

PREVENTION OF SYSTEMIC INFLAMMATORY RESPONSE DURING LONG-STANDING CARDIOPULMONARY BYPASS IN PATIENTS WITH COMORBIDITIES

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ПРОФІЛАКТИКА СИСТЕМОГО ЗАПАЛЬНОЇ ВІДПОВІДІ У ПЕРІОД ДОВГОСТРОКОВОГО ЗАСТОСУВАННЯ АПАРАТУ ШТУЧНОГО КРОВООБІГУ У ПАЦІЄНТІВ З СУПУТНІМИ ЗАХВОРЮВАННЯМИ

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Мета. Оцінити ефективність превентивних стратегій щодо виникнення синдрому системної запальної відповіді під час довгострокового застосування апарату штучного кровообігу (АШК) у пацієнтів з супутньою патологією.

Матеріали та методи. Проспективне рандомізоване клінічне дослідження, яке включало в себе 60 пацієнтів чоловічої статі з очікуваною тривалістю роботи АШК > 120 хв через супутню патологію. Критерії включення: пацієнти з ішемічною хворобою серця та/або захворюванням клапанів серця з фібриляцією передсердь та супутніми захворюваннями (хронічний пієлонефрит, хронічна обструктивна хвороба легень, цукровий діабет), що вимагають операції АКШ та/або операції на клапані і процедури «Maze». Пацієнти, які перенесли ургентну операцію, були виключені з дослідження. Був використаний стандартний протокол анестезії, Кардіоплегія була досягнута за допомогою розчину Custodiol ©. Дослідження включає 3 групи: 1-а група (контрольна, n = 20), включає пацієнтів зі стандартним по тривалості застосування АШК, 2-а група (n = 20), що включає перфузію з високооб'ємною гемофільтрацією та використанням полііонного буферізованого розчину протягом всього часу роботи АШК, 3-я група (n = 20) – АШК з гемодіалізатором з поліметилметакрилату (ПММА). Була проведена енвелопна рандомізація.

Рівні потрібних показників досліджували через 1 годину і 1 день після процедури (лейкоцити, Нв, тромбоцити, ІЛ-6, ІЛ -10, лактат, прокальцитонін, ЦРБ). Були оцінені клінічні дані, такі як респіраторні та ниркові ускладнення, втрата крові по дренажу, порушення гемостазу, які вимагають корекції та трансфузії, інтенсивної терапії та стаціонарного лікування.

Результати. Фільтраційні та сорбційні компоненти дозволяють знизити рівень запальних цитокінів, а також тригерних компонентів і маркерів системної запальної відповіді. Через 1 годину після сорбції рівень ІЛ-6 був значно нижче, ніж в контрольній групі. Також була тенденція до зниження концентрації ІЛ -6 через 1 день після процедури. Рівні протизапального ІЛ -10 через годину після процедури були незначно вище в порівнянні з такими у пацієнтів, які не проходили процедуру ПММА-сорбції, що призводить до

збільшення адаптивної протизапальної реакції організму. Рівень ІЛ-10 короткочасно підвищується (перші години після дії тригера), тому його рівень через 1 день після процедури був низьким і суттєво не відрізнявся в різних групах. Середнє значення концентрації sTREM-1 в крові через 1 годину було в 4 рази менше, ніж у контрольній групі, однак широкий діапазон рівнів sTREM-1 та невелика кількість пацієнтів не дозволяють говорити про яку-небудь статистично значущу різницю. Проте, вплив сорбції на sTREM-1 (молекулярна вага ~ 17 кДа) можна вважати доведеним. Середнє значення концентрації sTREM-1 в крові через 1 день в аналізованих групах було в 2 рази менше, ніж у контрольній групі, але не було статистично значущим. Швидкість переливання була однаковою в обох групах, але пацієнти з досліджуваних груп не потребували гемостатичної терапії. До кінця першого післяопераційного дня не було необхідності в інотропних і вазопресорних препаратах в досліджуваних групах, всі пацієнти були екстубовані в перші післяопераційні години. Ускладнення в післяопераційному періоді спостерігалися в 2 (10%) випадках в аналізованих групах проти 5 (25%) в контрольній групі; ниркова дисфункція, що вимагає діалізу, була діагностована у 6 (30%) пацієнтів з контрольної групи проти 2 пацієнтів (10%) з аналізованої групи №2; дихальна недостатність розвинулася у 3 пацієнтів (15%) тільки в контрольній групі. Тривалість перебування в стаціонарі була порівняна в обох групах, але більш коротке перебування у відділенні інтенсивної терапії було відзначено в аналізованих групах. Синдром поліорганної недостатності (СПОН) виник у 3 пацієнтів (15%) з контрольної групи.

Висновок. Більшеоб'ємна гемофільтрація з використанням полііонного буферного розчину або використання гемофільтрів з поліметілметакрилатом при тривалій роботі АШК знижує ризик органічної дисфункції в післяопераційному періоді.

Ключові слова: штучний кровообіг, гемодіафільтрація, сорбція, синдром поліорганної недостатності.

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Objectives. To evaluate the effectiveness of preventive strategies of systemic inflammatory response during long-standing cardiopulmonary bypass (CPB) in patients with comorbidities. *Materials and methods.* Prospective randomized clinical trial including 60 male patients with expected duration of CPB >120 min due to comorbidities. Inclusion criteria: patients with coronary artery disease and/or heart valve disease with the history of atrial fibrillation and comorbidities (chronic pyelonephritis, chronic obstructive pulmonary disease, diabetes mellitus), requiring CABG surgery and/or valve surgery and "Maze" procedure. Patients who underwent urgent surgery were excluded from the trial. Standard anesthesia protocol was carried out, cardioplegia was obtained by Custodiol © solution. Study includes 3 groups: 1st group (controlled, n=20) included standard CPB, 2nd group (analyzed №1, n=20) included perfusion with high-volume hemofiltration using polyionic buffered solution during all CPB time, 3rd group (analyzed №2, n=20) – CPB with polymethyl methacrylate (PMMA) hemodiafilter. Envelope randomization

was carried out. Target analytes' concentration was examined 1 hour and 1 day after the procedure (WBC, Hb, Plt, IL-6, IL-10, lactate, procalcitonin, C-RP). Clinical data, such as respiratory and renal complications, drainage blood loss, hemostasis disorders, requiring hemostatics and blood transfusion, ICU and in-hospital were evaluated. *Results.* Filtrative and sorptive methods can reduce the level of inflammatory cytokines, as well as the trigger components and markers of systemic inflammatory response. 1 hour after the sorption IL-6 levels was significantly lower, that in control group. There also was a tendency to the lower concentrations of IL-6 1 day after the procedure. Levels of anti-inflammatory IL-10 one hour after the procedure was insignificantly higher comparing to those in patients, who did not undergo a PMMA-sorption procedure, which leads to the increase in adaptive anti-inflammatory reaction of the body. IL-10 level rises briefly (first hours after the trigger), that's why its level 1 day after the procedure was low and did not vary in different groups significantly. Median value of sTREM-1 concentration in blood after 1 hour was 4 times less than in control group, however, a wide range of sTREM-1 levels and small amount of patients did not lead to any statistically significant difference. Nevertheless, sorption effect on sTREM-1 (molecular weight ~17 kDa) can be considered relevant. Median value of sTREM-1 concentration in blood 1 day after in analyzed groups was 2 times less than in control group, but it was not statistically relevant. Transfusion rate were the same in both groups, but patients from analyzed group did not require any hemostatic therapy. There was no need in inotropic and vasopressor medications in the analyzed group by the end of the first postoperative day, all patients were extubated in first postoperative hours. Complicated postoperative period occurred in 2 (10%) cases in analyzed groups vs 5 (25%) in controlled group; renal dysfunction, requiring dialysis, was diagnosed in 6 (30%) patients from controlled group vs. 2 patients (10%) from analyzed group №2; respiratory insufficiency has developed in 3 patients (15%) only in controlled group. In-hospital stay was comparable in both groups, but lower ICU-stay was significantly lower in analyzed groups. Polyorganic insufficiency syndrome (POIS) occurred in 3 patients (15%) from the controlled group.

Conclusion. High-volume hemofiltration using polyionic buffered solution or the use polymethyl methacrylate hemodiafilter for longstanding CPB reduces risks of organic dysfunction in postoperative period.

Key words: Cardiopulmonary bypass, hemodiafiltration, sorption, polyorganic insufficiency syndrome.

Introduction. One of the most relevant complications in cardiac surgery with cardiopulmonary bypass (CPB) is systemic inflammatory response. Despite the development of new technologies and CPB techniques, its negative effects still remain significant. Systemic inflammatory response makes serious contribution to the pathophysiology and it depends on surgical trauma, blood and artificial surfaces interactions during extracorporeal circulation, ischemia/reperfusion, endotoxemia and etc. [1]. Forementioned mechanisms lead to the activation of kinin-kallikrein system, complement system, coagulation and fibrinolysis. As a result of that, inflammatory mediators initiate a cascade of inflammatory reactions, which lead to the activation of the platelets, leukocytes, endothelial cells, inflammation in the myocardium, lungs and that leads to the cytokines release. [2] Systemic inflammatory response, caused by the surgery with CPB is characterized by the increase in interleukin-6 level that correlates with the imbalance of angiopoietins. Angiopoietin-2, which is believed to be a marker of endothelial dysfunction, causes an activation, inflammation and damage of the endothelium. Angiopoietin-1 and

angiopoietin-2 imbalance induces myosin-mediated contractions of endothelial cells that lead to intercellular gaps, extravasation of fluids, hypovolemia and organ dysfunction [3].

At the same time, number of patients with organic dysfunction due to comorbidities is increasing every year, as well as the age of patients, undergoing cardiac surgery [4]. That is why development of novel methods for systemic inflammatory response minimization during CPB is still very relevant [5].

There are several ways to reduce the inflammatory response, such as hemofiltration, hemosorption, that are been effectively used in various hospitals to neutralize the inflammatory response [6]. Currently, there are no guidelines to the CPB management during surgeries with different perfusion time. Correlation between mediators of inflammatory response level during and after CPB and the incidence of organic insufficiency is not evaluated in any studies.

Objectives. To evaluate the effectiveness of different methods of removing the inflammatory mediators after long-standing CPB in patients with comorbidities and its effect in decreasing the incidence of organic dysfunction in postoperative period.

Materials and methods. Prospective randomized clinical trial with 60 male patients included with CPB duration over 120 min during concomitant heart surgery. The study was approved by the local ethic committee; informed consent was signed by all patients. Inclusion criteria: patients with coronary artery disease and/or heart valve disease with the history of atrial fibrillation and comorbidities (chronic pyelonephritis, chronic obstructive pulmonary disease, diabetes mellitus), requiring CABG surgery and/or valve surgery and “Maze” procedure. Patients who underwent urgent surgery were excluded from the trial. Standard anesthesia protocol was carried out, cardioplegia was obtained by Custodiol © solution . Study includes 3 groups: 1st group (controlled, n=20) included standard CPB with «classic» extracorporeal circuit with roller pump, 2nd group (1st analyzed, n=20) included perfusion with high-volume hemofiltration using polyionic buffered solution 80 ml/min during all CPB time. Hemofiltration has been also supported by ultrafiltration for hydrobalance maintenance at the level of 8-10 ml/kg. For the study we are using Maquet Hemoconcentrators with priming volume 65 ml and membrane surface 0,7 m² and as a substitute solution MultiBic bicarbonate buffer solution with potassium concentration 4 mmol/l was used. Hemofiltration ends after weaning from CPB.

3rd group (2nd analyzed, n=20) – CPB with the use of hemodiafilter with polymethyl methacrylate (PMMA) (BK-2,1P, Torray, Japan) as a sorbing agent with the blood flow 300ml/min.

Main clinical data, such as age, weight, CPB duration and others (**table 1**), as well as initial laboratory test (**table 2**) were comparable in both groups. Envelope randomization was carried out. The effectiveness of different methods was analyzed by the changes of target analytes concentration in the first hour after the procedure and 24 hours later (WBC, Hb, Plt, IL-6, IL-10, lactate, procalcitonin, C-RP). Clinical data, such as respiratory and renal complications, drainage blood loss, hemostasis disorders, requiring hemostatics and blood transfusion, ICU and in-hospital was also evaluated. All results presented as mean value ± standard deviation (σ). To evaluate the diversity significance between all parameters Student’s T-test was used. P-level <0,05 was considered as significant.

Table 1. Clinical data

Data	Control (n=20)	Analyze № 1 (n=20)	Analyze № 2 (n=20)
Age, years (min, max)	72,1±12,7 (65;82)	69,3±11,3 (66;81)	70,3±12,9 (61;79)
Weight, kg (min, max)	71,9±12,6 (54;114)	74,9±9,4 (52;112)	73,2±12,8 (55;108)
HF (NYHA), n (%):	20 (100)	20 (100)	20 (100)
II	10 (50)	11 (55)	11 (55)
III	10 (50)	9 (45)	9(45)
Comorbidities:			
Renal failure (RIFLE), n(%)	5 (25)	8 (40)	6 (30)
R	2 (10)	3 (15)	3 (15)
I	2 (10)	3 (15)	2 (10)
F	1 (5)	2 (10)	1 (5)
Respiratory failure, n (%) (A.G.Dembo chronic respiratory insufficiency classification) [7]	7 (35)	8 (40)	6 (30)
I	1 (5)	2 (10)	2 (10)
II	4 (20)	4 (20)	3 (15)
III	2 (10)	2 (10)	1 (5)
Diabetes (Hb1Ac<8%) n (%)*	7 (35)	8 (40)	6 (30)
EuroSCORE 2	3,9±0,9	4,3±1,1	4,4±1,2
Operations, n (%):			
CABG + MV replacement + RFA	6 (30)	7 (35)	5 (25)
CABG + MV repair + RFA	8 (40)	8 (40)	7 (35)
CABG + MV replacement +LV aneurysm repair+ RFA	1 (5)	1 (5)	2 (10)
AV and MV replacement + RFA	2 (10)	3 (15)	3 (15)
AV replacement + CABG + RFA	3 (15)	2 (10)	3 (15)
CPB duration, min (min, max)	176±52 (108;212)	182±44 (112;201)	194±62 (118;220)
Cross-clamp time, min (min, max)	142±39 (88;174)	145±27 (88; 165)	135±40 (80;185)
Surgery duration, min (min, max)	340±60 (155;380)	330±56 (140;380)	360±70 (160;360)
Intraoperative blood loss, ml (min, max)	730±65 (500;950)	725±55 (550;900)	750±70 (690;850)

Note. Control group – with standard, Analyze№1 – group with the hemofiltration, Analyze№2 – group with PMMA hemodiafilter. P>0,05 for all data. HF – Heart failure(New York Heart Association Functional Classification). CABG – coronary artery bypass grafting. RFA – radiofrequent ablation (one of the Cox-Maze modifications).

Results. Analysis of biologically active molecules concentration in patient's blood has shown that filtration and sorption during CPB reduces level of inflammatory cytokines and trigger molecules and markers if systemic inflammatory response (**table № 3**)

Table 2. Initial laboratory data

Data	Control (n=20)	Analyze №1 (n=20)	Analyze №2 (n=20)
Oxygenation index	376 ±88	342±64	330±90
Creatinine, µmol/L	89±28	107±30	96±39
Carbamide, mmol/L	6,08±3,3	4,9±2,1	7,9±4,7
Diuresis, ml/h	150±70	135±55	105±45
AST, un/L	24±15	37±9	32±18
ALT, un/L	49±31	62±22	71±36
Lactate, mmol/L	0,8±0,5	0,8±0,4	0,6±0,5
IL-6, pg/ml	16,2±3,9	17,7±3,1	22,5±6,6
IL-10, pg/ml	7,4±4,1	8,2±2,9	7,1±5,0
Procalcitonin, ng/ml	1,1±0,7	1,4±0,6	1,2±1,1
CR-P, mg/L	7,9±5,1	9,8±3,3	10,3±5,3
Free hemoglobin, g/l	0,1±0,15	0,2±0,15	0,1±0,15
WBC, x9	7,89±2,9	7,2±4,3	8,1±4,9
Fibrinogen, g/l	4,1±2,1	3,4±1,2	4,2±2,4
APTT, sec	28±17	33±12	37±18

Note. Control group – with standard, Analyze№1 – group with the hemofiltration, Analyze№2 – group with PMMA hemodiafilter. P>0,05 for all data. AST – aspartate aminotransferase. ALT– alanine transaminase. IL – interleukyn. CR-P – C-reactive protein. APTT – activated partial thromboplastin time.

Table №3. Concentration of biologically active molecules

		Control, n=20			Analyze №1, n=20			Analyze №2, n=20			p	
		1			2			3			1:2	1:3
		M	[25]	[75]	M	[25]	[75]	M	[25]	[75]		
IL-6, pg/ml	1 ч	156,6	128,8	198,3	51,9	37,4	66,2	62,6	39,3	67,9	0,025	<0,01
	24 ч	176,4	116,1	228,5	62,7	47,1	122,1	47,5	15,78	135,8	0,033	0,029
IL-10, pg/ml	1 ч	256,2	224,8	355,8	281,4	239,8	315,5	462,6	314,4	480,4	0,065	0,049
	24 ч	12,1	7,8	16,4	16,0	12,6	18,3	14,7	11,1	17,21	0,411	0,667
sTrem-1	1 ч	219,1	56,5	699,8	111,2	61,3	182,4	53,9	34,85	65,9	0,079	0,092
	24 ч	118,9	64,1	530,7	59,8	42,8	102,3	67,1	34,4	72,5	0,095	0,146
PC, нг/мл	1 ч	11,4	8,15	26,5	6,1	4,15	9,05	3,2	0,43	6,2	0,105	0,095
	24 ч	115,7	41,2	856,5	5,6	3,1	12,7	1,85	0,336	13,8	<0,01	<0,01

Note. Control group – with standard, Analyze№1 – group with the hemofiltration, Analyze№2 – group with PMMA hemodiafilter. P value – (1:2 – control/analyze №1, 1:3 – control/analyze №2). M – mean; [25] [75] – percentile. IL-6, IL-10 – interleukines; sTrem-1 – triggering receptor expressed on myeloid cells-1; PC – procalcitonin

1 hour after the sorption IL-6 levels was significantly lower, that in control group. There also was a tendency to the lower concentrations of IL-6 1 day after the procedure, which shows extended decrease of inflammatory response because of the sorption on PMMA and elimination of activation molecules from blood. Moreover, levels of anti-inflammatory IL-10 one hour after the procedure was insignificantly higher comparing

to those in patients, who did not undergo a PMMA-sorption procedure, which leads to the increase in adaptive anti-inflammatory reaction of the body. IL-10 level rises briefly (first hours after the trigger), that's why its level 1 day after the procedure was low and did not vary in different groups significantly.

Median value of sTREM-1 concentration in blood after 1 hour was 4 times less than in control group, however, a wide range of sTREM-1 levels and small amount of patients did not lead to any statistically significant difference. Nevertheless, sorption effect on sTREM-1 (molecular weight~ 17 kDa) can be considered captured. Median value of sTREM-1 concentration in blood 1 day after in analyzed groups was 2 times less than in control group, but it was not statistically relevant. Soluble triggering receptor expressed on myeloid cells-1 sTREM-1 levels increase during systemic inflammatory response(septic and non-septic) and correlates with the severity of process.[8]

Apart from the benign changes in patient's cytokine status, there was relevant improvement in early postoperative period (**table №4**). Transfusion rate were the same in both groups, but patients from analyzed group didn't require any hemostatic therapy. There was no need in inotropic and vasopressor medications in the analyzed group by the end of the first postoperative day, all patients were extubated in first postoperative hours. Complicated postoperative period occurred in 2 (10%) cases in analyzed groups vs 5(25%) in controlled group; renal dysfunction, requiring dialysis, was diagnosed in 6 (30%) patients from controlled group vs. 2 patients (10%) from analyzed group №2; respiratory insufficiency has developed in 3 patients (15%) only in controlled group. In-hospital stay was comparable in both groups, but lower ICU-stay was significantly lower in analyzed groups. Polyorganic insufficiency syndrome (POIS) occurred in 3 patients (15%) from the controlled group.

Therefore, decrease in concentration of inflammatory cytokines and particular markers of systemic inflammatory response in blood right after the procedure proves

Table № 4. Clinical characteristics of postoperative period (M [25;75])

	Control (n=20)	Analyze №1 (n=20)	Analyze №2 (n=20)	P control/ analyze №1	P control/ analyze №2
Drainage blood loss, ml	310 [250;350]	270 [230;370]	290 [250;350]	0,79	0,85
PaO ₂ /FiO ₂	189 [126;220]	310 [276;323]	287 [255;325]	0,02	0,017
Ventilation time, min	530 [410;980]	205 [135;300]	220 [120;420]	<0,01	<0,01
Dopamine, µg/kg/min	3,3 [2,8;6,5]	0	0	-	-
Noradrenaline, µg/kg/min	0,05 [0,01;0,08]	0	0	-	-
ICU stay, hours	41,3 [24,3;186]	18,9 [16,1;48,2]	16,3 [18,2;112]	0,019	0,055
In-hospital stay, days	19,9 [14,5;22,1]	11,9 [8,6;18,3]	12,5 [9,1; 18,5]	0,045	0,055

Note. Control group – with standard, Analyze№1 – group with the hemofiltration, Analyze№2 – group with PMMA hemodiafilter. PaO₂/FiO₂ – oxygenation index. ICU – intensive care unit.

that both methods have their positive effect on trigger factors of systemic inflammatory response, and lower levels of analyzed parameters 1 day after the procedure show indirect positive effect on eliminating blood components, that cause systemic inflammation after long-standing CPB.

Discussion. Currently there are various pharmacological and mechanical methods have been developed to reduce systemic inflammatory response – intraoperative ultrafiltration, corticosteroids, minimally invasive extracorporeal circuits (MieCC) [9,10]. But these techniques have their disadvantages too: absence of venous reservoir can increase the risk of air embolism. Also membranes in new oxygenators have better biocompatibility, but prevent blood saturation with isoflurane, so it is impossible to use inhalational anesthetics and their better protective effect on myocardium, which limits the use of this technology. Leukocyte activation during CPB is one of the most important factors leading to polyorganic dysfunction in patients after cardiac surgery. That is why leukocyte removal filters have been developed in attempt to reduce the severity of systemic inflammation. [11]. Also leukocyte depletion was suggested, in order to reduce endothelial cell activation and transendothelial migration of leukocytes [12]. Main disadvantages of this method are increased resistance to the blood flow, creating turbulent blood flow and microembolism; besides, activated forms of neutrophils are not the only cause of the systemic inflammatory response. It has been reported lately that a new device called Leukocyte Modulator Device (L-MOD) had shown a good clinical potential in reducing inflammatory response during CPB. [13]. In recent years several Russian hospitals have used perioperative plasmapheresis for the prevention of systemic inflammatory response [14]. Starting from the pericardiotomy until the end of CPB, all the blood from the wound can be collected by the Cell Saver device without the cardiomy reservoir. Main disadvantages are: an additional circuit, which can provoke systemic inflammation itself, elimination of all cytokines – inflammatory and anti-inflammatory, as well as blood serum factors of hemostasis. In recent studies the usage of cytokine adsorbents, like «Cytosorb», is described, but it showed questionable efficacy in systemic inflammatory response minimization. [15,16,17]. And moreover, the cost of this device is far higher, than the cost of the whole CPB circuit. High-volume passive hemofiltration in a standard CPB by the roller pump and using PMMA hemofilter, by our preliminary results, shows the absence of these disadvantages.

Conclusion. Hemofiltration using polyionic buffer solution and usage of polymethyl methacrylate filtrative and sorptive ability during long-standing CPB can reduce the alterative effect of roller pump and can reduce the incidence of organic dysfunction in postoperative period.

Study limitations. Preliminary evaluative study, being carried out on a small amount of patients.

Conflict of interests. No financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this study.

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