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Review Article

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Cardiopulmonary Bypass and Oxidative Stress

Ayşe Dogan[1]*, Fevzi Sarper Turker[2]

[1]Bitlis Eren University Health High School Department of Physiotherapy and Rehabilitation, Bitlis, Turkey
[2]University of Health Sciences Elazığ Training and Research Hospital Cardiovascular Surgery, Elazığ, Turkey

Abstract Hemolysis, ischemic reperfusion injury and neutrophil activation that develop by cardiopulmonary bypass (CPB) have a primary role in the formation of oxidative stress. The use of antioxidants such as propofol, L-arginine, and N-acetyl cysteine in CPB intravenously or by adding cardioplegia can be a defense strategy against ROS production. The intravenous or cardioplegic administration of agents with antioxidant characteristics during the operation can reduce oxidative stress and ROS production in CPB. Alternatively, the use of mini-CPB can regulate both the proinflammatory response and oxidative stress. Still, it is required to conduct different clinical studies on CPB protocol.

Keywords CPB, Oxidative stress, Antioxidant, MDA

Introduction

Cardiopulmonary Bypass

In the development steps of heart surgery, Cardiopulmonary bypass (CPB) has a significant role and has seriously affected the surgical treatment outcomes [1]. On 6 May 1953, Dr. John H. Gibbon Jr. had performed the first successful secundum atrial septal defect (asd) surgery to an 18-year-old female patient through the first successful total cardiopulmonary bypass that had lasted for 26 minutes. After this successful operation, cardiac surgeons have performed millions of successful heart surgeries for generations. Dr. Gibbon had worked hard for 23 years to carry out this successful practice [2]. CPB is associated with the activation of various coagulation pathways, proinflammation, vital cascades, and modified redox state. Hemolysis, ischemic reperfusion injury, and neutrophil activation that develop during CPB have a primary role in the formation of oxidative stress. This situation can modify the clinical results by affecting the functions and of organs such as lungs and kidneys and primarily myocardium and also their recoveries by causing the activation of proinflammatory and preapoptotic signal pathways [1].

Off-pump coronary artery bypass (OPCABG) technique is an evaded situation due to hemodynamic instability during the revascularization on the beating heart. As a result of the technological development, a reduction can occur in this complication by developing new stabilization tools, the increase of the experiences of surgical team, and providing a better hemodynamic management during the operation [3].

Free Radicals

Free radicals are the molecules including unpaired electrons and they are quite reactive. They can be derived from

oxygen, nitrogen, or sulphur molecules. Free radicals derived from oxygen are called as reactive oxygen species (ROS); superoxide anion (O_2^{-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$), and peroxynitrite ($ONOO^{-}$) [4]. Although hydrogen peroxide is not a free radical, it is called as ROS because it is highly reactive [1].

ROS can occur as a natural metabolism product after ATP production in mitochondria [5] or can be caused by the interaction of exogenous components such as xenobiotic components [6]. In this case, the cells neutralize and balance the free radicals by the enzymatic and free radical *scavenging* activities. This is called as the *redox state*. In stress conditions, ROS levels significantly increase and cause the cellular structures such as lipids, proteins, and DNAs to deteriorate [5]. Oxidative stress develops as a result of the increase in ROS production or the decrease in the capacity of cellular antioxidant defense mechanisms. Oxidative stress directly or indirectly impairs nucleic acids, proteins, and lipids via ROS and causes carcinogenesis [7], neurodegeneration [8, 9], arteriosclerosis, diabetes [10], and ageing [11]. ROS does not develop the pathogenesis of the disease via the modifications at direct macromolecular level. It generally develops the pathogenesis by stimulating the signal pathways that will cause the disease such as gene activation in tumor metastasis [12]. Oxidative interface is the limit between ROS and the activated signaling molecules [1].

The Relationship between Cardiopulmonary Bypass and Oxidative Injury

In the presence of coronary artery disease requiring surgery, pre-operation oxidative stress and inflammation findings are present in the patient and this becomes evident through CPB [139. Also, the presence of concomitant diseases such as diabetes, kidney, and lung diseases in the patients coming to undergo open heart surgery is associated with abnormal redox state and oxidative stress [1]. During CPB in heart surgery, the contact of blood with non-endothelial surfaces develops a primary ROS source via the activation of polymorphous nuclear leukocytes primarily neutrophils. In heart surgery, inflammation develops via the pathways stimulated by complex cellular and humoral interactions in which thrombin production or coding, complement, cytokines, neutrophils, adhesion molecules, mast cells and numerous inflammatory agents take place. Excess stimulation of inflammatory cascades causes multiple organ dysfunction such as coagulopathy, respiratory insufficiency, myocardial dysfunction, renal failure, and neurocognitive defects. Also, vascular endothelial cells mediate inflammation and develops the association between coagulation and inflammation. Surgery alone activates the specific hemostatic response, activation of immune mechanisms and inflammatory response mediated by various chemokines and cytokines [14].

Since tissue perfusion is suboptimal during CPB, ischemic reperfusion injury occurs. This is associated with the reduction of cellular adenosine triphosphate after the breakdown of hypoxanthine [15]. Hypoxanthine enters in a reaction by converting the xanthine dehydrogenase enzyme and nicotinamide adenine dinucleotide (NAD) into nicotinamide adenine dinucleotide hydrogenase and forms xanthine dehydrogenase. On the other hand, during ischemia, on the contrary, xanthine dehydrogenase is converted into xanthine oxidase. Thus, it impairs the cell homeostasis of lactic acid that forms as a result of anaerobic metabolism as well as the ion gradients in the cell membrane [16]. Reperfusion after ischemia plays a primary role in the formation of oxidative stress and develops excessive amounts of ROS. Reduction of oxygen levels causes the production of superoxide anion and it passes through the cell membrane easier and is converted in more toxic oxygen species. Dismutase reaction that is catalyzed by superoxide dismutase converts the superoxide anion into hydrogen peroxide. This causes hypochlorite acid formation and interacts with iron salts and they are converted into highly toxic hydroxyl radicals as a result of Haber-Weiss reaction. Toxicity of hydroxyl radicals creates new radicals by getting electron from a wide group of molecules and provides the continuation of the reaction [16].

Ischemia causes the energy production to decrease in mitochondria depending on the absence of oxygen and nutrients. This is followed by intracellular ATP reduction, intracellular pH reduction and sodium (Na^{+}) and calcium (Ca^{++}) accumulation [15]. Then, cardiac myocytes exposed to ischemia react with proinflammatory cytokines and activated leukocytes and cause neutrophil accumulation in myocardium and also result in more ROS and proteolytic enzyme release. Thus, reperfusion causes mitochondrial dysfunction and irreversible myocardial damage together with cytosolic Ca^{++} accumulation and ROS production [17]. Also, ROS stimulates the mitochondrial permeability pores and causes them to be opened and swelling occurs in mitochondria and membrane damage and finally cell

death and apoptosis or necrosis develop [18, 19].

Shear stress forces formed by the CPB pump damage the ion pumps on the cell surface as a result of mechanical damage on erythrocytes and thus cause intracellular cation accumulation [20]. As a result of membrane decomposition, membrane attack complex (MAC) that forms by complement activation causes the erythrocytes to become defenseless and causes hemoglobin (Hb) leakage. Rapid increase of the concentration of free hemoglobin acts as a peroxidase in the presence of H_2O_2[21, 22].

Depending on reduction in antioxidant parameters of stored bank blood, blood transfusion during and after CPB increases oxidative stress. Modifications in the bank blood adenosine triphosphate and 2,3-diphosphoglycerate, nitric oxide-mediated functions and storage defects in erythrocytes depending on the increase in lipid peroxidation occur [23, 24]. Such erythrocyte membrane modifications cause hemolysis formation and thus, an increase in free hemoglobin and iron concentrations in circulation by inducing them to be less deformed and more vulnerable.

In open heart surgeries performed via CPB, acute renal damage can be triggered by ischemia reperfusion injury, modifications in blood flow pattern, hemolysis and blood transfusion [25]. Due to its preoxidant characteristics, combination of free hemoglobin that is formed after hemolysis with myoglobin having an elevated level in plasma are independent determinants of acute renal damage. After reperfusion damage, ischemia causes mitochondrial dysfunction in renal epithelial cells, the increase in ROS release and stimulation of proinflammatory signal pathways, cytoskeleton (cell skeleton) damage, and renal tubular damage. Reactive oxygen species cause protein oxidation, lipid peroxidation, DNA injury, and renal tubular cell damage via the stimulation of apoptosis [26].

The increase of ROS production and specifically, the increase of ROS levels in atrial tissue regarding the superoxide anion derived from atrial nicotinamide adenine dinucleotide phosphate oxidase are associated with postoperative atrial fibrillation (POAF) [27].

Cardiac surgeries operated via CPB are associated with acute pulmonary damage in a wide range with the most serious form of acute respiratory distress syndrome (ARDS). Although ARDS is rarely seen after cardiac surgery, its effect on mortality and morbidity is high. The injury and reoxygenation in lung tissue as a result of complement and neutrophil activation in erythrocytes are held to account for impairment of redox state under oxidative stress conditions. In the bronchoalveolar lavage performed in the patients with ARDS after cardiac surgery; chlorotyrosine, nitrotyrosine, and orthotyrosine showing high quantity of oxidative stress were observed [28].

The redox state impaired due to coronary artery disease, kidney and lung diseases the patients have before cardiac surgery becomes more evident since the patient undergoes CPB [13]. The effects of ROS are neutralized by making electron exchange by antioxidant molecules under physiological conditions. Antioxidant molecules can interact with reactive radicals, degrade them, and convert them into weaker and less dangerous free radicals that continue for a long term and can be neutralized [1].

Ways of Reducing the Oxidative Stress in CPB

Antioxidant Supplement

Antioxidants directly reacts with reactive radicals and decreases their activities by depleting them and shows an effect by converting them into a less dangerous state. The use of antioxidants such as propofol, L-arginine, and N-acetyl cysteine in CPB intravenously or by adding cardioplegia can be a defense strategy against ROS production [1].

Propofol (2,6-diisopropylphenol) is an agent that is generally used in anesthesia in cardiac operation. Because propofol includes a phenolic hydroxyl group in its structure, it resembles vitamin E known as a natural antioxidant. In the in-vivo and in-vitro studies, significant antioxidant effects of propofol have been determined [29-31]. It is reported that propofol inhibits lipid peroxidation by increasing the antioxidant capacity of plasma in humans and also protects the cells against oxidative stress [32].

Propofol reacts with peroxynitrite and thus, decontaminates peroxynitrite. Also, propofol can protect against peroxynitrite-mediated cytotoxicity, DNA injury, and apoptosis [32-34].

In the ischemia-reperfusion models in animal studies; it has been determined that propofol reduces the formation of t-butyl hydroperoxide (t-BHP)-induced 2-thiobarbituric acid reactive substances (TBARS) in liver, kidneys, heart, and lungs [29-31, 35]. In the previous animal studies, it is reported that propofol protects the rats in ischemia-reperfusion injury [36].

L-arginine is an amino acid that plays a significant role in vein homeostasis as a precursor in immune function and nitric oxide (NO) synthesis. In the patients undergoing cardiac transplantation; it is determined that the use of oral L-arginine reduces vascular endothelial cell dysfunction and also decreases the serum H_2O_2 level [379. When L-arginine is added into the cardioplegia solutions of the patients undergoing coronary artery bypass grafting (CABG), myocardial oxygen (O_2) intake increases and formation of malondialdehyde (MDA) decreases [38, 39].

N-acetyl cysteine (NAC) is another efficient free radical scavenger. In CABG, intravenous infusion and H_2O_2 reduces significantly the hypochlorous acid (HOCl) levels than the control group [40, 41]. Also, MDA level significantly decreases in the NAC-administered group in reperfusion [40]. When NAC is added into cardioplegia solution; serum MDA, glutathione, catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR) levels significantly decrease [42-44].

Mini-CPB

Mini-CPB reduces the surface area and it is designed similar to the CPB system and thus, it prevents air-blood contact. The use of Mini-CPB delays or decreases the secretion of different proinflammatory cytokines [45, 469. It was determined that Mini-CPB significantly reduced significantly the red blood cell damage by measuring the free Hb level. Also according to the traditional method used, it was found that it decreased the serum MDA and allantoin/urate concentration that is an oxidative marker [47, 48].

Conclusion

Although cardiopulmonary bypass is not perfect, it is a significant part of the cardiac operation. The use of CPB is associated with oxidative stress and ROS production.

Hemolysis, ischemia-reperfusion injury, and neutrophil activation in CPB have a vital importance in oxidative stress. Also, it affects the functions of various organs such as myocardium, lungs and kidneys.

Whether or not intravenous or cardioplegic administration of the agents having antioxidant characteristics during the operation can reduce oxidative stress and ROS production in CPB. Alternatively, the use of mini-CPB can both regulate the proinflammatory response and oxidative stress. Still, different clinical studies regarding the CPB protocol are required.

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