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Federal State Budgetary Institution
"Research Institute for Complex Issues of Cardiovascular Diseases" SB RAMS

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Objectives. To study and assess the reinfusion of cell saved blood as a possible option for preventing of systemic inflammatory response syndrome to valve surgery under extracorporeal circulation.

Materials and Methods. 100 patients with acquired valve heart disease undergoing heart surgeries on cardiopulmonary bypass were included in a prospective randomized trial. Subjects were allocated into two groups based on assigned by a prospective randomization (even/odd numbers). Group A comprised 50 patients received standard intraoperative fluid therapy (blood from the wound site was collected in the cardiotomy reservoir of the heart-lung machine without further processing). Group B comprised 50 patients with blood retrieved from the wound site, processed in a cell-saver device and returned to the systemic circulation. Clinical and biochemical parameters were evaluated, central hemodynamic values were assessed, concentrations of systemic inflammation markers were measured in the dynamics.

Results. The intraoperative application of the cell saved reinfusion reduced the severity of clinical manifestations of systemic inflammatory response in the early postoperative period. This fact is confirmed by a less pronounced levels of laboratory markers compared with the control group: hsCRP, sTREM-1, IL-6 and IL-10 (sTREM-1 66.04±17.30, IL-6 17.36±9.87, IL-10, 56.36±11.54), $p<0,05$. The hemodynamic profile was more favorable, accompanied by less pronounced hyperdynamic response: CI — (3.51±0.87) l/min/m^2, TPVR — (2357.22±562.28) din/s/cm^5/m^2, ($p<0.05$). Thus, the incidence of multiple organ dysfunction, a need in sympathomimetics, prolonged mechanical ventilation and patient stay in the intensive care reduced, as well as a need for extracorporeal blood purification techniques.

Conclusions. The reinfusion of cell saved blood from the wound site to the systemic circulation following surgical management of acquired valve heart defects on cardiopulmonary bypass initiates the systemic inflammatory response and, consequently, associated sequelae during the postoperative period: increased rates of multiple organ dysfunction syndrome, a need of sympathomimetics, prolonged mechanical ventilation and patient stay in the intensive care unit, promoting further extracorporeal blood purification techniques. Reinfusion of cell saved blood enhances to reduce systemic inflammatory response, multiple organ dysfunction, sympathomimetics need, a duration of mechanical ventilation and patients stay

in the intensive care unit, extracorporeal blood purification techniques in the intraoperative period.

Key words: acquired heart diseases, cell saved blood reinfusion, systemic inflammatory response syndrome, multiple organ dysfunction syndrome.

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ПРОФИЛАКТИКА СИСТЕМНОГО ВОСПАЛИТЕЛЬНОГО ОТВЕТА В ХИРУРГИЧЕСКОЙ КОРРЕКЦИИ КЛАПАННЫХ ПОРОКОВ СЕРДЦА

Цели. Изучение и оценка возможности предотвращения синдрома системного воспалительного ответа при операциях на клапанах с искусственным кровообращением путем реинфузии крови с помощью селл-сейвера.

Материалы и методы. В проспективное рандомизированное исследование было включено 100 пациентов с приобретенными заболеваниями клапанов сердца, которым выполнялись кардиохирургические вмешательства с искусственным кровообращением. Группу А составили 50 пациентов, которые получали стандартную интраоперационной инфузионной терапии (кровь из раны была собрана при кардиотомии в резервуар аппарата искусственного кровообращения без дальнейшей обработки). В группу В вошли 50 пациентов, у которых кровь, извлеченная из раны и обработанная с помощью селл-сейвера, возвращалась в системный кровоток. В динамике оценивались клинические и биохимические параметры, показатели центральной гемодинамики, концентрация системных маркеров воспаления.

Результаты. Применение интраоперационной реинфузии клеток позволило уменьшить тяжесть клинических проявлений системного воспалительного ответа в раннем послеоперационном периоде. Этот факт подтверждают достоверные различия в уровнях лабораторных маркеров по сравнению с контрольной группой: hsCRP, sTREM-1, IL-6 и IL-10 (sTREM-1 66,04±17,3; IL-6 17,36±9,87; IL-10 56,36±11,54), $p<0,05$.

Заключение. Реинфузия крови с помощью селл-сейвера у пациентов с приобретенными пороками сердца, которым выполнялись кардиохирургические вмешательства, позволила уменьшить уровень системного воспалительного ответа, полиорганной недостаточности, необходимость симпатомиметической терапии, продолжительность ИВЛ, длительность пребывания пациентов в отделении интенсивной терапии и необходимость в экстракорпоральных методах очищения крови.

Ключевые слова: приобретенные заболевания клапанов сердца, реинфузия крови с помощью селл-сейвера, системный воспалительный ответ, полиорганная недостаточность.

Introduction

The advances in cardiology, cardiac surgery, anesthesiology and critical care medicine have greatly expanded the range and complexity of the interventions available for adults with acquired valve heart disease. Thereby, because of the increased complexity of the surgery, operative time and cardiopulmonary bypass (CPB) duration have prolonged, expanding treatment indications. That resulted in high risk complications during and after surgery [8].

Systemic inflammatory response syndrome is known to be one of the most crucial complications in heart surgeries, characterized by the main triggering factors: blood exposure to nonendothelial surfaces, surgical trauma, endotoxemia and ischemia-reperfusion [4]. These mechanisms provoke the activation of kinin-kallikrein system, complement system, coagulation and fibrinolysis. The produced proinflammatory mediators initiate an inflammatory cascade activating platelets, leukocytes, endothelial cells, the onset of myocardial and lung inflammation, and release of proinflammatory cytokines. Excessive activation of pro- and anti-inflammatory mediators as well as their imbalance results in the most severe complication in the postoperative period — multi-

ple organ dysfunction syndrome [2; 3]. All mentioned above is relevant for patients affected by acquired heart valve disease, consequently, with long-term hypoxia worsening pronounced heart failure, associated with the development and maintenance of chronic organs and system dysfunction. The issue regarding the prevention and early aggressive treatment of intraoperative and postoperative complications following the cardiopulmanory bypass in initially critical ill patients remains significant [4].

Nowadays, various pharmacological and extracorporeal techniques target at the reduction of systemic inflammation with the implementation of perioperative organ protection strategies (intraoperative ultrafiltration, mini-circuit cardiopulmonary bypass resulting in less traumatization, corticosteroid administration) [6; 7]. Several studies suggested inflammatory mediators and tissue factor contained in blood from the pericardial cavity activate systemic inflammatory response, returning in the systemic circulation [13].

Some studies have shown limiting excessive activation of inflammatory mediators by preventing shed mediastinal wound blood to return in the systemic circulation during heart surgeries. However, these studies have been mainly focused on coronary artery bypass surgeries, whereas the problem is relevant for valve surgery. In addition, the efficacy of processed blood reinfusion, especially, in case of a massive blood loss during the inraoperative period, appears to be pending in the scientific medical literature [1; 10; 11].

Thus, we hypothesized the reinfusion of autologous red blood cells processed allows to reduce systemic inflammation trigger factors, subsequently, getting in the systemic circulation, and to prevent its onset as well as severe related complications.

Objectives

To study and assess the reinfusion of cell saved blood as a possible option for preventing systemic inflammatory response syndrome to valve surgery under extracorporeal circulation.

Material and Methods

100 patients affected by acquired valve disease, admitted in Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Diseases" SB RAMS, were included in a prospective randomized study. They underwent cardiac surgery on cardiopulmanory bypass (Table 1). The patients were randomized based on even/odd numbers (the sum of hospital record numbers) and classified into two groups.

Group A comprised 50 patients with a mean age of 46–69 (57.5±11.2) years. There were 37 (74%) of males, 13 (26%) — females. Functional class by NYHA was III–IV. All patients of this group received a standard intraoperative fluid therapy (strategy, volume and initial priming were performed according to the accepted clinical protocols, blood from the wound site was extravasated in the cardiotomy reservoir of the heart-lung machine by coronary suctions at all stages of the operation).

Group B included 50 patients with a mean age of 43–68 (56.9±10) years. Males comprised 40 (80%), females — 10 (20%). Functional class by NYHA was III–IV.

Patients received the reinfusion of cell saved blood in addition to standard fluid therapy. Thus, the Cell-Saver system (Brat-2 COBE, USA) prevented the direct shed blood return from the wound site into the systemic circulation during the surgical approach and the main stage of the operation. During the blood procession, plasma was collected, erythrocyte suspension drained to the cardiotomy of the heart-lung machine. The average amount of washed red blood cells was (356.9±89.9) ml, and the volume of discarded plasma (without wash solution) — (970±380), that corresponded to an average of (12.0±3.5) ml/kg.

Inclusion criteria: patients with acquired valve heart disease, undergoing heart surgery on cardiopulmonary bypass.

Table 1

Clinical Characteristics of Patients, M±SD, n=50

Characteristics	Group A	Group B
Males, n (%)	37 (74)	40 (80)
Females, n (%)	13 (26)	10 (20)
Age, yrs (min-max)	57.5±11.2 (46–74)	56.9±10.0 (43–72)
Body surface area, m^2 (min-max)	1.82±0.19 (1,56–2,18)	1.82±0.22 (1.40–2.11)
Weight, kg (min-max)	74.4±19.0 (52–105)	76.7±20.1 (51–107)
CF (NYHA functional class)	3.56±0.42	3.61±0.39
РБС, n (%)	19 (38)	21 (42)
Infective endocarditis, n (%)	14 (28)	16 (32)
Calcified defect, n (%)	17 (34)	13 (26)
AV replacement + MV replacement, n (%)	14 (28)	16 (32)
MV replacement + TV plasty, n (%)	25 (50)	21 (42)
MV replacement + TV plasty, n (%)	11 (22)	13 (26)
CPB duration (min-max)	138±36 (102–174)	152±46 (106–198)

Note. * — p<0,05 in comparison between the groups; CF — circulatory failure; AV — aortic valve; MV — mitral valve; TV — tricuspid valve; CPB — cardiopulmonary bypass.

Exclusion criteria: patients of less than 20 years old, diagnosed chronic decompensated extracardiac pathology, systemic and autoimmune diseases, cancer.

Operations were performed with a non-pulsatile cardiopulmonary bypass technique (Terumo, Japan) with normothermia in both groups. Cardioplegic solution Kustodiol (Dr. France Kehler Hemy, Germany) was used for myocardial protection. The patients were distributed by gender, age, cardiopulmonary bypass duration, heart failure severity, etiology of acquired heart disease and type of surgery. All data are summarized in Table 1. All patients underwent total intravenous anesthesia: induction and maintenance — propofol + fentanyl; myoplegia — esmerone or tracrium. Mechanical lung ventilation was performed by anesthetic MLV apparatus "Draeger Primus". Central hemodynamic values were assessed by the monitor BSM-4103K (Nihon Kohden, Japan), and Swan-Ganz catheter, introduced in the right jugular vein (7 Fr, Arrow). Cardiac index, pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance index, total peripheral vascular resistance, mean arterial pressure were measured.

The systemic inflammatory response was diagnosed in the early postoperative period according to ACCP/SCCM criteria [5]. Specific systemic inflammation markers such as high-sensitivity C-reactive protein (hs CRP), soluble triggering receptor, expressed on myeloid cells-1 (sTREM-1), tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-10 (IL-10) were measured using an enzyme-linked immunosorbent assay (ELISA) in addition to the standard clinical and laboratory parameters. Two sets of endpoints were established in the study: the primary end-point — patient's arrival in the operation room; the secondary end-point — at the morning of the first day after the surgery.

The postoperative course was evaluated by several factors: a need of continuous renal replacement therapy (CRRT), more than two administered sympathomimetics, including at higher than therapeutic doses, prolonged stay (over two days) in the intensive care unit and the need for mechanical ventilation more than one day, the incidence of multiple organ dysfunction assessed by the SOFA score [14].

The study protocol was approved by the local ethics committee and intuitional reviewer board of Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Diseases" SB RAMS. All subjects signed the informed consent form before the study inclusion.

Statistical Analysis

The statistical analysis was conducted using STATISTICA version 6.0, StatSoft, Inc. All data were presented as means±standard deviation (SD). Quantitative comparison of two independent samples was performed by the Mann–Whitney U-test and of two related samples by the Wilcox test. A P-value < 0.05 was considered significant.

Results

There were 91% of patients in Group A, who received a standard intraoperative fluid therapy, demonstrated the clinical manifestations of the systemic inflammatory response: two variables were defined in 51%, three — in 40% in the early postoperative period. In Group B, undergone the cell saved blood reinfusion, the clinical manifestations of the systemic inflammatory response were defined in 44% of patients, that was **two times less** than in Group A: 34% demonstrated two variables, 10% — three.

Baseline levels of the systemic inflammatory response laboratory markers in both groups were not significantly different (Table 2). A reliable increase of Hs CRP, sTREM-1, IL-6 and IL-10 levels in both groups was found at 1 day post-arrival in the intensive care unit. Thus, the increase in Group B was less pronounced with significantly lower values compared with Group A. Those particular changes contributed to the already established systemic inflammatory response interactions, and appeared to be laboratory confirmation of the reduction of its severity in Group B with the cell saved blood reinfusion.

Importantly, the TNF level is considered to be a dominant systemic inflammation mediator (see Table 2). Thus, there was a significant increase of its level in Group A at 1 day of the postoperative period, conversely, a significant reduction of TNF level was detected in Group B, which ascertained the efficacy of the intraoperative reinfusion of cell saved blood in preventing the systemic inflammatory response.

Table 2

Values of Central Hemodynamics in the Groups, M±SD, n=50

Marker	Group A		Group B	
	before the operation	1 day after the operation	before the operation	1 day after the operation
hsCRP	7.20±1.07	27.68±6.97*	7.9±3.9	12.71±5.23*, **
sTREM-1	53.21±12.32	79.91±14.54*	57.44±9.41	66.04±17.30*, **
TNF	2.39±0.26	3.08±0.33*	2.69±0.64	1.5±0.4*, **
IL-6	2.21±1.11	56.13±11.24*	2.70±1.05	17.36±9.87*, **
IL-10	17.26±5.23	121.34±16.12*	16.78±7.85	56.36±11.54*, **

Note. In table 2, 3: * — p<0,05 within the group comparison; ** — p<0,05 in comparison between the groups.

Table 3

Values of Central Hemodynamics in the Groups, M±SD, n=50

Value	Group A		Group B	
	before the operation	1 day after the operation	before the operation	1 day after the operation
CI, l/min/m^2	2.99±0.69*	4.29±1.07*, **	2.95*±0.45	3.51±0.87*, **
PCWP, mm Hg	11.00±4.21	12.80±7.27	12.90±4.38	10.30±3.27
mPAP, mm Hg	20.42±10.1	22.00±8.13	22.24±9.42	23.00±7.13
PVRI, dyn/(s·cm^5·m^2)	295.36± ±182.92	191.54± ±141.58	302.76± ±217.42	241.54± ±139.56
TPVR, dyn/(s·cm^5·m^2)	2801.48± ±682.30*	1770.22± ±748.39*, **	2673.93± ±682.13*	2357.22± ±562.28*, **
MAP, mm Hg	77±25*	62±12*, **	80±19*	76±13*, **

Note. CI — cardiac index; PCWP — pulmonary capillary wedge pressure; mPAP — mean pulmonary artery pressure; PVRI — pulmonary vascular resistance index; TPVR — total peripheral vascular resistance; MAP — mean arterial pressure.

Table 4

Characteristics of the Postoperative Period in the Groups, n=50, n (%)

Characteristics	Group A	Group B
Application of a continuous renal replacement therapy according to extrarenal indications	34 (68)	15 (30)
Need of higher than therapeutic doses of sympathomimetics	33 (66)	12 (24)
Need of two sympathomimetics	37 (74)	8 (16)
Prolonged mechanical ventilation (over 1 day)	39 (78)	9 (18)
Prolonged stay in the intensive care unit (over 2 days)	43 (86)	12 (24)
Multiple organ dysfunction onset	38 (76)	12 (24)

Baseline values of central hemodynamics in the groups reported significant differences due to the specific intracardiac hemodynamics characteristics of the cardiac defect (Table 3). However, the postoperative period in the group with standard fluid therapy revealed a more pronounced hyperdynamic response of the cardiovascular system, which is traditionally activated due to the systemic inflammatory response and contributed to the rapid depletion of myocardial functional reserves (see Table 3). Moreover, the mean arterial pressure was significantly higher with less sympathomimetic support in Group B than in Group A in the postoperative period — patients with the intraoperative cell saved blood reinfusion required an average of three times smaller doses of catecholamines for hemodynamic optimization (Table 4).

The group underwent the reinfusion of processed autologous blood demonstrated better clinical parameters compared with the group received the standard intraoperative fluid therapy by the early postoperative period assessment (see Table 4).

As expected, the reduction of the systemic inflammatory response severity reduction contributed to lessen rates of multiple organ dysfunction and multiple organ failure assesses by the SOFA score. In this case, the function of the targeted system (cardio-vascular system) was not considered because of its initial impair-

ment. Such a significant reduction of the multiple organ dysfunction incidence improved the length of the intensive care unit stay, and, hence, the rate of postoperative septic complications.

Discussion

The medical literature suggested the aspirated blood in the cardiotomy reservoir extravasated from the mediastinal wound to enhance the number of complications, described in coronary surgery as well as in valve surgery. Whilst, blood with inflammatory mediators, the complement activators, the calcific valve structures must be processed to avoid the systemic inflammatory response inducers [11].

The "classical" clinical manifestations of systemic inflammatory response, considered in the clinical practice, is known to be a subject of criticism. This is especially relevant for cardiac patients, because at least two of the four manifests — heart rate and respiratory rate may not be suitable for the assessment due to the initial cardiopulmonary failure and drug effects. Therefore, two remaining criteria — white blood cells level and body temperature may serve as a basis for the diagnosis of systemic inflammatory response, thus, do not allow to define its intensity and severity in the dynamics. The researchers are entirely possible to be motivated to identify new markers such as C-reactive protein, procalcitonin, IL-6, IL-8, soluble triggering receptor expressed on myeloid cells and others [9; 12]. Initially proposed biochemical markers have been already tested in the diagnosis and prognosis of infectious systemic inflammatory response, but the indications for the biochemical diagnosis and non-infectious systemic inflammation (trauma, pancreatitis, post-cardiopulmonary bypass state) have greatly expanded in the past decade. The sensitivity of prognostic and diagnostic tests is characterized by its drift toward the "universal" criteria of systemic inflammatory response [9; 12]. In this regard, our data, obtained basically on the measurement of the markers dynamics, reported the advantages of the intraoperative reifusion of cell saved blood as an option of preventing systemic inflammatory response [9].

There are options of the complete blood drainage from the circuit in addition to the cell saved blood reinfusion, which also allows to prevent the systemic inflammatory response onset. However, given the close attention to blood saving technologies in heart surgery, it is desirable, at least, to return erythrocytes in the systemic circulation. In this regard, the reinfusion technique seems to be an adequate option for mediastinal blood processing, following systemic inflammation mediators discarding and retrieving in cardiopulmonary bypass circuit. The disadvantage of this method is the elimination of clotting factors and platelets, which in case of the mass blood loss will require fresh frozen plasma transfusion, and in some cases, platelets [9; 10]. Thus, the reinfusion of cell saved blood proved to be preferable for patient safety comparing the processed blood reinfusion and complete blood drainage out of the circulation, as well as the standard aspiration technique and its return to the cardiotomy reservoir. This technique reported the possibility to avoid the own red blood cells loss unlike the technique of blood drainage out of the circulation, as well as to limit the systemic inflammatory response activation, promoting the postoperative quality improvement. The last mentioned is explained by the prevention of inflammatory mediators from the wound to get into the systemic circulation, as well as the removal of various endogenous toxic substances released before and during the operation from the patient's organism, because the reinfusion of cell saved blood, in its essence, appears to plasmapheresis.

Note, we did not find any significant differences between the groups with the standard blood evacuated to the cardiotomy reservoir and processed in the Cell-Saver, while analyzing the necessity of the intraoperative blood components transfusion. In both groups the amount of fresh frozen plasma transfused during the surgery was comparable and correlated with the bleeding rate and the aspiration amount.

The technique of cell saved intraoperative, presented in this article (as an option for preventing systemic inflammatory response and multiple organ dysfunction) requires

further clinical, biochemical, and instrumental material to study in order to clarify a number of indicators and data. Apparently, the economic costs do not allow to apply this technique in the routine clinical practice during all, without exception, valve surgeries. Therefore, designing and algorithm testing is necessary for the differential selection in favor of this particular method considering the multiple organ dysfunction risk factors and magnified systemic inflammation. Probably, this technique will be preferred to apply in patients with clinical predictors of complicated postoperative period — valve rereplacement, infective endocarditis and other comorbidities.

Conclusions

Application of the cell saved reinfusion technique in surgical management of acquired heart valve disease under extracorporeal circulation due to the trigger factor elimination may greatly limit the systemic inflammatory response and improve the postoperative course. Thus, the incidence of multiple organ dysfunction will decrease, as well as a need in sympathomimetics, prolonged mechanical ventilation and patient stay in the intensive care unit, diminishing a need for extracorporeal blood purification techniques.

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