factor kB (NF-kB) is a ubiquitous inducible transcription factor involved in the regulation of transcription of many pro-inflammatory genes. It is activated by stimuli such as IL-1, TNF-α, LPS, UV irradiation, growth factors, oxygen free radicals, oxidative stress and viral infection [23]. Different forms of NF-kB have been described, having different DNA targets and cell type specificity. Normally, NF-kB is bound to the inhibitory IkB protein in the cytoplasm of different cells including EC and leukocytes [24]. When stimulated, the NF-kB–IkB complex is phosphorylated and the IkB protein is dissociated and inactivated. Phosphorylation of the NF-kB–IkB complex is accomplished by two specific kinases (IKKα/IKK1 and IKKβ/IKK2). NF-kB translocates to the nucleus where, binding to DNA, it is able to induce the expression of several inflammatory mediators including pro-inflammatory cytokines, iNOS and adhesion molecules (Fig. 2). IL-10 blocks NF-kB activity through the inhibition of the IkB phosphorylation and NF-kB-DNA binding [25]. Ischemia rapidly reduces IkB cytoplasmic levels resulting in the translocation of NF-kB in the nucleus of rat myocardial cells [26]. A targeted approach to inhibition of IKK2 and thus NF-kB nuclear translocation has been achieved by recombinant adenoviral transinfection of human umbilical vein-derived EC (HUVEC). Adenovirus-transinfected HUVEC had markedly reduced production of IL-8 and varying adhesion molecules in response to a pro-inflammatory stimulus (LPS). In addition, marked inhibition of procoagulant activity, which is normally induced by tissue factor, was noted in the adeno-

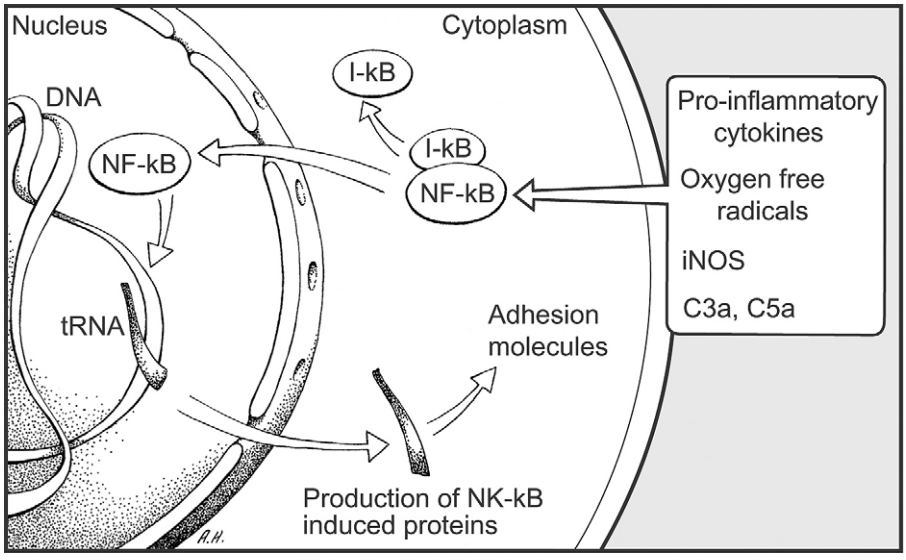

Fig. 2. Pathways leading to the activation of NF-kB and the production of adhesion molecules.

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virus-transinfected HUVEC, suggesting that NF-kB may play a role not only in the inflammatory response, but also in the modulation of several other EC functions [27].

4. Acute phase reaction — tissue injury

4.1. Adhesion molecules and reperfusion injury

Initially, the formation of selectins (E-selectin and P-selectin on EC and platelets, and L-selectin on the leukocyte cell membranes) allows a low affinity binding between leukocytes, platelets and EC which recruits neutrophils from the blood and initiates their rolling movement towards injured tissue. The binding between selectins is accomplished by glycoprotein ligands sialyl-Lewis^x. The subsequent activation of neutrophils by a number of pro-inflammatory mediators, including platelet-activating factor (PAF) and IL-8, provokes an increase of CD11/CD18 (MAC-1) integrin on the leukocyte surface [28]. Cytokines upregulate the expression of intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and platelet-endothelial cell adhesion molecule (PECAM), all members of the immunoglobulin superfamily, on the EC surface. The binding of integrins with ICAM and VCAM initiates firm adhesion of leukocytes on EC, leading to their transendothelial migration into the interstitial fluid phase (mediated by PECAM). Here, leukocytes release their lysosomal contents (proteolytic enzymes, leukotrienes and oxygen free radicals) (Fig. 3). These agents stimulate lipid peroxidation of EC and myocyte membranes, causing cellular dysfunction, edema and cell death [29]. The binding of integrins with P-selectin on platelet surface leads to the formation of leukocyte–platelet microaggregates. The inhibition of NO release from EC induced by oxygen free radicals provokes vasoconstriction that, together with leukocyte–platelet microaggregates [30] is responsible for microvascular obstruction and the no-reflow phenomenon observed during reperfusion. CPB is associated with increased levels of soluble adhesion molecules. Higher levels of adhesion molecules are briefly expressed and return to normal within a few hours but they are believed to be responsible for the dysfunction of multiple organ systems observed in the post-operative period. A relationship between adhesion molecule expression and inflammatory mediators during early reperfusion after aortic declamping has also been shown [30].

CPB induces platelet activation. In fact, following CPB, platelet release their granule contents (platelet factor 4, β thromboglobulin, thromboxane B) and express P-selectin on their membranes [31]. Heparin, hypothermia and trauma caused by the interaction with CPB circuits are considered the main triggers for platelet activation. Activated circulating platelets lose their ability to aggregate and this platelet dysfunction is considered the principle cause of coagulopathy and bleeding diathesis after CPB surgery. Moreover, the interaction between activated platelets and activated leukocytes (particularly monocytes) [30] allows platelets to be involved in the inflammatory reaction to CPB and amplifies the effects of the reperfusion injury.

Apoptosis is a form of genetically induced cell death characterized by the fragmentation of DNA. In experimental studies, the reperfusion injury mechanism previously described has been increasingly recognized able to induce cell death by means of apoptosis. Inflammatory mediators such as TNF-α, may induce apoptosis [32,33] and serum taken from patients who had undergone CPB may induce endothelial apoptosis [34]. It is likely that apoptosis plays a role in the tissue injury induced by CPB but its extent and its mechanism remain to be demonstrated.

This complex sequence of events is responsible for many of the complications observed after CPB. Loss of vascular tone, capillary fluid leakage and leukocyte extravasation lead to organ dysfunction. Some patients experience extreme vasodilation requiring vasoconstrictors, while others have postoperative low cardiac output syndrome, and still others develop significant respiratory or renal fail-

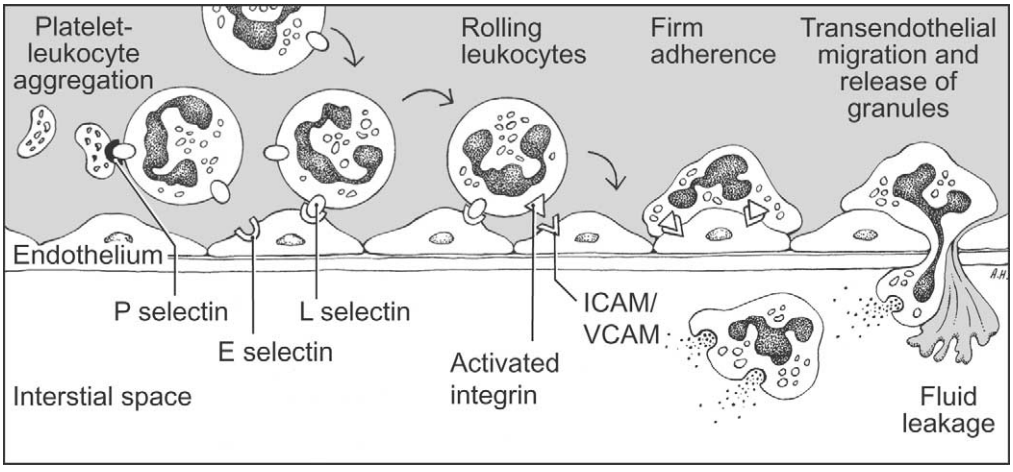

Fig. 3. EC, platelets and leukocytes interaction leading to leukocytes extravasation, granule release and fluid leakage into the interstitial space.

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ure. The microcirculation of patients undergoing cardiac surgery is affected more than that of patients receiving non-cardiac surgical operations.

There is a high degree of intraindividual variability in the extent of inflammatory reaction to CPB and the consequent clinical complications. The reasons for this extreme variability have yet to be elucidated. We have speculated that preoperative inflammatory status may influence the response to CPB. Many factors (e.g. smoking, psychological stress, infection, unstable angina, chronic inflammatory disease) may activate a systemic inflammatory reaction that may worsen the reaction to CPB. Moreover, an individual genetic predisposition to produce a greater inflammatory response to similar stimuli may also be important. Preoperative inflammatory markers, such as C-reactive protein, may prove to be markers of prognosis in cardiac surgery as they have already been shown to be in ischemic heart disease.

5. Pharmacological strategies

5.1. Glucocorticoids

Glucocorticoids have long been used to reduce inflammation. They act to reduce early inflammatory processes such as increased capillary permeability, edema formation, leukocyte migration and also later manifestations such as the proliferation of capillaries and deposition of collagen. The anti-inflammatory effects of glucocorticoid therapy have been demonstrated following CPB [35]. A significant reduction of pro-inflammatory cytokines has been observed after pretreatment with methylprednisolone in patients undergoing normothermic [9] and mildly hypothermic CPB [36]. Anti-inflammatory cytokine IL-10 concentrations are greater following preoperative glucocorticoid administration [36]. Steroid pretreatment also decreases endotoxin release [37] and leukocyte integrin expression [38]. The mechanisms behind the anti-inflammatory effects of glucocorticoid have been clarified recently [39]. Glucocorticoids suppress the stimulus-dependent expression of many pro-inflammatory proteins inhibiting different transcriptional pathways in various cells. Dexamethasone suppresses LPS-induced monocyte secretion of TNF-α, thereby reducing NF-kB DNA binding activity [40]. Dexamethasone also exerts an inhibitory effect on cytokine-induced iNOS expression and iNO production in rat smooth muscle cells through the preservation of IkB and consequent inhibition of NF-kB activation [41].

To our knowledge, there has been no study reporting a negative outcome associated with steroid treatment, particularly with regards to the prevalence of postoperative infections.

5.2. Protease inhibitors

The primary indication for the use of the serine protease inhibitor, aprotinin, in cardiac surgery is related to its role as an inhibitor of the contact pathway of intrinsic coagulation. A large number of studies have shown the ability of aprotinin to reduce blood loss during and after cardiac surgery, although the results are sometimes conflicting. Recently, an exhaustive meta-analysis emphasized that treatment with aprotinin decreases mortality to almost two-fold; decreases the proportion of patients receiving blood components and the frequency of surgical re-exploration without increasing the risk of perioperative myocardial infarction [42]. During the last few years, an anti-inflammatory role has been attributed to protease inhibitors and their use in cardiac surgery is becoming more widespread. Low dose aprotinin, as well as methylprednisolone, reduces the TNF-α release and neutrophil integrin expression in patients undergoing CPB [43]. Aprotinin (280 mg as a loading dose, 280 mg in the prime pump and 70 mg every hour until the end of operation) reduces the concentration of NO in the airways of patients undergoing CABG and reduces cytokine-induced iNOS production by murine lung epithelial cells [44]. Leukocytes extravasation is inhibited by aprotinin [45] and the concentration of IL-8 and neutrophils in bronchoalveolar lavage fluid is significantly reduced in patients receiving aprotinin (at the same dose as in the previous study), which may decrease neutrophil elastase release and oxygen radical-induced lung injury [46]. Aprotinin, at high concentrations, is also able to prevent platelet accumulation and skeletal-muscle injury after ischemia and reperfusion in pigs [47]. Finally, the administration of aprotinin before the onset of acute myocardial ischemia in normothermic dogs preserved systolic myocardial function and regional contractility during reperfusion [48]. Interestingly, recent publications have demonstrated that protease inhibitors, as well as glucocorticoids, act to prevent NF-kB activation and increase IkB concentration with consequent reduction of the expression of various inflammatory mediators [49–51]. Despite all this encouraging evidence, a recent large randomized study did not demonstrate any decrease in pro-inflammatory cytokines release and neutrophil activation when high doses of aprotinin were given, [52] indicating that further studies are needed to evaluate the clinical anti-inflammatory use of aprotinin.

5.3. Heparin and other glycosaminoglycans

Heparin has been used since the beginning of CPB assisted cardiac surgery in order to prevent blood clotting in the extracorporeal circuits. Despite the high plasma levels of heparin achieved during CPB, activation of the coagulation system and thrombin formation are not completely prevented [53,54].

Besides its anticoagulant effect, a growing number of studies show that heparin and other similar glycosaminoglycans have anti-inflammatory properties. Heparin sulphate (HS) glycosaminoglycans are ubiquitously attached to the EC surface and can mediate cellular interactions. Neutrophil

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and EC adhesion molecules interact with heparin released from mast cells or HS on EC [55]. In vitro, heparin oligosaccharides block L- and P-selectin interactions, which may inhibit neutrophil accumulation during acute inflammation [56]. At therapeutic concentrations, heparin binds to the integrin Mac-1 on stimulated monocytes, thereby inhibiting its binding to EC ligands [57]. Similar findings have been reported with both unfractionated and low molecular weight heparin [58]. Moreover, Attanasio et al. [59], evaluated the effect of heparin on LPS or interferonγ (IFNγ) stimulated monocytes and found that heparin inhibited IL-1β, IL-6 and TNF-α gene expression. Similar findings have been reported by other groups [60]. Several reports have demonstrated that various cytokines can bind directly to glycosaminoglycans. For example, heparin binding to IL-8 inhibits the IL-8-induced chemotactic response [61]. Pretreatment with either unfractionated heparin or a non-anticoagulant heparin prior to an ischemia and reperfusion injury preserved myocardial contractility in dogs, and was associated with increased cNO activity [62,63].

The specific anti-inflammatory role of heparin in patients undergoing CPB during cardiac surgery has not been evaluated, although the anti-inflammatory role of heparin in other settings such as exercise-induced bronchoconstriction is accepted [64]. The obligatory use of heparin as an anticoagulant during CPB renders it impossible to separate the effects of heparin on inflammatory markers from the effect of CPB. Current research is now concentrated on producing non-anticoagulant glycosaminoglycans with anti-inflammatory activity to be utilized alone or in association with anticoagulant heparin [63].

5.4. Phosphodiesterase inhibitors

Phosphodiesterase inhibitors interfere with the action of cyclic adenosine monophosphate (cAMP) phosphodiesterase. This increases intracellular cAMP and calcium levels, increasing myocardial inotropy and lowering systemic vascular resistance by causing peripheral vasodilatation. These actions make these drugs particularly useful for treatment of ventricular dysfunction after cardiac surgery [65].

The increase in intracellular cAMP levels may also be the mechanism by which phosphodiesterase inhibitors exert an anti-inflammatory effect. The phosphodiesterase inhibitors vesnarinone and amrinone reduced endotoxin-induced IL-1β, TNF-α and iNO release and improved systolic and diastolic myocardial function in rabbits [66]. Milrinone, a specific phosphodiesterase III inhibitor, when given as an infusion during CPB, reduces IL-6 and IL-1β production and improves left ventricular function in patients undergoing CABG. These results correlated with increased plasma levels of cAMP [67]. Moreover, milrinone improves splanchnic perfusion as assessed by an increase in gastric mucosal pH (pHi, an index of gastrointestinal perfusion), and suppresses mixed and hepatic venous concentrations of endotoxin and IL-6 in patients undergoing CABG [68]. The same investigators noted a similar reduction in endotoxin release when administering emoximone, another specific phosphodiesterase III inhibitor [69]. These encouraging preliminary results need to be confirmed by large clinical trials, which can evaluate the efficacy of perioperative phosphodiesterase inhibitors, as well as their potential drawback of excessive peripheral vasodilatation and hypotension.

5.5. Antioxidants

Oxygen free radicals are produced by neutrophils stimulated by pro-inflammatory cytokines. The endothelial damage caused by oxygen free radicals during ischemia–reperfusion is well established. CPB results in a depletion of endogenous oxygen free radical scavengers, such as α-tocopherol (Vitamin E) and ascorbic acid (Vitamin C). However, it has been difficult to demonstrate clinically significant benefits of exogenous antioxidants on the systemic response to CPB. A randomized clinical trial evaluating left ventricular function after CABG failed to demonstrate a significant benefit for patients pretreated with α-tocopherol and ascorbic acid, although plasma levels of these antioxidants were significantly higher than levels in control patients [70]. Another study reported subtle differences in diastolic function and reduced creatine kinase (CK)-MB release in patients randomized to pretreatment with high doses of α-tocopherol prior to CABG [71]. The addition of nitecapone, a potent scavenger of oxygen free radicals which recycles vitamin C and vitamin E, to crystalloid cardioplegia in 15 patients significantly reduced cardiac arrhythmias and free radical-induced lipid peroxidation [72] as well as cardiac neutrophil accumulation [73], but no differences in myocardial contractility were noted. A randomized clinical trial demonstrated no effect of the antioxidant pergogotein on neuropsychological deficits and myocardial performance following CABG [74]. There is growing evidence that antioxidants, by reducing the generation of reactive oxygen species, may prevent the activation of NF-kB [23]. However, a clinically relevant benefit of exogenous antioxidants in patients undergoing CPB has yet to be conclusively demonstrated.

5.6. Sodium nitroprusside (SNP)

Pro-inflammatory cytokines and endotoxin cause iNO production by activating iNOS and impair endothelial function. Administration of NO donor compounds can prevent the pro-inflammatory effects of iNO [75]. Recent in vitro studies show that NO donors are able to block neutrophil adhesion to EC induced by pro-inflammatory cytokines in a dose-dependent manner [76] as well as LPS-induced E-selectin expression [77].

SNP is an NO donor and vasodilator used to treat severe hypertension. Once administered, SNP is metabolized to cyanide (which leads to its toxicity when administered in high doses for longer durations) and NO [78]. Seghaye et

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al. first reported the anti-inflammatory properties of SNP in patients undergoing CPB. In 16 children who received an infusion of SNP for vasodilation during cooling and rewarming periods, they observed a significant reduction of complement activation [79]. Recently, Massoudy et al. have corroborated these findings. When given briefly (for 20 min) after the release of the aortic cross-clamp in patients with preserved ventricular function, SNP was associated with a reduction of systemic levels of IL-6 and IL-8, reduced cardiac production of IL-8 and less cardiac platelet/leukocyte accumulation during reperfusion [80]. They obtained similar results in patients with impaired ventricular function receiving SNP over a period of 60 min after aortic declamping [81]. In both studies, patients also received aprotinin. This confounding factor may have led to the lack of significant differences in clinical outcomes observed in those studies.

5.7. Complement inhibition and monoclonal antibodies

Prior laboratory studies of monoclonal antibodies directed against complement factor C5 [82,83] have spurred early clinical trials. The use of a humanized, single chain antibody that binds C5 has been shown to be safe and well tolerated. Administration of this antibody reduces C5a and C5-b9 serum levels in patients undergoing CABG on CPB, and was associated with a significant decrease in CK-MB levels, cognitive deficits and blood loss in a dose-dependent manner [84]. The results of this clinical study are provocative and underline the central role of the complement system in the inflammatory response to CPB.

Recently, the use of a novel drug (sCR1sL^{x}) combining the effects of soluble complement receptor 1 (sCR1) and sialyl-Lewis^{x} ligands has been the object of experimental studies aimed to reduce the ischemia–reperfusion injury. This compound is able to inhibit both the rolling phase of the leukocytes and complement chemotactic stimulating process. This wide anti-inflammatory activity has produced promising results in lung [85] and skeletal muscle [4] animal model of ischemia–reperfusion injury. Its safety and efficacy are now under investigation in clinical trials.

Antibodies against complement factors may represent a new option for the inhibition of the acute phase reaction and reduction of ischemia–reperfusion injury. However, monoclonal antibodies directed against specific inflammatory targets, such as specific adhesion molecules and pro-inflammatory cytokines, may be unable to inhibit the entire inflammatory cascade because of its multiple pathways and redundancy.

6. Technical strategies

6.1. Heparin-coated circuits

Heparin-coated CPB circuits were introduced to improve hemocompatibility and to reduce CPB-related complications. A layer of heparin molecules bound to the surface of the circuit is thought to reduce the direct contact of blood cells with foreign material and to act like HS molecules on EC. Although clinical studies have shown contradictory results, the majority has demonstrated that heparin-coated circuits improve hemocompatibility. Complement activation [86,87], cytokine release [88], kallikrein [89] and leukocyte activation [90] are all reduced using heparin-coated circuits. Despite these observations, a clear benefit in the clinical outcome has not always been demonstrated [91]. However, in a recent large, multicenter randomized trial, high risk patients undergoing CPB with heparin-coated circuits had better clinical outcomes, with shorter lengths of stay in the intensive care unit and the hospital, and less respiratory and renal dysfunction than control patients [92].

The issue of whether full dose or low dose heparin should be administered with heparin-coated circuits, however, is still a matter of debate. Ovrum et al. [93], concluded that low dose heparin (100 U/kg, ACT = 250 s) was as safe as high dose heparin (400 U/kg, ACT = 480 s) when using heparin-coated circuits because they did not observe any significantly increased levels of prothrombin fragment 1.2 and thrombin–antithrombin complexes (both markers of thrombin formation) in low dose treated patients. In another study, the same authors again concluded that low dose of heparin (100 U/kg, ACT = 250 s) was safe, although higher concentrations of prothrombin fragment 1.2 and thrombin–antithrombin complexes (both markers of thrombin formation) were measured in the low heparin group, compared to a fully heparinized uncoated circuit group [94]. These conclusions are in conflict with those of Despotis et al. [95], who demonstrated that thrombin formation was better suppressed by higher heparin concentrations, which were also associated with significantly reduced blood loss. Kumano et al., measured fibrinopeptide A, thrombin–antithrombin complexes and alpha 2 plasmin inhibitor (indices of fibrin formation and fibrinolysis) in two groups of patients undergoing heparin-coated CPB with high (300 U/kg) and low (150 U/kg) dose heparin. Concentrations of these macromolecules were elevated during and after the operation, but there was no difference between the two groups [96]. Other authors [97] have reported similar findings. None of these reports, however, has shown a reduction in postoperative bleeding using low dose heparin, one of the purported goals of reducing heparin doses. In operations on the thoracic aorta utilizing heparin-coated CPB, no significant differences have been observed with respect to inflammatory mediators, markers of neutrophil degranulation and thrombin generation when low dose heparin was used [98]. Since heparin-coated circuits do not reduce thrombin formation during CPB [99], the use of low dose heparin is not associated with any advantage and does not seem justified.

6.2. CPB flow and pumps

Under physiological conditions, blood flow occurs in a pulsatile manner [21]. There have been a large number of

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studies evaluating the potential benefit of maintaining pulsatility during CPB. However, there has been no conclusive evidence that pulsatile CPB leads to improved clinical outcomes. Some studies have reported a reduction of endotoxin and other pro-inflammatory mediators [100,101] while others have not [102]. The lack of pulsatility during CPB should not represent a major trigger for the activation of the inflammatory system.

Centrifugal pumps are often used for short-term mechanical assistance in patients with cardiac failure [103]. Their routine use for CPB has not shown clear clinical advantages compared to roller pumps [104,105]. Several reports have documented increases in the levels of complement anaphylotoxins, pro-inflammatory cytokines, adhesion molecules and leukocyte elastase when centrifugal pumps were used [106,107].

6.3. Filters

The use of ultrafiltration during pediatric open-heart surgery has been shown to reduce excess body water accumulated during CPB, and to improve hemodynamic parameters [108]. Reduced complement activation and pro-inflammatory cytokine release, together with hemodynamic, pulmonary and hemostatic improvement, have also been shown in these patients [109]. These benefits may be greatest in a pediatric population; in adult patients undergoing elective CABG, the reduction of cytokines and adhesion molecules obtained with ultrafiltration has not been associated with any clinical advantage [110].

Techniques which deplete leukocytes and platelets during CPB in adult patients have produced similar results [111,112]. The clinical benefit of leukocyte and platelet filters in routine or high risk adult patients remains to be demonstrated and may be dependent on both the efficacy and the biocompatibility of the filters.

6.4. Temperature

Studies comparing the effect of normothermic versus hypothermic CPB on the acute phase reaction have given conflicting results, due in part to discrepancies in what temperature is considered 'normothermic' by the investigators. Some authors refer to a temperature of 33–34°C as normothermic, while for others 36–37°C is the target temperature to be actively maintained by means of the heat exchanger. Menaschè et al. have shown that levels of adhesion molecules and leukocyte proteolytic enzymes are increased at temperatures of 34°C compared to moderate hypothermia (26–28°C). They have concluded that hypothermia delays but does not completely prevent the expression of inflammatory mediators [113–115]. Other authors have not found any difference between patients randomly assigned to two (>36 versus 27–28°C) [116] or three different temperatures (28, 32 and 37°C) [117]. The production of NO is increased when temperature is maintained at 34°C (compared to 28°C) resulting in the decrease of systemic vascular resistance [118].

The analysis of studies in which clinical outcome was the endpoint does not provide a clear picture. A large randomized trial (1732 patients) of patients undergoing CABG with normothermic (33–37°C) or moderately hypothermic (25–30°C) CPB showed no differences in mortality, myocardial infarction and stroke [119]. Left ventricular function was improved in the normothermic group, but this effect was likely due to the administration of warm, rather than cold, cardioplegia in this group. Atrial fibrillation is more frequently associated with moderate hypothermia during CPB (28°C) than mild hypothermia (34°C) [120]. Temperatures may differentially affect varying organ systems; warm cardioplegia has been reported to improve myocardial metabolism and function [121,122], but hypothermia may provide better neuroprotection in both clinical [123,124] and experimental studies [125].

6.5. Biventricular bypass

The Drew–Anderson technique [126] consists of biventricular bypass, a technique in which the patients' own lungs are used for gas exchange therefore avoiding the use of an oxygenator. Double arterial cannulation (in the aorta and in the pulmonary artery) and double atrial cannulation (in both left and right atria) are performed and mechanical ventilation of the lungs is maintained during CPB. The advantages of this technique with respect to pulmonary function and the inflammatory reaction to CPB have recently been reported. In an experimental study in dogs [127], biventricular bypass resulted in better pulmonary performance and significantly preserved leukocytes and platelets compared to standard CPB. A randomized controlled trial involving 30 patients showed that the Drew–Anderson technique resulted in significantly reduced levels of pro-inflammatory cytokines (IL-6, IL-8) and increased levels of the anti-inflammatory cytokine (IL-10). In addition, time to extubation, postoperative blood loss and transfusion requirements were all reduced in patients undergoing biventricular bypass [128]. These improved outcomes are attributed to continuous perfusion of the lungs during CPB, thereby avoiding stasis-related reperfusion injury, as well as to reduced contact of blood with foreign materials in the form of an oxygenator. This technique is promising, and may represent a useful option for high risk patients with impaired lung function, although it may not be applied universally because of the requirement for double arterial and double atrial cannulation.

7. Conclusions

Despite the introduction of endovascular interventional techniques and off pump CABG, the use of CPB is still necessary for many cardiac surgical procedures. Several pathways are involved in the complex pathogenesis of the

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inflammatory reaction to CPB. The inhibition of a single mediator or of a single pathway, such as that obtained with antioxidants and monoclonal antibodies, may not achieve sufficient inhibition of the entire pro-inflammatory cascade to significantly improve clinical outcomes. Interventions directed at a central mediator, or one involved in multiple pathways, may be more successful, and some intriguing studies have suggested that NF-kB may play such a central role. Greater understanding of the mechanisms of action of NF-kB [129] will permit the use of compounds able to selectively antagonize its activation and perhaps reduce the morbidity of CPB. Some of these compounds are already under investigation [130,131]. The administration of steroids may significantly reduce the inflammatory response to CPB, but both the safety and efficacy of routine perioperative steroids must be demonstrated in a large, randomized controlled trial. Recent improvements in the biocompatibility of CPB circuits and components suggest that new technology will have a beneficial impact on CPB, and may act synergistically with new pharmacologic compounds. Nevertheless, as demonstrated by this review, it is not always possible to correlate the benefits of novel anti-inflammatory compounds and devices demonstrated in laboratory studies with significant clinical benefits in patients. Studies with similar objectives and methods have often yielded contradictory results, a finding which suggests that the predisposition and perhaps the specific mechanisms of the pro-inflammatory response to CPB may vary between patients. The inhomogeneity of patients within clinical studies in this respect may complicate the interpretation of these data. Greater homogeneity may be achieved by identifying those patients at greatest risk of an exaggerated inflammatory response to CPB, in whom the use of novel anti-inflammatory strategies may be most beneficial. Those studies are ongoing, and their findings may help to clarify the muddied waters of this complex field.

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