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Review Article

Development of Complications and Analysis of The Role and Pathogenesis of Oxidative Stress, Nitric Oxide and Intraoperative Hemolysis.

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Abstract

The pathogenesis of CABG-related arrhythmias is complex and not fully understood. Perioperative and early postoperative arrhythmias likely represent a reaction of the conduction system to the altered blood flow during the surgery, including the transition from cold cardioplegia to reperfusion. Coronary artery bypass surgery in patients with coronary heart disease (CHD) is frequently associated with postoperative complications, with arrhythmias being a significant concern. Potentially life-threatening arrhythmias, such as ventricular fibrillation and tachycardia, and third-degree atrioventricular block, as well as hemodynamically significant arrhythmias like atrial fibrillation (AF), severe bradycardia, and severe sinus tachycardia, are common.

Keywords: oxidative stress; nitric oxide; intraoperative hemolysis; CABG; CHD; CPB; AP

Introduction

The pathogenesis of CABG-related arrhythmias is complex and not fully understood. Perioperative and early postoperative arrhythmias likely represent a reaction of the conduction system to the altered blood flow during the surgery, including the transition from cold cardioplegia to reperfusion. Coronary artery bypass surgery in patients with coronary heart disease (CHD) is frequently associated with postoperative complications, with arrhythmias being a significant concern [1, 2]. Potentially life-threatening arrhythmias, such as ventricular fibrillation and tachycardia, and third-degree atrioventricular block, as well as hemodynamically significant arrhythmias like atrial fibrillation (AF), severe bradycardia, and severe sinus tachycardia, are common. AF, a highly prevalent and dangerous postoperative arrhythmia, is frequently observed (25-65% of cases) [3] and is associated with adverse outcomes, including increased risk of heart failure progression, thromboembolism, prolonged hospitalization, and mortality [4]. Patients experiencing AF after CABG have a higher risk of mortality related to cerebrovascular accidents and myocardial infarction [5]. Reoxygenation following the restoration of coronary blood flow can induce oxidative stress, metabolic disturbances, and electrical heterogeneity in the myocardium [6]. Further, the use of cardiopulmonary bypass (CPB) during CABG, necessary for maintaining blood circulation during the operation, is associated with potential red blood cell damage. Carrying out reconstructive surgery on the heart involves restoring blood flow in the previously ischemic myocardium, i.e., the state of ischemia that existed in the heart before coronary bypass surgery is replaced by a state of blood flow restoration or reperfusion [7]. The presence of information about the possible development of reperfusion syndrome in a previously ischemic organ indicates its possible development and participation in the development of complications.

As is known, reperfusion syndrome is a symptom complex of disorders in an ischemic organ after restoration of blood flow in it [8]. CABG surgery involves the initiation of reperfusion syndrome in the myocardium due to restoration of blood flow for several reasons, firstly, in the area of blood supply to the occluded coronary artery, and secondly, throughout the body after artificial cardioplegia to stop cardiac activity [8-10].

As is known, reperfusion processes, along with the main – restorative effect, have a pathogenic effect on heart tissue 9]. Elimination of myocardial ischemia by creating a bypass shunt does not lead to a complete stop in the development of ischemic damage, promoting additional alteration by reperfusion and reoxygenation factors. There are various mechanisms that play a role in post-ischemic myocardial dysfunction: hypercontracture, metabolic disorders [11], dysfunction of the coronary artery endothelium [12], electrical instability, impaired neurogenic regulation of the heart.

Myocardial reperfusion injury is characterized by myocardial, electrophysiological and/or vascular dysfunction [13].

The consequence of ischemia-reperfusion may be the development of irreversible myocardial damage with a significant expansion of the zone of necrosis caused by previous ischemia (lethal reperfusion injury) [14].

Morphological signs of myocardial reperfusion injury are detected at autopsy in 25-45% of patients who died soon after CABG [15]. As a result of short-term reperfusion, more pronounced damage to cardiomyocytes is observed than after prolonged ischemia.

Disorders that occur during ischemia-reperfusion in the myocardium due to reoxygenation depend on the duration of the previous ischemic period, leading to aggravation of the damaging effects of ischemia, such as energy deficiency, oxidative stress, inflammation, edema, apoptosis, causing the death of cardiomyocytes and the development of necrosis of the myocardial area [16].Along with the massive formation of reactive oxygen species (ROS) and products of lipid peroxidation (LPO), a major role in the damage belongs to the formation of hypercontracture of cardiomyocytes, disruption of metabolism and osmolarity of the interstitium, and the opening of pores that regulate the permeability of the inner mitochondrial membrane [16].

One of the manifestations of myocardial damage caused by ischemia-reperfusion is its "stunning". "Stunned" or "stunned" myocardium (stunned myocardium, from the English "stun" - to stun, stun) is characterized by reversible contractile dysfunction and cessation of coronary blood flow (no-reflow phenomenon) while maintaining the viability of cardiomyocytes [17]. A sign of stunned myocardium is a discrepancy between blood flow and myocardial function. Despite the complete or almost complete restoration of coronary blood flow, disturbances in the contractile function of the myocardium are noted [18]. Another manifestation of reperfusion syndrome in the heart, as evidence of successful restoration of coronary blood flow, is the occurrence of arrhythmia. This reflects the connection of heart rhythm disturbances with the impact of reperfusion and reoxygenation factors on atypical cardiomyocytes of the cardiac conduction system with the occurrence of their electrical heterogeneity [19].

The clinical manifestation of myocardial "stunning" during reperfusion is the occurrence of heart failure or its aggravation [19].

When performing operations under IR conditions, stanning may cause temporary left ventricular failure. Subsequently, there is a gradual restoration of the contractile function of the myocardium, the speed of which depends on the severity of ischemic and reperfusion damage [20]. Despite the constant improvement of IR methods, anesthesia and cardio protection, the incidence of acute heart failure after open heart surgery is 3.6-15.4%.

The reason for the development of persistent heart failure is the lack of adequate myocardial perfusion due to the no-reflow phenomenon, which is clinically manifested by a decrease in systolic function of the left ventricle (LV), dilatation of the heart chambers or their aneurysm [20], contributing to death. According to some data, the no-reflow phenomenon occurs in 10-40% of revascularization cases [21].

The leading mechanism of the ischemia-reperfusion syndrome is oxidative stress - a pathological condition characterized by excessive formation of ROS of radical and non-radical nature in quantities exceeding the ability of antioxidant defense mechanisms (AOD) to neutralize them. The reason for the increased formation of ROS during ischemia-reperfusion is the resumption of oxygen flow (reoxygenation) into the ischemic tissue. Restoring oxygen supply to the heart in patients after CABG enhances the generation of oxygen superoxide anion, hydrogen peroxide, and hydroxyl radical. The development of oxidative stress during ischemia-reperfusion may be a consequence of damage to the mitochondrial respiratory chain and the occurrence of a mismatch between electron donors and acceptors.

The sources of excess ROS production during ischemia-reperfusion are the mitochondrial electron chain, as well as activation of the xanthine-xanthine oxidase system, a "respiratory explosion" in leukocytes sequestered in the pre-ischemia zone, and the formation of prostaglandins and catecholamines. A significant role in the generation of ROS is played by the activation of enzymatic systems, such as xanthine oxidase, cytochrome P450, cyclooxygenase and leukocyte NADPH oxidase.

NO synthase acts as a source of active forms of nitrogen, promoting the production of nitrogen monoxide.

Reactive oxygen species, acting in concentrations significantly higher than physiological ones, initiate the processes of lipid peroxidation (LPO) of the cell membranes of cardiomyocytes, cause irreversible oxidative modification of proteins and their proteolytic degradation, damage the structure of nucleic acids and high molecular weight carbohydrates, inactivate antioxidant enzymes and deplete antioxidant non-enzymatic systems. To initiate lipid peroxidation processes after prolonged myocardial ischemia, a smaller amount of oxygen is sufficient than for an intact organ. This is due to the fact that during ischemia, the ability of the energy-producing systems of mitochondria to consume oxygen decreases, which creates an excess of it in the cell, facilitating the conditions for the initiation of lipid peroxidation processes: the activity of enzymatic and non-enzymatic antioxidant systems decreases, the number of initiator metabolites increases and systems that produce ROS are activated.

Oxygen radicals initiate chain processes of peroxidation in membrane lipids of cardiomyocytes.

Oxidative damage to cellular lipids, proteins and nucleic acids caused by free radicals leads to dysfunction of the cell. LPO is the cause of the accumulation of cellular defects. The effect of ROS on the cell leads to a change in the redox state of cellular compartments, which leads to changes in the activity of a number of cellular enzymes, transcription factors, the formation of molecular chaperones, the functioning of ion channels and to the inactivation of membrane receptors, enzymes (glucose-6-phosphatase and Na+-K+-ATPase), which ensure the maintenance of ionic homeostasis of the cell. In mitochondria, matrix enzymes and components of the respiratory chain are damaged. The cause of postoperative rhythm disturbances can be microRNA.

Damaged membranes lose their energy potential, electrical excitability, control over ion flows and messenger systems, resulting in pathological changes in cardiomyocytes, which leads to their death.

The main substrate of LPO are polyunsaturated fatty acids, which are part of cell membranes, as well as lipoproteins. ROS attack leads to the formation of hydrophobic radicals that interact with each other. Alcohols, ketones and aldehydes formed during the oxidation of free fatty acids also have a damaging effect on the cytoskeleton and membranes of cardiomyocytes, increasing their permeability, including for calcium. As a result, cross-links of biopolymers are formed, mitochondria swell and oxidative phosphorylation uncouples, thiol enzymes involved in respiration and glycolysis are inactivated, the lipid basis of membranes is destroyed, resulting in various disturbances in the structure and function of the myocardium. By interacting with phospholipids of the sarcolemma of cardiomyocytes and forming short-lived compounds - lip peroxides, ROS increase membrane rigidity, contribute to their destabilization and rupture, acting together with other damaging reperfusion factors. Oxidation of membrane bilayer lipids causes damage to membrane-bound proteins, resulting in cell death, including vascular endothelium [19-21].

Excess ROS causes disruption of the permeability of cardiomyocyte membranes, changes in ionic homeostasis, damage to the genetic apparatus

and activation of programmed cell death mechanisms, endothelial damage, vasoconstriction, platelet activation and aggregation, leading to the development of "no-reflow" syndrome

Not only membrane phospholipids, but also intracellular proteins and DNA molecules can act as targets for ROS. The resulting oxygen radicals (mainly the hydroxyl radical and, to a lesser extent, the superoxide anion of oxygen) cause DNA damage [22]. The hydroxyl radical OH* can act on purine and pyrimidine bases, as well as ribose and deoxyribose residues. Superoxide anion reacts with guanine bases, resulting in the formation of a variety of oxidized derivatives, including the final oxidation product –7,8-dihydro-8-hydroxyguanosine.

Oxidative stress leads to the opening of the mitochondrial pore, which contributes to the depletion of the ATP pool, activation of apoptosis due to the release of pro-apoptotic factors into the cytoplasm [23]. Damage to mitochondria during reoxygenation is more pronounced than during ischemia. ROS inhibit Na+/K+-ATPase and Ca2+-ATPase, which leads to an overload of the cell with sodium and, due to damage to the sarcoplasmic reticulum, causes an increased intake of calcium into the cell and its overload of Ca2+. At the same time, ROS reduce the sensitivity of myofilaments to calcium by selectively damaging certain contractile proteins due to the oxidation of thiol groups. There are disturbances in the distribution of ions inside the cell and in the extracellular space, which leads to electrical instability, the development of disturbances in the excitability of cardiomyocytes, promotes the development of arrhythmias, contracture, and cell hyperhydration .A high calcium content, which initiates the activation of phospholipase A2, under the influence of which arachidonic acid is released from membrane phospholipids, promotes the formation of inflammatory mediators - leukotrienes, prostaglandins, thromboxane, which leads to migration of neutrophils to the damaged area and the development of an inflammatory response. An increase in intracellular Ca2+ concentration is a key link in the pathogenetic chain leading to the transition of the reversible stage of ischemic damage to irreversible due to the activation of Ca2+-sensitive proteases, lipases and phospholipases, inhibition of biological oxidation in mitochondria and their damage, depolarization of the sarcolemma, contracture of cardiomyocytes. Important mechanisms leading to the progression of damage are a violation of the integrity of the sarcolemma of cardiomyocytes, the release of potassium ions from the cells and the entry of sodium and water ions into them, the entry of calcium ions into the cell, degradation of membrane phospholipids and further delipidation of membranes occurs. An increase in the osmolarity of cardiomyocytes due to the accumulation of sodium, calcium ions, fine organic compounds in them, hyperhydration, can lead to their overextension, rupture and cell death. Damaged membranes lose their energy potential, electrical excitability, control of ion flows and mediator systems, pathological changes and death of cardiomyocytes occur.

Oxidative stress leads to cell death through apoptosis. The current scientific literature addresses the concept of a relationship between ischemia/reperfusion and apoptosis. The apoptotic program is initiated due to the excessive formation of hydroxyl radicals during reoxygenation, the result of which is massive death of cardiomyocytes. Myocardial apoptosis may be involved in the pathogenesis of myocardial stunning and the persistence of long-term myocardial dysfunction after cardiac surgery.

Conclusion

Thus, numerous literature data show the involvement of oxidative stress in cardiac reperfusion injury. However, there is no information about its activity on the degree of intraoperative hemolysis. Determining the relationship between the degree of hemolysis, the activity of oxidative processes and the development of complications in patients with coronary artery disease in the early period of coronary bypass surgery is an important scientific and practical task.

Abbreviations:

CABG: coronary artery bypass grafting

IOH: intraoperative hemolysis

CAD: coronary artery disease

Conflict of Interest: The authors declare that there are no conflicts of interest.

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