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REVIEW

The systemic inflammatory response syndrome and cardiopulmonary bypass

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Cardiopulmonary bypass;
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Abstract Cardiac surgery using cardiopulmonary bypass (CPB) provokes a systemic inflammatory response. This is mainly triggered by contact activation of blood by artificial surfaces of the extracorporeal circuit. Although often remaining subclinical and resolving promptly at the end of CPB, in its most extreme form this inflammatory response may be associated with the development of the systemic inflammatory response syndrome (SIRS) that can often lead to major organ dysfunction (MODs) and death. Here, we review the pathophysiology behind the development of this ''whole body'' inflammatory response and some of the methods currently used to minimise it.

Introduction

When tissues are injured they attempt to eliminate the cause of injury by mounting an inflammatory response. When the injury is particularly severe, or when the injury is more generalised, a systemic inflammatory response can take place. This systemic inflammation manifests itself clinically as the systemic inflammatory response syndrome (SIRS).[1] Multiple factors associated with the use of cardiopulmonary bypass (CPB) contribute toward the generation of perioperative SIRS. These include the generation of shear forces from roller pumps driving blood through the bypass circuit, hypothermia as blood is passed through the extracorporeal circuit, and contact activation of plasma protein systems as circulating blood is exposed to artificial surfaces in the bypass circuit. This is then followed by the generation and release of endogenous inflammatory mediators leading to the development of SIRS. Here, we will review the pathophysiology of the plasma protein systems that become activated during CPB leading to SIRS and also some of the therapeutic strategies employed to counterbalance the deleterious effects of their activation.

Cardiopulmonary bypass activates the coagulation system

Although new concepts have been proposed,[2] the coagulation cascade which results in thrombus

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formation is classically thought to be the result of two pathways, intrinsic and extrinsic, which consist of a series of enzyme cascades utilising blood coagulation factors, the most important being thrombin.[3]

The intrinsic pathway begins after contact activation of blood from exposure to collagen in a damaged vascular wall, or exposure of the blood to an artificial surface such as an extracorporeal circuit. In response to these stimuli, two events occur. Firstly, Factor XII (*Hageman Factor*) is converted from its inactive form (*zymogen*) to an active form Factor XIIa. Secondly, platelets are activated. This activation of Factor XII to XIIa is further amplified by plasma kallikrein via a positive feedback loop. Factor XIIa then enzymatically activates Factor XI to Factor XIa which then converts Factor IX to Factor IXa and Factor IXa then converts Factor X to Factor Xa. This activation of Factor X is greatly accelerated by the presence of Factor VIIIa — deficiency of which results in haemophilia. Activated Factor X functions as a protease to convert the inactive molecule prothrombin to the active form thrombin. Thrombin then cleaves fibrinogen to fibrin, which then polymerises to form fibrin strands.

In the extrinsic pathway, the initial stimulus is trauma to the vascular wall, resulting in exposure of blood to non-vascular tissue cells that express an integral membrane protein called 'tissue factor'. Factor VII is a circulating plasma protein that then binds to tissue factor, creating a complex. In doing so, Factor VII is activated to Factor VIIa. This complex, in the presence of Ca^{++} and phospholipids, activates Factor X to Factor Xa. Once Factor Xa is generated, the remainder of the cascade is similar to the intrinsic pathway (Fig. 1).

Surgery using CPB results in extensive activation of both intrinsic and extrinsic pathways of the coagulation system.[4] This necessitates the use of systemic heparinisation to prevent clot formation in the extracorporeal circuit, which brings with it risks of platelet activation (heparin induced thrombocytopenia)[5] and aldosterone inhibition leading to hyperkalaemia.[6] However, despite heparinisation inhibiting clot formation, activation of the coagulation system still occurs as heparin inhibits the coagulation system only at the end of the cascade (by promoting the activity of antithrombin III).[7,8] Molecular markers of thrombin generation such as thrombin—antithrombin III complex (TAT) and prothrombin fragment (PF1 + 2) remain elevated perioperatively in patients undergoing CPB demonstrating that thrombin generation is still occurring.[4]

Cardiopulmonary bypass activates the fibrinolytic system

To prevent excessive activation occurring, regulatory mechanisms exist that serve two main functions — firstly to limit the amount of fibrin clot formed to avoid ischaemia of tissues and secondly to localise clot formation to the site of tissue or vessel injury, thereby preventing widespread thrombosis. The continuous generation of cross-linked fibrin would create a clot capable of obstructing normal blood flow. Therefore, the fibrinolytic system exists as a counterbalance to the coagulation system. Plasminogen is an inactive protein synthesised mainly by the endothelium,[9] and can be converted to its active form plasmin by tissue plasminogen activator (t-PA). Plasmin then has the ability to degrade fibrin strands, preventing the build-up of excess clot.

The use of cardiopulmonary bypass results in increased fibrinolytic activity as shown by increases in D-dimer levels, and t-PA activity.[4] This activation of fibrinolysis is caused by elevated levels of Factor XIIa and kallikrein as well as by an increase in t-PA. Elevated D-dimer levels have been correlated with increased blood loss and postoperative bleeding time. Additionally, activation of fibrinolysis may also affect other aspects of haemostasis such as reduced platelet adhesion and aggregation capabilities due to redistribution of glycoprotein Ib and IIb/IIIa receptors.[10]

Cardiopulmonary bypass activates the complement system

The complement system provides an innate defence against microbial infection and is a ''complement'' to antibody mediated immunity. The complement system consists of 35 interacting plasma and membrane associated proteins which contribute to host defence by initiating and amplifying the inflammatory response. Also, contained within this system are several soluble factors that prevent spontaneous complement activation from occurring, as well as several regulatory proteins that protect host cells from accidental complement mediated attack.[11,12]

Activation of the complement system is achieved through three major pathways: the classical pathway, which is activated by certain antibodies bound to antigens (immune complexes); the alternative pathway, which is activated on microbial cell surfaces in the absence of antibody; and the lectin pathway, which is activated by a plasma lectin that binds to mannose residues on microbes.[11—13]

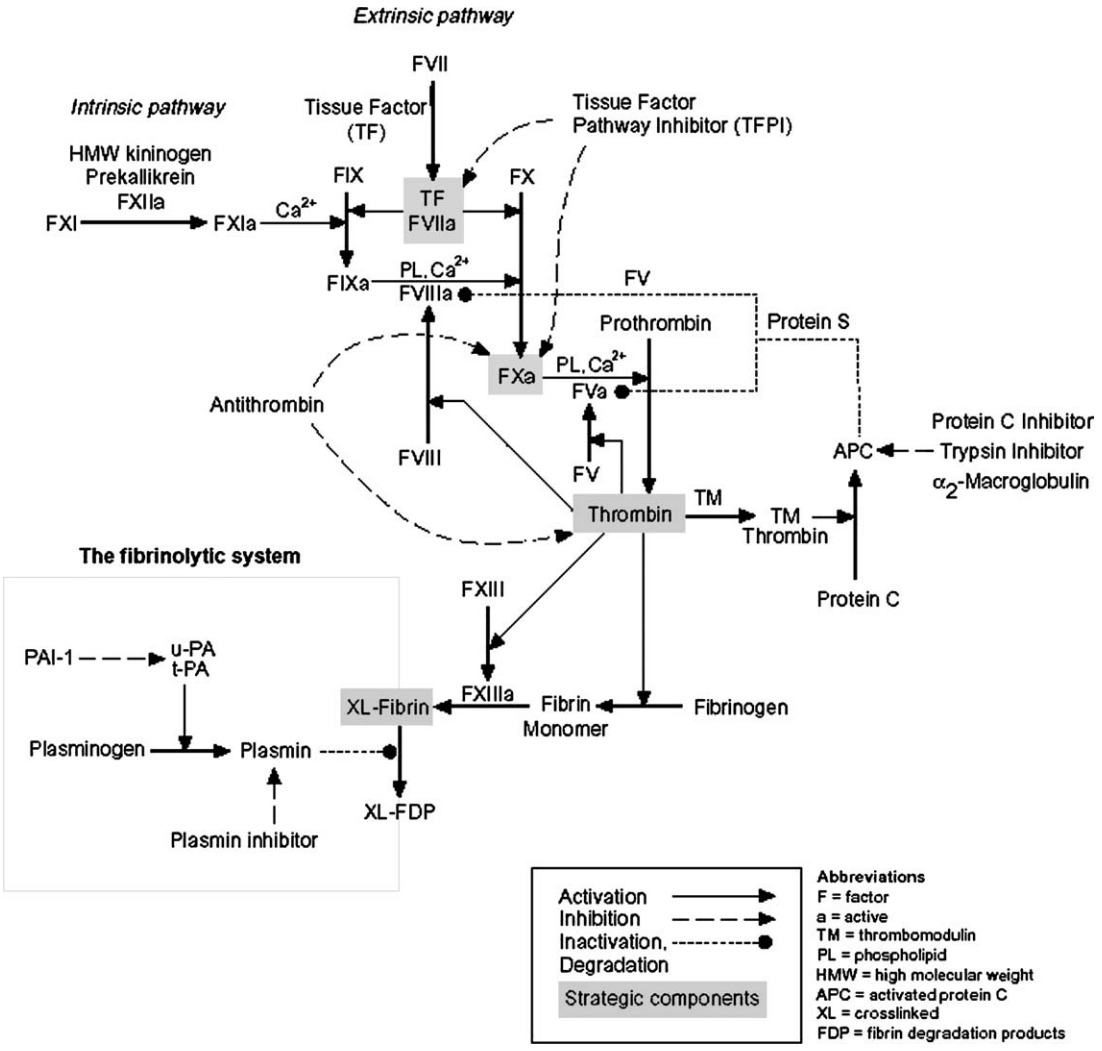

Figure 1 Schematic representation of the coagulation and fibrinolytic systems.

Following the activation of complement pathways, several peptides are generated that help to increase the number of circulating leukocytes, promote leukocyte adhesion to vascular endothelium, and attract phagocytes to the sites of inflammation.[14]

During CPB complement activation occurs after blood contacts non-endothelial cell surfaces,[15] after protamine administration with formation of protamine–heparin complexes[16] and after reperfusion of the ischaemic myocardium.[17] Complement activation during surgery requiring CPB may play a particularly important role in the development of perioperative tissue injury due to the pro-inflammatory effects of the terminal complement products of C5 cleavage, C5a, and C5b-9. C5a is an extremely potent anaphylatoxin, whereas C5b-9, otherwise known as the membrane attack complex, can directly lyse cells, including cardiac myocytes.[14] Both C5a and C5b-9 mediate cellular damage, alteration of vascular permeability and tone, leukocyte chemotaxis, initiation of cardiac myocyte apoptosis, initiation of thrombosis and promotion of both cellular activation and adhesion.[14]

Cardiopulmonary bypass activates leukocytes

The use of CPB during cardiac surgery causes leukocyte (monocyte and neutrophil) activation, characterised by elevated levels of neutrophil elastase,[18] pro-inflammatory cytokines, and the formation of platelet–leukocyte conjugates.[19] Leukocyte activation occurs as a result of elevated levels of thrombin, kallikrein and C5a. C5a is generated soon after the onset of CPB and is a particularly potent protein that induces neutrophil chemotaxis, degranulation, and superoxide generation. Other important mediators of leukocyte

activation during CPB include interleukin (IL)-1β, TNF-α, IL-8, C5b-9, Factor XIIa, heparin, and histamine.

Activated neutrophils can degranulate releasing cytotoxic enzymes (neutrophil elastase, lysozymes, and myeloperoxidase), oxygen free radicals, and hydrogen peroxide. Activated neutrophils also directly activate endothelial cells thereby increasing perivascular oedema and leukocyte transmigration into extracellular matrix.[20] Furthermore, monocyte activation during CPB plays a major role in thrombin generation via expression of tissue factor[21] and release of inflammatory mediators such as TNF-α, IL-1β, IL-6, and IL-8.[22]

Monocytes also express the receptor CD163[23] which mediates the endocytosis of haemoglobin: haptoglobin (Hb:Hp) complexes[24] thereby countering Hb-induced oxidative tissue damage due to haemolysis after CPB.[25,26] Elevated CD163 levels are detectable on circulating monocytes after surgery using CPB and binding of Hb:Hp to CD163 on monocytes elicits a potent anti-inflammatory interleukin-10 response, and this, in turn, induces haeme oxygenase-1 stress protein synthesis. These anti-inflammatory and cytoprotective pathways, may have relevance to athero-protection, wound healing, and patient recovery postoperatively.[27]

Cardiopulmonary bypass activates endothelial cells

Endothelial cells are activated during CPB by a variety of agonists. The principal agonists for endothelial cell activation during CPB are thrombin, C5a, and the cytokines IL-1β and TNF-α.

IL-1β and TNF-α induce the early expression of P-selectin and the later synthesis and expression of E-selectin, which are involved in the initial stages of neutrophil and monocyte adhesion. These two cytokines also induce expression of ICAM-1 and VCAM-1, which firmly bind neutrophils and monocytes to the endothelium and initiate leukocyte trafficking to the extravascular space.[28] Regional vasoconstriction reduces blood flow rates within local vascular beds allowing neutrophils to play an important role in the multi-step model of leukocyte interaction with the endothelium, consisting of ''attachment'', ''rolling'', ''activation'', ''firm adhesion'' and ''extravasation''.[29] E-selectin (CD62E) and P-selectin (CD62P) are expressed on activated endothelium and mediate ''rolling'' of leukocytes under hydrodynamic shear flow by binding PSGL-1, a glycoprotein ligand expressed on leukocytes, through a high affinity interaction.[28] L-selectin (CD62L) is expressed on leukocytes and is primarily involved in leukocyte recirculation through lymphoid tissues, binding to counter-receptors GlyCAM-1, CD34 and endoglycan on high endothelial venules. It also plays a role in mediating ''secondary rolling''[20] at sites of inflammation via adhesion to PSGL-1 expressed on leukocytes previously attached to endothelium. A predominant role for P- and L-selectin in leukocyte recruitment in inflammation has been demonstrated in studies comparing E-, P- and L-selectin deficient mice.[31–33] During CPB the release of these vasoactive and cytotoxic substances into the circulation and the transmigration of leukocytes across activated endothelium mediate many of the manifestations of SIRS associated with CPB (Fig. 2).

Cardiopulmonary bypass activates platelets

Platelets are the smallest of the blood cells and are known to be activated during cardiopulmonary bypass. Both quantitative and qualitative platelet defects have been demonstrated, with resulting complications including haemorrhage.[35,36] As the interactions of activated platelets with the endothelium and other blood cells are unravelled, the important contributions they make toward the development of SIRS after CPB are becoming increasingly evident.

Numerous factors associated with CPB contribute toward the changes that occur in platelets. These include physical factors[37] (such as hypothermia and shear forces), exposure to artificial surfaces,[38,39] the use of exogenous drugs, and the release of endogenous chemicals.[6,34,40]

Thrombocytopenia is well documented in association with CPB. Early haemodilution occurs from the use of crystalloid fluids for priming the extracorporeal circuit. The decrease in platelet count during CPB however is in excess of that accounted for by haemodilution alone.[41] Mechanical disruption as well as adhesion to the extracorporeal circuit along with sequestration in organs may also contribute to this true drop in circulating platelet counts.

Platelets express a range of surface molecules that mediate their haemostatic and inflammatory functions. For instance Glycoprotein Ib levels have been shown to be decreased by CPB with expression returning to normal level 3 h post-CPB.[42] CD31 (also known as platelet endothelial cell adhesion molecule-1/PECAM-1 because of its occurrence on both platelets and endothelium) is also down-regulated on platelets during CPB.[43] P-selectin (CD62) expression, secreted by activated platelets from alpha granules, is known to increase within 5 min of commencing CPB.[42]

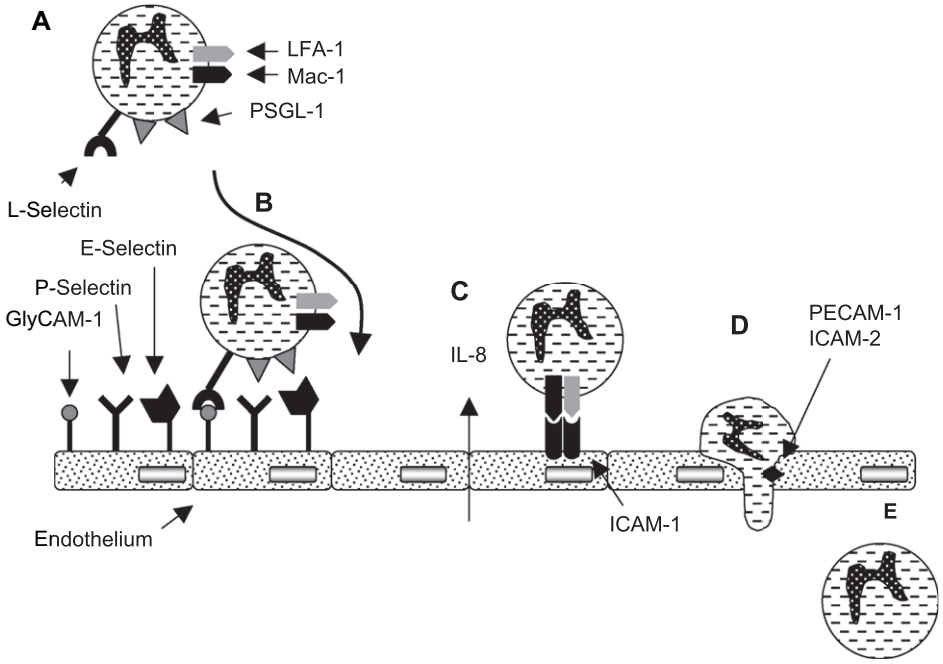

Figure 2 Simplified hypothetical diagram of the multi-step model of leukocyte interaction with inflamed vascular endothelium. Inflamed endothelium expresses P-selectin and E-selectin that binds PSGL-1 expressed on leukocytes, thus mediating — A: ''attachment'' and B: ''rolling''. L-selectin participates in leukocyte recruitment at sites of inflammation by mediating ''secondary rolling'' (leukocyte on leukocyte) through its interaction with PSGL-1. C: ''Activation'' of integrins due to chemokines such as IL-8 results in D: ''firm adhesion'' of leukocytes to endothelium via binding of LFA-1 and Mac-1 to ICAM-1. Finally E: ''extravasation'' occurs. Adherent leukocytes move towards endothelial cell junctions and transmigrate into the extracellular matrix with interaction involving PECAM-1 and ICAM-2. Reprinted with permission from Elsevier.[34]

Platelets activated during CPB form conjugates both between themselves and with leukocytes. P-selectin is expressed by activated platelets, which contributes to leukocyte conjugate formation by binding P-selectin glycoprotein (PSGL)-1.[44] Activated platelets use this P-selectin/PSGL-1 adhesion pathway to stimulate conjoined monocytes, thus leading to secretion of the pro-inflammatory cytokines IL-1β, IL-8 and monocyte chemo attractant protein (MCP)-1.[45,46] P-selectin also induces tissue factor expression and fibrin deposition by monocytes, thus contributing to the evolution of thrombus.[47,48]

Evidence is accumulating that activated platelets attach to vascular endothelium and play an important role in neutrophil adhesion and transmigration. Endothelial cells express the adhesion molecule CD40 and activated platelets express on their surface a complementary binding molecule (ligand), CD40L. This transmembrane ligand protein is structurally related to tumour necrosis factor-α (TNF-α) and induces endothelium to secrete chemokines and express further adhesion molecules. Substantial secretion of IL-8 (chemotactic for neutrophils), and MCP-1 (chemotactic for monocytes) was noted on platelets binding to endothelium. Thus, activated platelets bound to endothelium are able to initiate recruitment of neutrophils and monocytes.[49]

Inhibiting the inflammatory response

The modern era of cardiac surgery began with the safe introduction of cardiopulmonary bypass (CPB) in the early 1950s. Although it is clear that CPB is indispensable for most open heart operations, we are left with the problem that the undesirable SIRS still occurs. The factors particular to CPB that predispose our patients to this problem still remain; including the exposure of blood to artificial surfaces, surgical trauma, ischaemia-reperfusion injury, changes in body temperature, and endotoxin release. Our attempts at inhibiting this unwanted exacerbation of the inflammatory response must therefore be based around: (1) avoiding CPB altogether (*off pump surgery*); (2) modifying the bio-incompatible CPB circuit (*heparin bonded circuits*); (3) removing activated neutrophils (*leukodepletion filters*); and (4) by using

pharmaceutical drugs (*glucocorticoids, complement inhibitors and aprotinin*).

Off pump surgery

Coronary artery bypass grafting (CABG) is now possible without the use of CPB — off pump coronary artery bypass (OPCAB). OPCAB has been shown to reduce postoperative morbidity,[50] including reduced myocardial injury,[51] renal dysfunction,[52] neurocognitive deficit,[53] and SIRS.[54] However, as ''off-pump'' cardiac surgery still results in tissue trauma, cardiac manipulation, pericardial suction, and administration of exogenous drugs such as heparin, protamine, and many anaesthetic agents, a physiological stress response with resulting increases in pro-inflammatory markers still occurs. The magnitude of the response, however, is significantly less than that observed when using CPB.[54] OPCAB surgery is now widely practised in many cardiac surgical units worldwide.

Heparin bonded circuits

The use of heparin bonded circuits in CPB has enabled reductions in the dosage of heparin administered prior to initiation of bypass. This has theoretical advantages as the large doses of heparin given during CPB are associated with deranged platelet function, as demonstrated by activation of GP IIb/IIIa receptors, expression of P-selectin, and enhanced platelet aggregation.[55] Heparin coating improves the biocompatibility of extracorporeal circuits as demonstrated by improved clinical outcomes,[56] and reduced neurocognitive dysfunction,[57] complement activation,[58] transfusion requirements,[59] and ischaemic myocardial damage.[60,61]

Alternative surface coatings are undergoing investigation in clinical trials. Recently, a surface-modification technique called surface-modifying additive (SMA) has been introduced. The SMA technology is based on a family of polysiloxane-containing co-polymers that can be either blended with base polymer resins before processing or coated to blood-contacting surfaces. Initial investigations have demonstrated that SMA-treated biomaterial surfaces reduce platelet activation[62] but not blood loss or transfusion requirements during CPB.[63] Poly-2-methoxyethylacrylate (PMEA), is another coating material for artificial membranes, designed to reduce surface adsorption of plasma proteins, and appears to show improved biocompatibility. Studies of PMEA-coated circuits have demonstrated some advantages including reduced platelet activation,[64] pro-inflammatory cytokine production,[65] and thrombin, fibrinogen and bradykinin generation.[66]

Leukocyte filters

Activated monocytes and neutrophils play a significant role in the development of SIRS after CPB and this has led to the introduction of leukocyte-depleting filters into the CPB circuit. Reported benefits include reduced circulating activated leucocytes,[67] transfusion requirements,[68] renal dysfunction[69] and pulmonary inflammation leading to expedited extubation and improved clinical outcomes.[67,70]

Glucocorticoids

The physiological effects of corticosteroids are numerous and widespread. They influence carbohydrate metabolism, protein metabolism, lipid metabolism, electrolyte and water balance, the cardiovascular system, skeletal muscle, the CNS, the formed elements of blood, and they possess anti-inflammatory properties and affect other organs and tissues in a wide variety of ways. In essence, glucocorticoids promote the ability of organisms to resist noxious stimuli and environmental change. When given in the context of cardiac surgery using CPB, glucocorticoids have been shown to reduce levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-8)[71,72] and to enhance release of anti-inflammatory cytokines (IL-10).[73] Additionally, glucocorticoids attenuate complement activation,[74] increase bronchial epithelial nitric oxide concentration,[75] and decrease neutrophil integrin CD11b/CD18 (Mac-1) up-regulation,[76,77] all of which are beneficial in minimising SIRS (Fig. 4). Other clinical benefits include an increased cardiac index (CI),[78] a decreased pulmonary capillary wedge pressure,[78] and a decreased incidence of postoperative hyperthermia.[79] Due to the complex interactions of the inflammatory pathways, inhibition of a common upstream target might appear initially attractive. However, undesirable effects such as postoperative hyperglycaemia,[80] and delayed endotracheal extubation have also been reported.[81]

Complement inhibitors

Complement inhibitors are currently attracting much interest as an area of potential therapeutic

benefit in reducing morbidity post-CPB. For instance, Pexelizumab is a recombinant antibody fragment that binds to the C5 complement component thereby blocking the generation of C5a and C5b-9. The generation of C3b however, the critical mediator of bacterial opsonization, remains uninhibited. In the PRIMO CABG trial where Pexelizumab was compared with placebo, there was a statistically significant reduction in risk of MI or death 30 days after surgery.[82]

Serine protease inhibitors (aprotinin)

Aprotinin (Trasylol®) was first used clinically in the 1960s, to treat acute pancreatitis.[83] Only later in the 1980s, at the Hammersmith Hospital, was the ability of aprotinin to reduce blood loss after surgery using CPB noted.[84,85] This discovery was a serendipitous finding as the researchers' original hypothesis was not related to haemostasis but to inflammation, specifically the potential for aprotinin, in a high kallikrein-inhibitory dose, to attenuate the inflammatory response to CPB.

Aprotinin is a serine protease inhibitor isolated from bovine lung tissue, now used widely in cardiac surgery. It inhibits trypsin, chymotrypsin, plasmin, tissue plasminogen activator, kallikrein, elastase, urokinase and thrombin. Multiple studies support aprotinin's efficacy to decrease blood loss and transfusion requirements in cardiac surgery[86–89] and in other types of major surgery (e.g., liver transplantation and major orthopaedic surgery).[90,91] The haemostatic action of aprotinin is related to its effects on limiting fibrinolysis via inhibition of plasmin and kallikrein.[92] In addition to haemostasis it is also reported to preserve platelet function,[93–95] reduce the incidence of SIRS[76,97,98] and even perioperative stroke.[99]

The mechanism by which aprotinin is known to preserve platelet function lies in its ability to inhibit platelet activation by preventing proteolysis of the thrombin receptor protease-activated receptor 1 (PAR1),[100,101] the major thrombin receptor on platelets.[102] This counters the concern that aprotinin by having such potent haemostatic effects might also be prothrombotic and suggests otherwise, that aprotinin may in fact have antithrombotic effects. It is likely that the reported reduction in the incidence of stroke[99] post-CPB when aprotinin is used is also due to PAR1 protection in the central nervous system (Fig. 3).[100,103,104]

Aprotinin has been shown to reduce substantially multiple markers of inflammation and complement activation following CPB. The drug is associated with reduction of leukocyte accumulation in the lungs of patients exposed to CPB — possibly through inhibition of leukocyte extravasation and transmigration across endothelial surfaces.[105] Potentially beneficial effects of aprotinin include decreases in IL-6 and IL-8, an increase in IL-10, and a reduction in Mac-1, the leukocyte integrin adhesion molecule CD11b/CD18 (Fig. 4).[106–110] Aprotinin may therefore reduce the cell-mediated inflammatory response of platelets indirectly through effects on plasma proteases and directly through protease-activated receptors on platelets and endothelial cells. Therefore, in addition to its haemostatic properties the anti-inflammatory effects of aprotinin are being increasingly recognized.

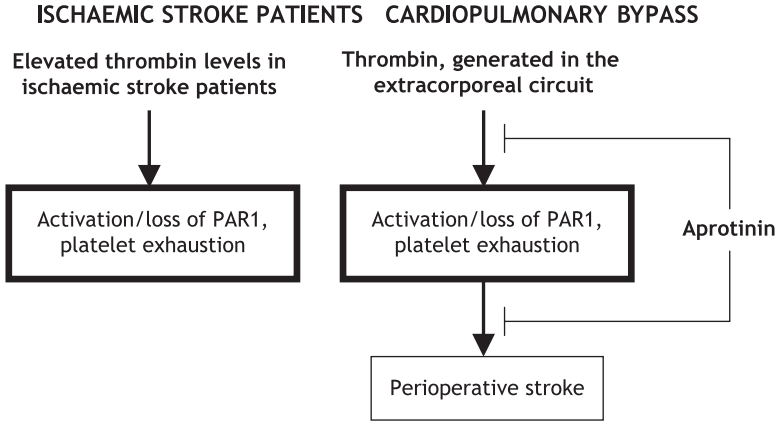

Figure 3 PAR1 is activated due to elevated thrombin levels in cardiopulmonary bypass and also in ischaemic stroke patients. Aprotinin protects platelets from thrombin induced dysfunction post-cardiopulmonary bypass by protecting the PAR1 receptor. Aprotinin also reduces the risk of perioperative stroke.[99] It is therefore possible that aprotinin mediated PAR1 protection is the underlying mechanism behind this pharmacotherapeutic effect.[100,103,104]

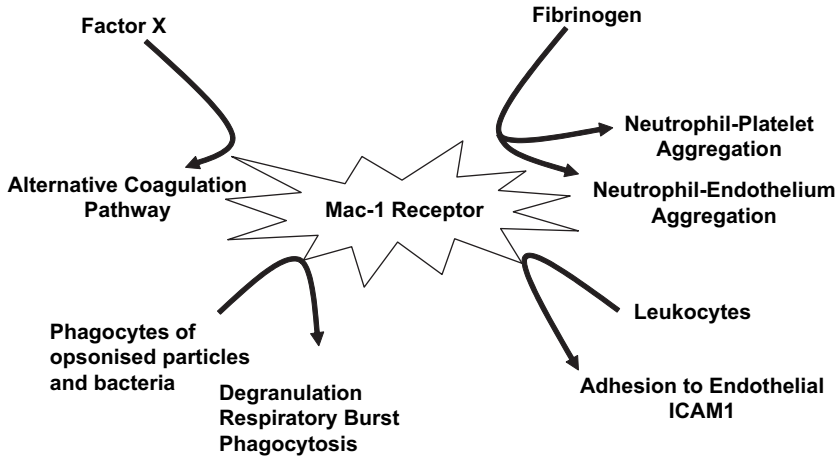

Figure 4 Schematic representation of some of the functions mediated via the β-2 integrin receptor Mac-1. Binding of Factor X to Mac-1 plays an important part of a cell bound alternative pathway of initiation of the coagulation system, resulting in the acceleration of the conversion to Factor Xa and the release of proteases that activate coagulation factors.[111] Furthermore, binding of soluble fibrinogen to Mac-1 constitutes a bridging function to platelet integrin GpIIb/IIIa, as well as to the endothelial adhesion molecule ICAM-1.[112] Neutrophil—platelet and neutrophil—endothelial cell interactions are involved in producing intravascular coagulation and endothelial permeability that characterise the inflammatory response during CPB.[19] Mac-1, identical to complement receptor type 3 (CR3), is expressed on phagocytes and is responsible for the recognition of iC3b opsonised bacteria and yeast, and the initiation of phagocytosis, degranulation, and respiratory bursts.[114] Reprinted with permission from Elsevier.[34]

Conclusions

The use of CPB in clinical cardiac surgery provokes an acute inflammatory response that is often unpredictable and carries significant risk of morbidity and mortality. This is due to contact activation of blood by surgical wounds, and synthetic perfusion circuits, to which is often added blood aspirated from the pericardial and pleural cavities. Due to the diversity and intricacy of the multiple pathways involved in manifesting an acute inflammatory response, it appears unlikely that a single drug will ever be completely effective. However, because cardiac surgical patients are vulnerable to postoperative respiratory and wound infections and because the inflammatory response is an important step in wound healing, a thorough understanding and fine control of our therapeutic interventions is necessary so as to optimise patient recovery and ameliorate the development of SIRS.

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