

Effect of Hemolysis Products in the Development of Events After Coronary Artery Bypass Grafting

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ABSTRACT

According to the degree of intraoperative hemolysis (IOH), determined by the level of free hemoglobin, Hbfree, patients after coronary artery bypass grafting (CABG) were divided into 3 groups: group 1 - without IOH (Hbfree ≤ 0.1 g/l, n=43, group 2 - with low IOH (lIOH) with Hbfree > 0.1 g/l and < 0.5 g/l, n=42, group 3 with high IOH (hIOH) - Hbfree ≥ 0.5 g/l, n=38. The study of changes in iron levels was carried out on the basis of determining the content of serum iron (Fesyv.), transferrin (Tr), total iron-binding capacity of serum (TIBC), latent iron-binding capacity of blood, LIBC, ferritin (F) in blood plasma. The NO level was determined by the total concentration of nitrites and nitrates in blood plasma – NOx. In patients with intraoperative hemorrhagic pulmonary disease, the change in the parameters was maximum: an increase in [Fesyv.] by 91.9%, $p < 0.001$, [F] – by 165.9% ($p < 0.001$), a decrease in [Tr] – by 22.0%, $p < 0.001$ and [LVSS] – by 45.0% $p < 0.001$. The revealed changes in the iron pool parameters in patients with coronary artery bypass grafting indicate the effect of iron on the activity of oxidative processes, predisposing to the development of complications. This is confirmed by the nature of the change in the concentration of nitrites and nitrates, which depended on the severity of intraoperative hemolysis, indicating the effect of hemolysis products, including iron, on the processes of formation and utilization of nitric oxide.

Keywords

Coronary bypass surgery, Iron, Nitric oxide.

Abbreviations

CABG: coronary artery bypass grafting, IOH: intraoperative hemolysis, CAD: coronary artery disease.

Relevance

The development of complications after coronary noise (KSh) is due to the reperfusion syndrome due to the restoration of blood flow in the ischemia zone, the main pathogenetic mechanism of which is oxidative stress [1-3]. Among the oxidizing stress molecules, along with active oxygen forms, nitrogen oxide (No) is released-an active form of oxygen and nitrogen), capable of initiating nitrositis stress. Nitrogen oxide is one of the key signal molecules in vascular homeostasis, which has in small concentrations due to its basal products, the ability to inhibit platelet aggregation, proliferation

of smooth muscle cells, as well as their migration, reduce the expression of cellular adhesion molecules, suppress the migration of the activated Leukocytes in the intimacy of the arteries [4,5]. The playotropic nature of the effects of NO proves the importance of its adequate products for the prevention of the development of cardiovascular complications of the operation. NO deficiency is the cause of endothelial dysfunction, manifested by excessive vasoconstriction, proadgesic and pro -aggregation effects in relation to platelets and leukocytes, contributes to the development of oxidative stress, activation of inflammation and proapoptotic effects. The transformation of positive NO effects into negative is facilitated by a significant increase in the products of active forms of oxygen that convert NO into highly toxic peroxinitrite (ONOO-) [6]. Given the possibility of the development of complications after coronary noise surgery (KSh) in the conditions of artificial circulation (AC), many of which have vascular genes (myocardial infarction, arrhythmia, heart failure, acute cerebral circulation),

it is obvious that their development may be associated with a change in the balance of no, the consequence of which may be activated by a number of pathogenetic mechanisms (oxidative stress, inflammation, thrombosis, etc.). The use of AC during the operation of the KSH allows you to create optimal conditions for the operation on a “dry” heart, maintaining blood circulation in organs and tissues. However, due to the influence of a number of intraoperative factors: the turbulence of blood flow, expressed by the tension of the shift, the effect of positive and negative pressure, hydrodynamic forces and surface tension, AC contributes to hemolysis [7]. A large role in the occurrence of hemolysis belongs to such patient - dependent factors as smoking, intake of alcohol, etc. [8].

The use of the AC apparatus, in the contours of which the conditions for hemolysis are created, indicates a possible change in the iron pool released from the hem of free hemoglobin [6]. As you know, an increase in free hemoglobin, hem and iron in blood serum is a risk factor for cardiovascular diseases [9,10]. At the same time, the level of free hemoglobin and iron - the hem component can influence the metabolism of nitrogen oxide and its level of metabolites. The inflammatory process initiated by the fragments of the cellular membranes of red blood cells can also contribute to a change in level of NO due to the activation of inducible NO-synthase [11]. It is obvious the need to study violations of the homeostasis of iron and nitrogen oxide, the marker of which is the content of its stable metabolites in the blood of nitrites and nitrates (NOX) in patients who underwent the Operation of KSh in the IR.

The purpose of the study was to identify changes in the level of iron and nitrogen oxide in patients after coronary artery bypass grafting, depending on the degree of intraoperative hemolysis.

Materials and Research Methods

Research was carried out in patients after coronary artery bypass grafting operation: 123 people with varying degrees of IOH (group 1-3). The study corresponded to the principles of the Helsinki declaration of the World Medical Association “Ethical principles of scientific medical research with human participation” and approved by ethical committees of UO “GrSMU” and healthcare institutions “Grodno Regional Clinical Cardiological Center” [http://www.med-pravo.ru/archives/helsinki.txt], informed consent received from all patients. Patients of all groups were comparable by age (63.0 (58; 67) years, $p > 0.05$) with the possession of men's sex (81.3 %, $p > 0.05$). According to the degree of intraoperative hemolysis (IOH), determined by the level of free hemoglobin, Hbfree, patients after coronary artery bypass grafting (CABG) were divided into 3 groups: group 1 - without IOH (Hbfree ≤ 0.1 g/l, $n=43$, group 2 - with low IOH (lIOH) with Hbfree > 0.1 g/l and < 0.5 g/l, $n=42$, group 3 with high IOH (hIOH) - Hbfree ≥ 0.5 g/l, $n=38$ [12,13]. Assessment of the degree of IOH was carried out according to the level of free hemoglobin using the analyzer Nemocue Plasma/Low HB, Sweden [14]. The groups did not differ in age, gender, the number of myocardial infarctions in history ($P > 0.05$), the frequency of ischemic cardiomyopathy ($P > 0.05$) and the frequency of heart rhythm disturbances ($P > 0.05$).

Blood took from the AC apparatus at the beginning, before the coronary shunt and at the end of the AC after its imposition, the determination of iron indicators (serum iron, the total iron-binding ability of blood serum, transferrin, ferritin) was carried out on the automatic biochemical analyzer of the Mindray BS-200 with the use of reagents (Diasist RB). The concentration of iron in the blood serum was determined by spectrophotometrically with a wavelength of 560 nm using ferrosine, which forms a painted complex with Fe^{2+} , which is determined after its restoration [15]. The total iron-binding ability of blood serum represents the largest amount of iron, which can attach transferrin to complete saturation [15]. The determination of changes in the content of transferrin in the blood serum is based on measuring changes in the optical density of the test sample due to agglutination of latex particles of the reagent covered with antibodies, to transferrin, with a wavelength of 340 nm. The determination of the content of ferritin in the blood serum is based on a photometric definition of a change in the optical density of the examined sample due to agglutination of latex particles covered with antibodies to ferritin [11]. A study of the concentration of stable metabolites of nitrogen oxide - nitrites and nitrates [Nox] according to the generally accepted method using the cadmium and the Griss reagent by spectrophotometry [16]. Statistical processing of the received data was carried out using the Statistica 10.0 program. With the use of descriptive statistics for quantitative (method of Kraskella-uolis), the method of comparing dependent variables with the use of the Wilcoxon criterion. Data of descriptive statistics are presented in the form of ME (Q25; Q75), where the Median is a variable, Q25 is the value of the lower tenant; Q75- the meaning of the upper apartment. Differences were considered reliable at $p < 0.05$.

Results and their Discussion

At the beginning of coronary shunting, the differences between the value of free hemoglobin in the studied groups were not noted, $p > 0.05$. After coronary shunting, there was an increase in free hemoglobin in the 2nd (with low IOH) and 3rd (high IOH) groups. At the same time, in a group with low IOH, the concentration of free hemoglobin increased by 3.3 (2.5; 5) times ($p < 0.001$), in a group with a high IOH 12 (7; 15) times ($p < 0.001$). In the 1st group, changes in the level of free hemoglobin in blood plasma were not observed, indicating the absence of IOH ($P > 0.05$). The study of iron indicators in patients with the operation revealed the presence of changes. In a group of patients without IOH, compared with the initial level, there are no excretions of iron indicators at the end of the coronary artery bypass grafting ($P > 0.05$), but there was a change in indications in patients with IOH. Changes in indicators, in comparison with their initial values, were more significant in patients with high IOH - an increase in $[Fe^{2+}]$ in blood plasma by 91.9 (4.8; 117.5) %, $p < 0.001$, ferritin- by 165.9 (135.1; 212.6) %, $p < 0.001$ and reducing the level. Transferrin - at 22.0 (19.7; 30.2) %, $p < 0.001$, and Latent iron-binding ability - at 45.0 (31.3; 68.7) % $P < 0.001$. In blood plasma by 22.9 (14.58; 35.48) % ($p < 0.001$), ferritin - by 37.5 (25.06; 45.9) % ($p < 0.001$), as well as a decrease in the level of transfer - by 8.1 (3.8; 13.8) %, $p < 0.05$ and falsess - by falsess on 9.7 (4.4; 24.9) %, $p < 0.001$. A decrease in the content of the transport protein of transferrin in patients with high

IOH may be due to its binding to free iron. Excessive saturation of transferrin with iron leads to its rapid elimination from vascular channel. In turn, an increased saturation of transfer, as a result of an increase in free iron in blood plasma in patients with high IOH, indicate a decrease in Latent iron-binding ability. An increase in ferritin is consistent with the literature on the nature of the change in the depositing iron of protein in patients with sickle cell anemia [17]. At the end of the coronary shunting, a decrease in [NOx] in the blood plasma of patients of the 1st, 2nd and 3rd groups was noted. Compared to the initial level, the most significant decrease in [NOx] was observed in patients with a high IOH group - by 43.0 (19.4; 58.9) %, $p < 0.001$, while in groups without IOH and with low IOH the decrease was less pronounced (by 12.2 (7.63; 17.001 and 13.8 (9.04; 19.1) %, $p < 0.001$, respectively, a week after the coronary shunting, compared with [NOx] at the end of the operation, an increase in [NOx] was noted in patients of the first group of 1.39 (1.18; 1.66), $p < 0.001$ times, groups with low IOH - 1.69 (1.36; 2.23) times, $p < 0.001$.

So, an increase in the level of serum iron, a decrease in transferrin and Latent iron-binding ability and an increase in the level of ferritin in patients with a high degree of IOH indicate an increase in plasma of blood levels of free iron, contributing to the development of complications after the coronary shunting due to activation of oxidative and inflammatory reactions [9]. The studies have shown a decrease in [NOx] in blood plasma at the end of the coronary shunting and its increase within 5-7 days after surgery. The severity of the noted changes depended on the degree of IOH. The decrease [NOx], which is mostly noted in the group with high IOH, may be the result of excessive consumption of NO in the reaction of mutual forms with active forms of oxygen, as the initiators of oxidative stress, in particular, in the reaction of interaction with superoxidanine and its transformation into peroxinitritis, as well as the interaction of ne with oxy and oxy The hemoglobin deox forms with the formation of metghemoglobin and nitrosyl hemoglobin, respectively [4,10,12,14,18]. Excessive NO consumption in patients with high IOH can contribute to a decrease in antiadhesive, ant aggregation and antiinflammatory properties of the vascular wall, which predisposes to the development of complications caused by thrombosis. It is important to note that free hemoglobin circulating in the blood, effectively consuming no, reduces its level in blood plasma, contributing to the processes of NO-dependent vasoconstriction and to the develop [5,14,15,17].

Conclusions

1. The increase in nitrites and nitrates in the blood plasma 5-7 days after the Operation reflects the increased activity of inducible NO-synthase (iNOS) in groups with IOH.
2. Excessive production of NO with the participation of iNOS helps the formation of large quantities of peroxinitrite, which has a nitrosyle effect in relation to proteins, which leads to damage to cell membranes, cytotoxic damage to the cells of the vessels, myocardium, the development of a systemic inflammatory response, predisposing to thrombosis and the development of complications and adverse outcomes after the operation of the operation.

3. Conducting the operation in the conditions of artificial circulation in patients with coronary heart disease is the cause of ambiguous changes in the level of nitrites and nitrates [NOx] in blood plasma: a decrease-immediately before the end of the operation and an increase 5-7 days after it.
4. The destruction of red blood cells in the contours of the artificial circulatory apparatus during surgery in patients with coronary heart disease leads to a change in iron indicators in blood plasma, indicating an increase in its free fraction.
5. A directly proportional dependence between a change in the level of free iron and the concentration of nitrites and nitrates from the degree of intraoperative hemolysis is established. Changing iron levels and NO caused by hemolysis can contribute to the development of complications of coronary noise.

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