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# IMMUNOBIOCHEMICAL MARKERS OF CARDIAC REVASCULARISATION DURING AORTOCORONARY BYPASS SURGERY IN PATIENTS WITH CORONARY HEART DISEASE UNDER ARTIFICIAL CIRCULATION

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**Abstract:**

Background. Coronary heart disease (CHD) is one of the leading causes of mortality worldwide, and aortocoronary bypass surgery (ACS) continues to be the gold standard for the treatment of patients with CHD. ACH surgery can be performed with or without the use of artificial circulation. A number of studies have shown that ACS operation, mainly in the mode of artificial circulation, leads to changes in cellular immunity in the preoperative and early postoperative period. The mechanisms of immune response regulation in patients during and early after surgical revascularisation are not fully understood. Previous studies have emphasised the fundamental role of cytokines and chemokines in coronary atherogenesis, atherosclerotic plaque formation, cardiovascular inflammatory changes, acute coronary thrombosis and CHD. The aim of this review is to study the currently available significant immunobiochemical markers of prognosis of complications during aortocoronary bypass surgery under artificial circulation, as well as various immune mechanisms involved in the pathogenesis of CHD in patients undergoing ACS.

**Keywords:** atherosclerosis, CHD, aortocoronary bypass, artificial circulation, immunopathogenesis, immunoparalysis

**RELEVANCE:** Among circulatory diseases that continue to lead the overall mortality rate worldwide, coronary heart disease (CHD) remains the most significant pathology in terms of both morbidity and mortality in the general human population [WHO, 2019]. CHD is characterised by inadequate myocardial oxygen supply, due to endothelial dysfunction of large or small coronary arteries. CHD is mainly characterised by chronic inflammation due to the presence of densely accumulated atherosclerotic plaques causing occlusion of the lumen of two or more coronary arteries [ 1 ]. These plaques are mainly composed of fatty streaks with macrophages containing excessive amounts of absorbed lipids and T lymphocytes. These immune cells further contribute to coronary artery endothelial dysfunction [ 2 ] and maintain progressive inflammation [3 ]. Local inflammation associated with atherosclerotic plaques produces a variety of inflammatory cytokines, including type 1,type 2 (especially IL-4) [ 5 ] and type 3 [ 6 ] immune-related cytokines, which subsequently enter the bloodstream. Studies have also shown the association of TNFα, IL-1β, MCP-1, MIP-1a and eotaxin with the pathogenesis of CHD [ 9 , 10 ]. It should be noted that serum IL-6 is considered a highly prognostic marker of CHD when screened in a population at cardiovascular risk [ 11 ]. In addition to IL-6, elevated serum IL-1 receptor antagonist (IL-1RA) levels are also considered a significant independent predictor of CHD mortality These inflammatory cytokines additionally activate monocytes, contributing to the maintenance of systemic inflammation .

Although there is optimal drug therapy to curb the progression of atherosclerosis in CHD, most patients with multivessel CHD undergo surgical intervention, commonly known as "aortocoronary bypass surgery" (ACB). During surgery, ex vivo contact of circulating blood with non-physiological surfaces further exacerbates the degree of inflammation, which may worsen the condition of patients at high risk of comorbid CHD with renal failure and diabetes. Elevated systemic levels of circulating neutrophils, elastase, neutrophils, complement components (C3a and C5a), platelet activation factors, C-reactive protein (CRP), pro-inflammatory cytokines, adhesion molecules (E-selectin, P-selectin, ICAM-1) and cardiac troponin I . It is known that chronic persistent inflammation contributes to the

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development of postoperative complications of ACS [14]. The development of complications is caused, on the one hand, by the presence of comorbid pathology, shunt dysfunction and related complications, and, on the other hand, by the progression of atherosclerosis of coronary arteries and shunts [13].

Given the lack of a clear understanding of the contribution of individual components of the immune response to the development of complications after myocardial revascularisation, further research in this area is required to better understand the complex pathogenesis of CHD and the interventional aspects of preoperative and/or postoperative cardiac bypass. Immunopathogenesis of CHD: CHD is a chronic inflammatory disease caused by atherosclerosis and affecting both the middle and intimal layers of coronary arteries [ 8 ]. The complex and multifactorial etiology of atherosclerosis includes contributions from both metabolic and immune mediators. Atherogenesis begins with endothelial dysfunction in sensitive areas of arteries characterised by impaired blood flow. The process of inflammation plays a key role in the initiation and progression of CHD through the release of pro-inflammatory cytokines, which in turn induce the activation of inflammatory cells (macrophages and monocytes) [ 9 ]. In arterial vessels, HDL and LDL lipoproteins with a diameter of less than 70 nm can cross the endothelial layer and penetrate the vessel intima. Infiltrated lipoproteins may undergo modification by oxidants, proteases and lipases, which in turn may contribute to the formation of inflammatory atherosclerotic lesions by activation and recruitment of the inflammatory complex and leukocytes. A key role in this process is played by macrophages, which engulf modified lipoproteins, promoting the formation of foam cells. In the initial stages, acute inflammation is a protective and resolving process controlled by anti-inflammatory molecules, such as IL-10, which help to reduce leukocyte recruitment [ 3]. While early lesions known as fatty streaks are characterised by the presence of foam cells loaded with cholesterol esters that accumulate due to unregulated uptake of native and modified lipoproteins, predominantly macrophages and vascular smooth muscle cells (VSMCs), more advanced lesions contain a central area of activated immune cells, cholesterol crystals and extracellular lipids, surrounded by a fibrous sheath of VSMCs and collagen [ 11]. Over time, excessive death of immune cells in the lesion focus makes it difficult to remove them by efferocytosis. Insufficient efferocytosis leads to secondary necrosis and necrotic core formation in addition to primary necrosis . Pro-inflammatory forms of programmed cell death such as necroptosis and pyroptosis are also observed in the vascular wall [ 2] and may contribute to the progression of atherosclerosis. Both the growth and stability of progressive plaques may affect the outcome of the disease in different ways. Plaque growth is due to the predominance of continued recruitment of immune cells and macrophage proliferation over their apoptosis and outflow. The plaques become unstable due to increased inflammatory activity, a growing necrotic core and thinning of the fibrous capsule due to decreased collagen synthesis and increased secretion of matrix metalloproteinases. Calcinates in the fibrous cap contribute to rupture or erosion of these plaques [ 13]. Exposure of thrombogenic plaque material to platelets and clotting factors results in thrombus formation, which can immediately block blood flow and cause target organ damage. Although an anti-inflammatory network of immune cells and resolving factors attempts to counteract atherogenesis and mitigate the side effects associated with immune cell activation [ 4 ], the chronic self-sustaining inflammation prevalent during plaque progression continues to exacerbate the pathological process.

ACS : Aortocoronary artery bypass grafting (ACBG) remains the most commonly performed cardiac surgical procedure worldwide.And risk assessment for patients undergoing cardiac surgery has become increasingly important. Over the last decades, several risk assessment systems have been developed, such as STS Risk Score and EUROSCORE II [3, 6 ]. They are able to predict the likelihood of a patient to experience postoperative complications after cardiac surgery such as mortality, renal failure, irreversible stroke, prolonged ventilatory support, deep wound infection and prolonged hospital stay. Predicting the risk of morbidity and mortality after cardiac surgery based on comorbidities and other clinical problems establishes benchmarks for measuring the quality indicators of cardiac surgical interventions performed [16].

It is known that ACS can induce systemic inflammatory response syndrome (SIRS) characterised by leukocytosis, capillary leakage, multi-organ dysfunction and imbalance in the production of pro-inflammatory cytokines (e.g. IL-6, IL-8) [7 ]. SIRS partially counteracts the compensatory anti-inflammatory response syndrome (CARS), characterised by the release of anti-inflammatory cytokines (e.g. IL-4, IL-10), and occurs in 40% of ACS cases [38]. An imbalance in immune homeostasis due to SIRS and/or CARS may increase the risk of postoperative infection in patients with ACS, especially when CARS dominates over SIRS [9].

Of note, researchers have observed lower SIRS, faster postoperative recovery, and shorter hospital stay with non-CARS than with CARS; however, local myocardial

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inflammation, was not attenuated. Even after adjustments in surgical technique, perioperative myocardial infarction remains the most frequent adverse complication, probably due to thinning of the glycocalyx during specific stress conditions . The glycocalyx is a very fragile and unstable surface layer of endothelium that is mainly composed of syndecan-1, hyaluronic acid, heparan sulfate and chondroitin sulfate. Rejection or complete absence of the glycocalyx layer leads to direct mechanical stress on the membrane of apical endothelial cells and suppression of their NO production, which in turn leads to increased blood pressure, disruption of intercellular contacts with increased endothelial permeability and increased endothelial activation status. Recently, impaired endothelial glycocalyx has been shown to be observed in patients with chronic kidney disease, type II diabetes mellitus, tumour angiogenesis, acute coronary syndrome and in patients at the time of ACS. However, the relationship between proinflammatory cytokines and glycocalyx damage is still not widely understood.

Changes in the patient's immune profile after ACS can be divided into early and late phases. Direct contact of the patient's blood with non-endothelial shunt surfaces triggers the early phase of the response, activating processes such as coagulation, fibrinolysis, complement activation, and cell types such as lymphocytes, monocytes, and neutrophils . The late phase of the response is triggered by neutrophil-endothelial cells and is conditioned by cardiac/lung ischaemia and reperfusion injury. Ischaemia damages endothelial cells, leading to neutrophil activation and release of pro-inflammatory mediators.The release of pro-inflammatory mediators can also modulate immunoregulatory cells such as dendritic cells (DCs) and monocytes. DCs are antigen-presenting cells that play a central role at the interface between the innate and adaptive immune response. In human peripheral blood, DCs comprise <1% of the leukocyte population and release cytokines and chemokines required for antigen presentation and immune regulation [4]. Monocytes also link the innate and adaptive immune response and mediate antimicrobial host defence and removal of apoptotic cell debris. Monocytes comprise 2-12% of the leukocyte population and are a source of myeloid precursors, macrophages and DCs. Understanding the role of DCs and monocytes in ACS-related immunomodulation and whether dysfunction of these cells contributes to adverse patient outcomes is limited. A recent prospective study evaluating the phenotype of DCs and monocytes in patients with ACS found evidence of suppression of monocyte, cytokine and chemokine production by DCs in patients undergoing ACS [20].

Alterations in immune homeostasis caused by ACS may also lead to cellular immunoparalysis, whereby the immune system becomes immune to secondary damage (e.g. inflammation or infection).

ACS-induced immunoparalysis: Persistent imbalance of immune homeostasis can lead to a state of immunosuppression and consequently to immunoparalysis. Immunoparalysis is thought to be a protective adaptation to the suppressive pro-inflammatory response, rendering key immune response cells immune to secondary damaging effects . When cells are paralysed, their ability to respond adequately to additional stimuli is reduced.There is a decrease in surface expression of HLA-DR by monocytes and TNF-α production [19]. As a result, immunoparalysed patients may have an increased risk of infectious complications after trauma or surgery. The effects of immunoparalysis have been reported in trauma, sepsis, cardiac surgery, and ICU settings [6]. A group of researchers, using LPS as a stimulant to simulate bacterial infection, showed that monocyte and DC cytokine production was immunoparalysed after ACS and throughout the postoperative period. However, recovery of monocyte and DC cytokine profile was not observed in the postoperative period, suggesting a persistent dysfunction of cytokine and chemokine signalling, which may affect antimicrobial defence, cell recruitment, mediating an increased risk of postoperative infection and prolonged ICU stay . LPS-induced immunoparalysis of key pro-inflammatory cytokines (e.g. IL-6, IL-8, IL-10, IL-12, TNF-α) released from monocytes in patient plasma and supernatants collected from culture of in vitro models in healthy donors [9] , cardiac surgery patients and patients with sepsis [10] has also been previously reported. However, the pathogenesis of immunoparalysis is poorly understood, so the mechanisms underlying it require further investigation.

Immunological markers of ASA: To date, sufficient data have been accumulated to demonstrate the role of various immunological markers in the pathological processes associated with bypass surgery and used in predicting future outcomes after myocardial revascularisation. Thus, it is known that significantly elevated levels of cytokines IL-6, IL-1RA and IL-8 are characteristic of patients with CHD and indicate persistent chronic inflammation. It was also found that the levels of these cytokines were much higher after cardiac bypass surgery, indicating a more pronounced degree of inflammation among the postoperative CHD cohort. In addition, it appeared that among postoperative patients, elevated levels of the cytokine IL-4 may be pro-inflammatory in nature, which may lead to the formation of reactive oxygen species (ROS)

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and subsequent vascular inflammation, thereby enhancing atherogenesis. Another study also showed that IL-4 levels showed an increased tendency to directly correlate with CRP levels among postoperative patients. It should be noted that decreased GM-CSF secretion in the postoperative CHD group compared to the preoperative CHD group may possibly exacerbate atherosclerosis, as evidenced by the accumulation of macrophages low in PPAR-γ, which positively regulate inflammation. and cholesterol metabolism. Moreover, the elevated IL-5 levels among the postoperative CHD cohort could possibly explain their involvement in repair mechanisms of damaged tissues by participating in eosinophil recruitment and polarisation towards M2 type CD206+ macrophages, which is supported by experimental evidence. Similarly, an increase in the cytokine IL-10 was more evident among postoperative IBS patients, reflecting the activation of anti-inflammatory responses to counterbalance the escalation of inflammation after surgery. Thus, it is evident that a significant increase in both anti-inflammatory cytokine IL-10 and pro-inflammatory cytokines tends to maintain their balance during the increased inflammation resulting from cardiac bypass surgery. Another study also showed the possible regulatory nature of cytokines IL-5 and IL-10, which showed a higher tendency to be inversely related to CRP in postoperative patients. Although plasma TNFα did not differ significantly between the preoperative and postoperative cohort of IBS patients, postoperative TNFα levels directly correlated with baseline serum troponin, creatinine, glucose, and BMI levels, which may be a predictor of severity and poor prognosis among postoperative IBS patients with comorbidities such as chronic renal failure, type 2 diabetes, and obesity. Levels of the preoperative anti-inflammatory cytokine IL-10 and the possible anti-atherogenic GM-CSF were positively correlated with serum troponin, suggesting the existence of attenuation of inflammation after troponin release, which remains to be investigated. However, very interestingly, it has been shown that monocyte cytokine IL-6 synthesis and STAT-3 phosphorylation are mediated by the CCR1 receptor, which is also associated with IL-8 cytokine secretion, and enhanced IL-6 and IL-8 production and increased monocyte CCR1 expression have also been demonstrated among the postoperative CHD cohort. Thus, unbalanced cytokine levels and high macrophage CCR1 macrophage polarisation potential in monocytes cause an increased state of inflammation and a greater propensity for atherosclerotic plaque rupture among postoperative patients. Another cytokine IL-18, which is a key pro-inflammatory mediator in the pathogenesis and deterioration of patients with heart and vascular disease also mediates plaque rupture and the development of acute coronary syndrome, which is a prognostic factor for myocardial infarction and heart failure , potentially through increased cytotoxicity of activated T and NK cells recruited to the subintimal layer. Patients undergoing ACS and valve replacement had a similar increase in circulating plasma IL-18 protein levels. However, in the epicardial adipose tissue of patients who underwent myocardial revascularisation, gene expression of IL-18 system components was higher than in patients who underwent valve replacement.These data indicate that local production of the proinflammatory protein IL-18 and its autocrine or paracrine effects may provide more information about endothelial dysfunction in coronary arteries than IL-18 concentration in peripheral blood [15].

Pathophysiology of systemic changes and systemic inflammatory response to artificial circulation: Cardiac surgery using artificial circulation (AC), although not perfect, is still important in the intraoperative management of various pathologies. IC is associated with a systemic inflammatory response and endothelial dysfunction arising from blood contact with artificial surfaces, as well as from surgical trauma, which lead to the development of ischaemic-reperfusion (IR) myocardial injury [16]. Aortic constriction and subsequent global cardiac ischaemia lead to further damage to susceptible myocardial tissue. Although a number of measures have been used to control inflammation, none of them has yet proven conclusively effective.

During artificial circulation, circulatory physiology is completely altered by the introduction of non-pulsatile flow on the arterial side, which counteracts the increased venous pressure on the venous side of the circulation. This situation generates adaptation mechanisms, thus providing a "shunt" effect, sometimes harmful to the circulation, which may lead to the development of SIRS [ 17 ]. Factors associated with IR, such as haemodilution, contact activation and induction of a systemic inflammatory response, are thought to impair microcirculatory perfusion, affecting both transport and diffusion of oxygen at the microvascular level. Another form of microcirculatory damage associated with IR application is the formation of microbubbles that circulate in the bloodstream and settle in capillaries causing obstruction, promoting ischaemia, inflammation, complement activation, platelet aggregation and thrombus formation. In addition, IR is responsible for other circulatory changes such as the replacement of pulsatile physiological flow with continuous flow, which increases the pressure on the venous side. In the microcirculation, continuous flow causes phenotypic adaptation of cells, which may

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also lead to the development of SIRS [18 ]. Hypothermia associated with artificial circulation is known to reduce the metabolic demands of patients, providing additional protection to the body, especially vital organs, to avoid anoxia-related injuries.However, hypothermia reversibly inhibits clotting factors and platelets, and rapid warming and hyperthermia have been associated with brain damage.During the first moments of IR, hypotension often occurs due to decreased perfusion flow, decreased blood viscosity due to haemodilution and increased bradykinin levels. After this period, a compensatory response begins in the body, which, especially with hypothermia, increased systemic vascular resistance and lack of pulsation in the circulation, leads to hypertension. However, as a consequence, renal vasoconstriction occurs, predisposing the kidneys to ischaemia and damage.In addition, haemodilution with crystalloid solutions in excess predisposes the patient to oedema formation and watery diuresis rich in electrolytes, contributing to hydroelectrolytic imbalance . Haemorrhagic disorders associated with IR are associated with changes in blood coagulation as blood circulates through tubes and devices that are non-endothelial surfaces. This imbalance of blood haemostasis during IR is the most frequent manifestation of thrombotic events, whereas bleeding is commonly reported after IR. As for the lungs, there is an increase in water entry into the interstitium due to inflammatory cells, inactivation of surfactant and atelectasis, and decreased lung capacity, which together with the effects of hypothermia maintained during IR, leads to pulmonary endothelial damage .

IR is associated with microvascular changes in several pathological aspects. Endothelial cell damage and subsequent acute inflammation with vascular injury, changes in the coagulation cascade, reperfusion injury and gas microemboli confirm organ dysfunctions during and after IR [ 7]. The pathophysiology of the systemic inflammatory response to IR is multifactorial and can be divided into two main phases: "early" and "late" phases. The first phase occurs when blood comes into contact with non-endothelial surfaces of systemic cannulas ("contact activation"). The late phase is due to ischaemic-reperfusion injury (I/R injury), endotoxaemia, coagulation abnormalities and heparin/protamine reactions. There are two main mechanisms of endothelial injury, neutrophil-mediated and non-neutrophil-mediated. In the former, integrins on the surface of neutrophils bind to molecules on endothelial cells, generating oxidative stress by reducing trivalent iron to divalent iron induced by superoxide anion, which is formed from xanthine oxidase produced by neutrophil elastase introduced into endothelial cells. Endothelial neutrophil-mediated cytotoxicity can also be induced by intracellular mechanisms involving nitric oxide synthase . In non-neutrophil-mediated injury, circulating pro-inflammatory cytokines (TNFa and IL-1) directly stimulate endothelial cells, leading to a pathological increase in permeability, causing tissue oedema and impaired oxygen metabolism, which contributes to the development of multi-organ dysfunction [ 3].

Aortic clamping during artificial circulation blocks coronary blood flow with decreased oxygen supply to myocytes, altering electrical activity and stopping mechanical activity of the heart. This manoeuvre of aortic clamping and subsequent release of the clamp during artificial circulation provides favourable conditions for the formation of free radicals that trigger oxidative stress [ 4 ]. In ischaemia, the supply of oxygen to mitochondria stops, interrupting the Krebs cycle. Thus, ATP formation becomes predominantly anaerobic. This change is accompanied by an increase in cytosolic lactate and a decrease in intracellular pH. The decrease in cellular ATP concentration interrupts the activity of pumps that are important for ion homeostasis, such as the sodium and potassium pumps and the calcium-ATPase of the sarcoplasmic reticulum, resulting in cytosolic Na + and Ca 2+ overload that prevents cell repolarisation and leads to contractile dysfunction. In addition, high concentrations of Ca 2+ in the cytosol activate enzymes associated with lipid peroxidation, production of reactive oxygen species (ROS), dysfunction of contractile proteins, loss of cellular function and ultimately cell death. In tissue reperfusion with the end of aortic occlusion, it promotes the formation of AFCs in the cytosol, mitochondria, peroxisomes, lysosomes and plasma membrane of polymorphonuclear leukocytes activated during ischaemia. Thus, the reintroduction of an oxygen molecule into ischaemic heart tissue causes free radicals to react with polyunsaturated fatty acids from the cell membrane. This triggers a chain of oxygen-dependent lipid degradation in which lipid peroxides and hydroperoxides are formed, which are rapidly generated by the NADPH-oxidase complex in response to cytokines, resulting in the formation of excessive amounts of AFCs, increased membrane permeability and subsequent cell membrane damage that contributes to functional impairment during . When these AFCs accumulate out of proportion to the body's antioxidant capacity, we encounter a situation called oxidative stress. The excess of reactive forms causes arrhythmias, decreased systolic function and altered myocyte membrane permeability. To avoid this, hydroperoxide radicals are removed from cells by enzyme systems with antioxidant functions normally

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present in the myocardium. These enzyme systems with antioxidant action are responsible for limiting the intracellular accumulation of reactive species during normal metabolism, reducing oxidative damage to proteins, lipids and DNA [ 11].

**CONCLUSIONS:** Based on our retrospective analysis of the currently available scientific literature regarding the role of immunological mechanisms in the pathogenesis of myocardial revascularisation in IBS patients, it became evident that the immunopathogenesis of inflammatory reactions occurring in the pre-, intra- and postoperative period of ACS is extremely complex and insufficiently studied. Consequently, the search for additional predictors of etiopathogenetic mechanisms of immune disorders before and after ACS requires further study in complex examination in patients with CHD.

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