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Kardiyopulmoner Bypass Sürecinde İnflamatuvar Yanıt
Inflammatory Response in Cardiopulmonary Bypass Process

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ÖZET

Kardiyopulmoner baypas (KPB) ile yapılan kalp cerrahisi, çeşitli postoperatif komplikasyonların patogenezinde rol oynayan bir akut faz reaksiyonuna neden olur. Kalp cerrahisi hastalarında inflamasyon, trombin, kompleman, sitokinler, nötrofiller, adezyon molekülleri, mast hücreleri ve diğer inflamatuar mediatörlerin aktivasyonu, üretimi veya ekspresyonu gibi bir dizi yolak aracılığıyla karmaşık bir humoral ve hücresel etkileşim ağı aracılığıyla meydana gelir. Enflamatuar kaskadların fazlalığı nedeniyle koagülopati, solunum yetmezliği, miyokardiyal disfonksiyon, böbrek yetmezliği ve nörokognitif defisitler gibi çoklu organ sistemi disfonksiyonlarına yol açan derin amplifikasyon meydana gelir. Temas sisteminin aktivasyonu, endotoksemi, iskemi ve reperfüzyon hasarı ve cerrahi travma, KPB sonrası inflamasyonun potansiyel tetikleyicileridir. Pro- ve anti-inflamatuar mediatörler (sitokinler, adezyon molekülleri) arasındaki etkileşimde, hücre içi transkripsiyon faktörleri bu mediatörlerin salınımını düzenler. Bu derlemenin amacı, kardiyopulmoner baypas sırasında enflamatuar yanıtın nasıl işlediğini incelemek, bu sürecin vücutta bir bağışıklık yanıtını nasıl tetiklediğini, enflamasyonun hangi potansiyel komplikasyonlara yol açabileceğini ve bu komplikasyonların nasıl yönetilebileceğini anlamaktır.

Anahtar Kelimeler: Kardiyopulmoner Baypas, İnflamatuvar Yanıt, Sitokin, İnflamasyon

ABSTRACT

Cardiac surgery with cardiopulmonary bypass (CPB) causes an acute phase reaction that plays a role in the pathogenesis of various postoperative complications. Inflammation in cardiac surgery patients occurs through a complex network of humoral and cellular interactions through a number of pathways, such as activation, production or expression of thrombin, complement, cytokines, neutrophils, adhesion molecules, mast cells and other inflammatory mediators. Due to the redundancy of inflammatory cascades, profound amplification occurs, leading to multiple organ system dysfunctions such as coagulopathy, respiratory failure, myocardial dysfunction, renal failure and neurocognitive deficits. Activation of the contact system, endotoxaemia, ischaemia and reperfusion injury and surgical trauma are potential triggers of inflammation after CPB. In the interaction between pro- and anti-inflammatory mediators (cytokines, adhesion molecules), intracellular transcription factors regulate the release of these mediators. The aim of this review is to examine how the inflammatory response works during cardiopulmonary bypass, to understand how this process triggers an immune response in the body, what potential complications inflammation can lead to and how these complications can be managed.

Keywords: Cardiopulmonary Bypass, Inflammatory Response, Cytokine, Inflamation

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INTRODUCTION

Inflammation functions as a protective response of vascularised tissue as part of normal host surveillance mechanisms to eliminate or isolate both harmful agents and damaged tissue (1,3). The essential feature of an inflammatory response is the occurrence of complex humoral and cellular interactions, with many pathways contributing to inflammation, including activation, production or expression of thrombin, complement, cytokines, neutrophils, adhesion molecules and various inflammatory mediators (4,5). Cardiac surgery with cardiopulmonary bypass (CPB) leads to systemic inflammatory response syndrome (SIRS). Contact of blood components with the artificial surface of the bypass circuit, ischaemia-reperfusion injury, endotoxaemia and operative trauma are among the possible causes of SIRS. This inflammatory reaction may contribute to the development of postoperative complications such as myocardial dysfunction, respiratory failure, renal and neurological dysfunction, bleeding disorders, altered liver function and ultimately multiple organ failure (MOF). In the last few years, several strategies have been implemented to minimise the impact of SIRS on the outcome of cardiac surgery patients, including new pharmacological agents, CPB circuits and components, and surgical techniques (6).

Coagulation and Inflammation

The activation of coagulation and inflammation are closely linked through a network of both humoral and cellular components, and proteases of the coagulation and fibrinolytic cascades (particularly tissue factor) are involved in this process. Inflammation-induced thrombin generation can occur through tissue factor (TF), a process that allows it to be expressed in cytokine-activated mononuclear cells with an important role in host defence responses. The formation of the coagulation cascade is classically thought to be the result of two pathways, intrinsic and extrinsic. These pathways consist of a cascade of enzymes that utilise blood clotting factors, the most important of which is thrombin. The intrinsic pathway begins after exposure to collagen in a damaged vascular wall or after blood comes into contact with an artificial surface, such as an extracorporeal circuit. Two events occur in response to these stimuli. Firstly, Factor XII (Hageman Factor) is converted from its inactive form (zymogen) to its active form, Factor XIIa. Secondly, platelets are activated. The conversion of Factor XII to XIIa is further potentiated by plasma kallikrein in a positive feedback loop. Factor XIIa enzymatically activates Factor XI to Factor XIa. This activation 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, the deficiency of which results in

haemophilia. Activated Factor X acts as a protease to convert prothrombin into its active form, thrombin. Thrombin then cleaves fibrinogen into fibrin, which polymerises to form fibrin threads. The first stimulus in the extrinsic pathway is trauma to the vascular wall, which causes the blood to be exposed to a membrane protein called 'tissue factor', which is expressed by non-vascular tissue cells. Factor VII is a circulating plasma protein that forms a complex by binding to tissue factor. During this binding, Factor VII is activated to Factor VIIa. This complex, in the presence of phospholipids, activates Factor X to Factor Xa. Once Factor Xa is formed, the rest of the cascade continues as in the intrinsic pathway (Figure 1) (7). Coagulation is activated as a central element of both a local and systemic inflammatory response (8). Many of the basic coagulation components and products have proinflammatory effects, including thrombin and factor Xa. Thrombin also shows direct chemoattractant activity for polymorphonuclear leukocytes and monocytes and is a potent activator of mast cells (9,10). Vascular endothelial cells play a crucial role in mediating responses to systemic inflammation and in the interaction between coagulation and inflammation (11, 12). Endothelial cells re-store cytokines expressed and released by activated leukocytes and can also release cytokines on their own (13, 14).

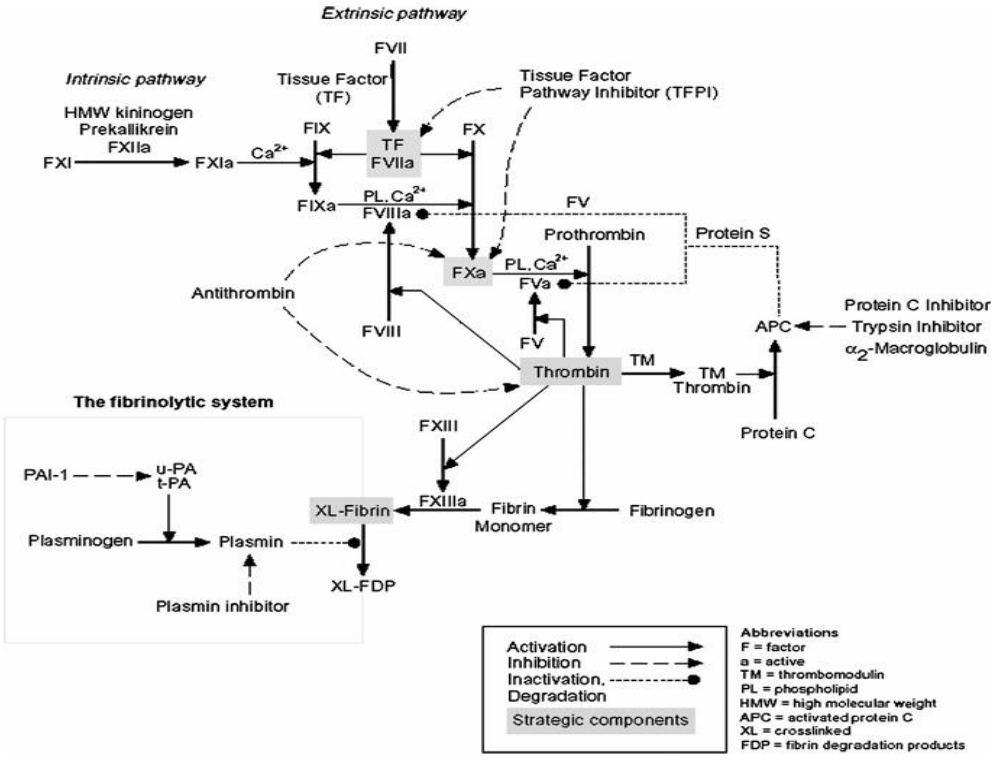

Figure 1 Schematic representation of the functioning of coagulation and fibrinolytic systems (7).

Activation of Acute Phase Reaction during CPB; Stimulants and Mediators

Activation of the acute phase reaction during CPB is an extremely complex process. It occurs at different times and has various triggers, including surgical trauma, blood contact with non-physiological surfaces of the extracorporeal circuit, endotoxaemia and ischaemia. The various mediators involved in this process exert synergistic effects and thus potentiate the process.

1. Contact and Complement systems

Exposure of blood to the extracorporeal circuit triggers activation on the contact system. The active form of factor XII converts prekallikrein to kallikrein and thus initiates the intrinsic coagulation cascade leading to thrombin formation. Activation of the complement system is achieved by three main pathways: The classical pathway, activated by immune complexes (specific antibodies bound to antigens); the alternative pathway, activated on microbial cell surfaces without antibodies; and the lectin pathway, activated by a plasma lectin that binds to mannose residues on microbes. The CPB circuit lacks inhibitors that limit the activation of cofactor C3 on the surface of endothelial cells (EC). This, together with contact activation, triggers kallikrein stimulation and results in the formation of the anaphylotoxins C3a and C5a, which have anaphylactic and chemotactic activity (15). The classical pathway can also trigger activation of C4 and C2. However, C4 and C2 are specifically induced only by heparin-protamine complexes, and this activation is not observed in patients undergoing on-pump coronary artery bypass grafting (CABG) without protamine administration (16).

2. Cytokines

Complement factors and their degradation products may exert an immunomodulatory effect by increasing the synthesis of proinflammatory cytokines (17). Cytokines are intercellular messengers produced by tissues in response to different stimuli. Although they are generally recognised as products of mature leukocytes in the lymphatic system, recent reports suggest that their secretion can also be modulated by cell lines such as platelets. The role of cytokines in the pathophysiology of acute phase reaction associated with CPB has been studied in detail. In addition to increased levels of proinflammatory cytokines such as tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6) and interleukin-8 (IL-8), the role of anti-inflammatory cytokine IL-10 and the balance between these cytokines is an important factor in determining the level of inflammatory response (18).

3. Endotoxin

Endotoxaemia is another factor triggering acute phase reaction associated with CPB. Bacterial lipopolysaccharide (LPS) is released by gram-negative bacteria during growth and proliferation processes or as a result of disruption of bacterial cell membranes after antibiotic administration. Endotoxin in plasma binds to LPS binding protein, a human serum protein whose concentration increases during the acute phase reaction, forming an endotoxin-LPS binding protein complex. This complex binds to the macrophage receptor CD14 and markedly increases macrophage production of TNF-a (19).

4. Nitric oxide (NO)

Proinflammatory cytokines and endotoxin can trigger NO release by endothelial cells (EC) and smooth muscle cells by activating the inducible form of nitric oxide synthase (iNOS) through the nitrous oxide system (NOS). Constitutive nitric oxide (cNO) is produced by endothelial cells (EC) from the amino acid l-arginine via the calcium-dependent enzyme nitric oxide synthase (NOS). NO modulates vasomotor tone in response to physiological stimuli such as pulsatile flow and shear stress (20). iNOS produces higher amounts of NO as a result of activation of a number of transcription factors. iNOS-derived nitric oxide (iNO) is involved in the pathophysiology of the inflammatory state and leads to vasodilatation and increased vascular permeability. Many reports highlight the direct role of iNO in inducing organ dysfunction during SIRS. As mentioned previously, TNF-α-induced iNOS production increases lung vascular permeability, while selective inhibition of iNOS prevents vascular barrier dysfunction (21).

5. Ischaemia

CPB and aortic cross-clamping both act as proinflammatory stimuli that trigger myocardial hypoxia and ischaemia. Ischaemia, together with other factors such as complement, histamine, proinflammatory cytokines, endotoxin and thrombin, promotes the activation of endothelial cells (ECs) and leukocytes, which are effectors of inflammatory cytotoxicity.

Activated transcription factors transmit pro-inflammatory stimuli from the cytoplasm of cells to the nucleus, initiating transcription, translation and activation of inflammatory mediators leading to eventual tissue damage.

Activation of Acute Phase Reaction During CPB; Transcription Factor

Nuclear factor Kb

Nuclear factor kB (NF-kB) is a widely available and inducible transcription factor that regulates the transcription of a number of pro-inflammatory genes. It can be activated by stimuli such as IL-1, TNF-a, LPS, UV radiation, growth factors, oxygen free radicals, oxidative stress and viral infection (22). Several forms of NF-kB have been identified with different cell type specificities and DNA targets. Under normal conditions, NF-kB binds to the IkB inhibitory protein found in the cytoplasm of cells such as endothelial cells (ECs) and leukocytes (23). Upon stimulation, the NF-kB-IkB complex is phosphorylated, which cleaves and inactivates the IkB protein. This phosphorylation process is carried out specifically by the kinases IKKa/IKK1 and IKKb/IKK2. NF-kB binds to DNA and travels to the nucleus to trigger the expression of various inflammatory mediators such as proinflammatory cytokines, iNOS and adhesion molecules. IL-10 blocks the activity of NF-kB by inhibiting IkB phosphorylation and preventing NF-kB-DNA binding (24).

Activation of Acute Phase Reaction during CPB; Tissue damage

Adhesion Molecules and Reperfusion Damage

CPB is associated with increased levels of soluble adhesion molecules. These molecules are expressed transiently and return to normal levels within a few hours, but are thought to be responsible for the dysfunction of multiple organ systems observed in the postoperative period. An association between the expression of adhesion molecules and inflammatory mediators during early reperfusion after aortic declamping has also been demonstrated (25).

During cardiopulmonary bypass, heparin used to prevent blood clotting and protamine used for neutralisation may lead to the formation of oxidative stress. The immune response that develops and continues during CPB may cause organ dysfunction. Catecholamines, neutrophils, complement system, cytokines, free oxygen radicals generated during ischaemia-reperfusion, endothelial damage and endotoxin are among the effective factors in the initiation and maintenance of this response (26). These traumas, resulting from the interaction of heparin with hypothermia and CPB circuits, are considered to be the main triggers for platelet activation. Activated circulating platelets lose their ability to aggregate and this platelet dysfunction is considered the main cause of coagulopathy and bleeding diathesis after CPB surgery. Furthermore, the interaction between activated platelets and activated leukocytes

(especially monocytes) allows platelets to be involved in the inflammatory reaction to CPB, thus increasing the effects of reperfusion injury (27).

Cardiopulmonary Bypass and Systemic Inflammatory Response Syndrome

Cardiopulmonary bypass is often compared with the pathophysiological changes observed in sepsis or systemic inflammatory response syndrome (SIRS) (28). Disseminated intravascular coagulation (DIC) may develop after SIRS and may also occur after cardiopulmonary bypass. In DIC, overactivation of thrombin or coagulation mechanisms leads to microvascular dysfunction and thrombic state, resulting in depletion of coagulation proteins, platelets and bleeding complications due to endothelial dysfunction. DIC is characterised by elevated D-dimer levels with decreased platelet count, low fibrinogen, elevated PT and PTT. These changes can also be observed in pharmacologically sensitive cases undergoing cardiopulmonary bypass (29). ATIII deficiency during perioperative cardiac surgery may be associated with preoperative heparin use, hemodilution effects, and CPB-related consumption (30).

Genomic Variants

Studies examining the complexity of genome and disease relationships have addressed the shortcomings of the candidate gene approach, enabling a more comprehensive evaluation of genotype and phenotype. For example, the development of methods known as 'genome-wide association studies' has made it possible to identify intragenic region variants in specific genes associated with postoperative acute myocardial infarction (MI) after CABG, and some of these variants have been found to be associated with inflammation and ischaemia/reperfusion injury (IRI) In addition, postoperative MI is one of the most common cardiac complications after CABG and may not always be associated with systemic inflammation (31).

Functional Genomics / Transcriptomics and Proteomics

The inflammatory response to CPB has been predominantly analysed by linking biomarkers to triggers and outcomes. In addition, some studies have described gene expression profiles using a deductive approach, thus revealing the expression patterns of genes involved in the inflammation process and their association with clinical outcomes. In fact, oligonucleotide microarray analyses of 12,625 genes performed on atrial and skeletal muscle samples from CABG patients revealed unique expression patterns in which inflammation and apoptosis processes were prominently involved (32).

Inhibition of the Inflammatory Response

The modern era of cardiac surgery began in the early 1950s with the safe use of cardiopulmonary bypass (CPB). Although it is recognised that CPB is indispensable for most open heart surgery, the continued occurrence of adverse SIRS remains a major problem. CPB-specific factors predispose cases to this problem, including exposure of blood to artificial surfaces, surgical trauma, ischaemia-reperfusion injury, changes in body temperature and endotoxin release. Therefore, efforts to prevent this undesirable inflammatory response have been based on approaches such as complete avoidance of CPB (off-pump surgery), replacement of the biocompatible CPB circuit (heparin-bound circuits), removal of activated neutrophils (leucodepletion filters) and the use of pharmaceutical drugs (glucocorticoids, complement inhibitors and aprotinin).

Complement Inhibitors

Complement inhibitors are currently of great interest as they may provide significant therapeutic benefits in reducing morbidity after CPB. For example, Pexelizumab is a recombinant antibody fragment that inhibits the formation of C5a and C5b-9 by binding to the C5 complement component. However, the production of C3b, the key mediator of bacterial opsonisation, continues unimpeded. In the PRIMO CABG study comparing pexelizumab with placebo, a statistically significant reduction in the risk of MI or death within 30 days after surgery was observed (33).

Serine Protease Inhibitors (Aprotinin)

Aprotinin (Trasylol) was first used clinically in the 1960s for the treatment of acute pancreatitis. However, in the late 1980s at the Hammersmith Hospital, aprotinin's ability to reduce blood loss after surgery with CPB was discovered. This discovery turned out to be an incidental finding as the researchers' original hypothesis was not related to haemostasis. The main focus was on inflammation, in particular the potential effect of aprotinin at a high kallikrein inhibitor dose to attenuate the inflammatory response to CPB.

Aprotinin is a serine protease inhibitor isolated from bovine lung tissue and is now widely used in cardiac surgery. This substance has the ability to inhibit trypsin, chymotrypsin, plasmin, tissue plasminogen activator, kallikrein, elastase, urokinase and thrombin. Current studies support the efficacy of aprotinin in reducing blood loss and transfusion requirements in cardiac surgery. The haemostatic effect of aprotinin is attributed to its capacity to limit fibrinolysis through inhibition of plasmin and kallikrein. In addition to haemostasis, aprotinin has also been

reported to preserve platelet function, reduce SIRS and even lower the risk of perioperative stroke (34). However, the use of aprotinin was banned in some countries as a result of safety assessments conducted in 2008. The use of aprotinin to control bleeding during cardiopulmonary bypass and major surgical procedures has been restricted due to serious side effects such as adverse effects on renal function and increased risk of death. Therefore, drugs such as tranexamic acid and aminocaproic acid, which are safer alternatives to aprotinin, have started to be preferred.

Complete avoidance of CPB (Non-pump surgery)

Coronary artery bypass grafting (CABG) can now be performed without the use of CPB, i.e. off-pump coronary artery bypass (OPCAB). OPCAB has been shown to reduce postoperative morbidity such as myocardial injury, renal dysfunction, neurocognitive deficit and SIRS. 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 resulting in increases in pro-inflammatory markers still persists.

Heparin-bound circuits

This has theoretical advantages, as high-dose heparin given during CPB is associated with impaired platelet function as shown by activation of GP IIb/IIIa receptors, P-selectin expression and increased platelet aggregation. Heparin coating improves the biocompatibility of extracorporeal circuits as demonstrated by improved clinical outcomes and reduced neurocognitive dysfunction, complement activation, transfusion requirements and ischaemic myocardial damage.

Leukocyte filters

Activated monocytes and neutrophils play an important role in the development of post-CPB SIRS and this has led to the introduction of leukocyte-depleting filters into the CPB circuit. Reported benefits include reduced circulating activated leukocytes, transfusion requirements, renal dysfunction and pulmonary inflammation, accelerated extubation and improved clinical outcomes.

Glucocorticoids

They affect carbohydrate metabolism, protein metabolism, lipid metabolism, electrolyte and water balance, cardiovascular system, skeletal muscle, CNS, blood-forming elements and have

anti-inflammatory properties and affect other organs and tissues in a wide variety of ways. Glucocorticoids increase 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 decrease the levels of pro-inflammatory cytokines (TNF-a, IL-6, IL-8)71,72 and increase the release of anti-inflammatory cytokines (IL-10) (35).

The age, comorbid conditions and gender of the patient may have a marked effect on the inflammatory response. In elderly individuals, inflammation may be stronger as the immune system is usually weak. Comorbid conditions such as diabetes and hypertension may increase the inflammatory response. Also, taking into account the differences between men and women, hormones can influence the inflammation process, leading to different inflammatory responses between the sexes. Apart from drug therapies, non-pharmacological approaches such as diet, exercise and rehabilitation also play an important role in managing inflammation. Foods with anti-inflammatory properties and regular exercise can reduce inflammation. In addition, rehabilitation after surgery can keep the inflammatory response under control by accelerating patients' recovery. These approaches can increase the effectiveness of the treatment process and promote postoperative recovery.

CONCLUSION

Cardiopulmonary surgical procedures lead to the activation of natural defence mechanisms in the body and the emergence of a complex inflammatory response. In this process, the use of cardiopulmonary bypass (CPB) stands out as one of the main triggers of the inflammatory response. Mechanical and biochemical stress during CPB activates the immune system by increasing the release of inflammatory cytokines. The most common inflammatory reactions include cytokine storm, activation of leukocytes, activation of the complement system and endothelial damage. These events are associated with systemic inflammatory response syndrome (SIRS), which can progress to organ dysfunction and have serious consequences. Contact of the devices used during the operation with foreign surfaces, exposure of blood cells to mechanical trauma, the effect of oxygenators and haemodynamic changes may further increase this inflammatory response. In addition, factors such as the age of the patient, comorbidities and duration of surgery also play an important role in determining the severity of inflammation. Controlling the inflammatory response in this process may favourably affect the patient's recovery after surgery. Strategies such as corticosteroids, anti-inflammatory drugs and heparin-coated circuits have been applied for this purpose. The development of modern CPB devices and innovations in surgical techniques also contribute to the reduction of

inflammation. A better understanding of the inflammatory response during CPB will allow the development of treatment approaches. With the studies conducted, it is expected that more specific treatment methods that will target inflammation as well as technologies that can better manage the biological effects of CPB will be developed in the future. In addition, personalised treatment approaches stand out as an important area to minimise the inflammatory response and accelerate the recovery process of patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Ethics Approval and Consent

Ethical approval was not required since it was a review article.

Conflict of Interest

No conflict of interest was declared by the authors.

Author Contributions

Gülşah Celik Korhan: Article hypothesis, Literature review, Writing.

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