equal to 122.5 ± 0.94 ^{0}, and at 3-year-old girls of 2nd group on average makes 121.0 ± 1.62 ^{0} (right side), 123.0 ± 1.08 ^{0} (left side).

At 3-year-old boys of 3rd group CBJ is on average equal to 123.1 ± 1.82 ^{0} (right side), 123.2 ± 1.82 ^{0} (left side), and at 3-year-old girls of this group on average makes 122.5 ± 0.94 ^{0} (right side), 123.2 ± 1.08 ^{0} (left side).

AF not only does not provide children with necessary quantity of nutrients, but also does not give high-grade functional loading on MS of growing organism, for which account there is backlog of some morphometric parametres of parts of human body.

Conclusions:

1. MHF and PHF at children with AF is less than at children with natural food. It is especially expressed at children from the children's homes, being on artificial food.

2. Parity of top, middle and bottom parts of the face at girls of all groups are closer to the rule of Gold Proportion, after comparison of boys. Middle part of face is more constant, than top (depends on the beginning of line of hair) and bottom (depends on term of eruption and quantity of teeth).

3. In all groups, the parity of parametres of parts of face is close to number of Fibona-chchi or parametres of a gold proportion. These parities are more authentic at 3-year-old girls in comparison of boys.

4. At 3-year-old children of both sexes and all groups basically meet the open form of occlusion where corners of the CBJ is more blunt (120–125^0), it is rare (5–6 %) neutral form where corners of the bottom jaw is more than 135$^{0.}$

5. CBJ is more blunt at 2nd and 3rd groups of children at of both sexes. It tells about backlog of formation of the bottom jaw. Besides, at all groups the corner of the bottom jaw on the left side is more blunt than the right side. This parametre testifies to more physical development of right side of the bottom jaw after comparison of left (right side is more functional in the masticatory act).

References:

1. Andreishev A. R. Associated maxillodental and facial anomalies and deformations//Publishing house: GEOTAR-MEDIA.: library of doctor-expert. – 2008. – P. 257.
2. Dmitrienko S. V., Vorobyov A. A., Krayushkin A. I.//Morphological features of maxillofa-cial area at anomalies and deformations and methods of their diagnostics. Publishing house: ElBi-Spb; – 2009. – P. 213.
3. Chetvertnova G. A. Influence of natural and artificial feeding on colonization resistance of oral cavity and condition of maxillofacial area: dissertation of Doctor of Medicine. – Volgograd, – 2008. – P. 137.
4. Shaporenko P. F., Shipitsyna A. V., Yermoleva V. A. Features of morphological standards of head at newborns, young men and girls 17–21 years//Morphology. – 2004. – vol. 126, – No. 4. – P. 139.
5. Shmurak M. I, Tvere V. M, Simanovskaya E. Yu., Nyashin Yu. I. Problem of feeding of children at early age//Youth science. Prikamye: Scientific labour collection. – Perm. – 2006. – 7th release. – P. 27–30.
6. Dubner H., Keller W. "New Fibonacci and Lucas primes," Math. Comp. – 68:225 (2003 417–427. S1 – S12. MR p. 99.)
7. Marti I. et al. Effect of lactose on rheology of milk protein dispersions//3 International Sympo-sium on food Rheology and Structure. – 2004. – P. 207–211.
8. Tverier V. M., Simanovskaya E.Yu., Nyashin Yu. I. et al. R. Biomechanical description of the breast feeding//5th World Congress of Biomechanics: Intern. Proc., Munich (Germany), 2006. Bologna. – 2006. – P. 521–525.

Yarovenko Vladimir Vladimirovich,
Dnipropetrovsk Regional Clinical Center of Cardiology
and Cardiosurgery, Dnipropetrovsk, Ukraine
E-mail: vowayar@yandex.ua

Dynamics of proinflammatory cytokines using conventional ultrafiltration after cardiac surgery

Abstract: The work is devoted to the influence of ultrafiltration for manifestations of inflammatory response and the dynamics of proinflammatory cytokines in patients after cardiac surgery.

Keywords: cardiopulmonary bypass, ultrafiltration, inflammation, cytokines.

Introduction

Cardiac surgery and cardiopulmonary bypass (CPB) initiate a systemic inflammatory response syndrome [3, 7] that may lead to considerable postoperative mortality as well as complications such as bleeding, thromboembolism, fluid retention and temporary organ dysfunction [12]. This syndrome arises mainly due to contact between the blood and the artificial surfaces of the bypass circuit [10]. Attempts to prevent CPB-mediated inflammation by different methods are warranted, because a reduction in the inflammatory response may contribute to organ function protection and hence to improved recovery and

to decreased mortality from surgical procedures, particularly in critically ill patients.

Diverse therapeutic strategies to modulate the systemic inflammatory response after cardiac surgery are being examined: reduction in the area of foreign surfaces «minimized extra-corporeal circuit» [5; 13], removal of inflammatory mediators by ultrafiltration [11], pharmacologic strategies for combating the inflammatory response [8], use of leukocyte-depleting filters [1], improving the biocompatibility of the CPB circuit [2; 4].

CPB-induced systemic inflammatory response syndrome is characterized by the activation of complement system, monocyte/macrophages and neutrophils, and the release of cytokines and vasoactive substances [14].

Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, can be induced by a wide variety of stimuli and act on a large number of effector cells [14; 7]. Thus, their concentrations may reflect the status of the inflammatory response when multiple initiating processes are involved.

Previous clinical studies have suggested that the serum levels of IL-6 are the best parameter for assessing the status of the inflammatory response to surgical stress [15]. IL-6 is a pleiotropic cytokine involved in the regulation of immune responses and also plays an important role during acute-phase responses, which include fever, corticosterone release and hepatic production of acute phase proteins. This cytokine is produced by a variety of cells after some form of stimulation, such as an infection, trauma or immunological challenge, which stimulates the release of immune-competent proteins, such as CRP from the liver and, together with TNFα and IL-1β, causes activation of T cells [14; 15].

We investigated the effects of ultrafiltration of CPB on systemic inflammatory response and clinical outcome following open heart surgery.

Material and Metods

After obtaining institutional review board approval and written, informed consent, 42 adult patients with primary valvular disease were prospectively enrolled in this study.

Patients were randomly divided into two groups: (1) conventional ultrafiltration (CUF group) (n = 21); or (2) control group (n = 21) use of a non ultrafiltration of CPB.

Exclusion criteria were impaired renal function with serum creatinine levels > 1.6 mg/dL, liver function test results indicating impaired liver function, a history of diabetes mellitus and preexisting chronic inflammatory disease. Patients enrolled in this protocol did not receive aprotinin.

Anesthetic management was standardized and consisted of induction with propofol, fentanil and vecuronium. Anesthesia was maintained with sevoflurane and fentanil, with vecuronium and/or pancuronium for muscle relaxation. Fluid management consisted of crystalloid solution administration during the pre- and post- CPB periods.

All patients received an intraoperative infusion of tranexamic acid (1 g. in 20 minutes before skin incision, followed by a continuous infusion of 400 mg/h until completion of surgery).

Systemic heparinization was performed by applying 300 IU/kg body weight prior to cannulation, and the activated clotting time (ACT II; Medtronic) was maintained above 400 seconds during CPB. After termination of CPB and surgical hemostasis, heparin was neutralized with protamine sulphate (1:1 ratio). Cardioplegic solution (Custodiol, Alsbach-Hahnlein, Germany) was administered for myocardial protection through a combination of anterograde and retrograde techniques.

The extracorporeal circuit in both groups consisted of a roller pump (Terumo System 1, Terumo CVS Co, USA), a membrane oxygenator with phosphorylcholine coating (Skipper with A. g.i. l.e.™ treatment; Eurosets), an arterial filter, a cardiotomy reservoir, and a pack of custom polyvinyl chloride tubing. All patients underwent standard non pulsatile hypothermic CPB to a core temperature of 30 °C. Pump prime consisted of 600 mL. of crystalloid solution, 500 mL. of HES 130/0,4, 400 mL. of 15 % mannitol and 5000 U of heparin. Perfusion pressure during CPB was maintained between 50 and 70 mm. Hg. CPB was discontinued after rewarming the patient to a core temperature of 36 °C.

Patients in the control group received no ultrafiltration. In the CUF group, the patients were treated using conventional ultrafiltration during CPB that removed any excess fluid and hemoconcentrated the patients' blood using a hemoconcentrator (DHF 0.6 Sorin Group USA, Inc.). Suction was applied to the filtrate port to achieve an ultrafiltration rate of 100–150 ml/min. The total amount of fluid filtered by conventional ultrafiltration was 31,8 ± 6,4 mL/kg.

Leukogram and concentration of inflammatory markers (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]) were detected in arterial blood samples before intubation, 30 minutes after the end of CPB and 24 hour postoperative.

Measurements of TNF-α and IL-6 levels were performed by means of commercially available enzyme-linked immunosorbent assays (Orgenium Laboratories, Vantaa, Finland). The appropriate volume of sample or standard was applied to a 96-well microtiter plate precoated with the corresponding monoclonal antibody. After the aspiration of the wells, plates were washed with a specific surfactant provided by the manufacturer. A solution of enzyme-linked polyclonal antibody and substrate was added to each well. The optical density of each well was read at the appropriate wavelength.

Statistical processing was carried out using the software package SPSS 19.0. All data are presented as the mean ± SD. Dichotomous variables were analyzed with the Fisher exact test. A P value of < 0.05 was considered statistically significant. Results were considered significant for $P < 0.05$.

Results

Clinical Outcome Parameters

Seventy percent of the patients in both groups were men. There were no significant differences between the groups in age distribution, male-female ratio, preoperative creatinine concentration, CPB time, and crossclamp time (Table 1).

Table 1. – Demographic characteristics end perioperative data*

Parameter	CUF group (n = 21)	Control group (n = 21)	P Value
Age, y	60 ± 11	62 ± 10	0.63
Gender,% male	73	67	0.78
Weight, kg.	73 ± 11	77 ± 10	0.91
Creatinine, mg/dL	1.1 ± 0.36	1.2 ± 0.36	0.72
Body surface area, m^2	1.9 ± 0.16	1.8 ± 0.16	0.82
Ejection fraction,%	62 ± 8	66 ± 8.6	0.44
EuroSCORE,%	2.19 ± 0.79	2.5 ± 1.1	0.91
Bypass time, min.	109 (79–128)	97 (80–121)	0.65
Aortic cross-clamp time, min.	77 (60–104)	77 (60–104)	0.92

*Note: * — Measurements are presented as the mean ± SD. The p values are unadjusted for multiple comparisons*

During the postoperative course, 2 units of packed red blood cell were transfused to 1 patient in the CUF group and 2 patients in the control group. No patient underwent surgical reexploration for bleeding. Postoperative bleeding was similar in the two groups (p = 0.12). A significant difference in other clinical parameters. Under ultrafiltration reduces the time of mechanical ventilation (p = 0.03), and length of stay of patients in the intensive care unit (p = 0.05), are shown in Table 2.

Table 2. – Postoperative clinical parameters*

Parameter	CUF (n = 15)	Control (n = 15)	Value
Patient transfused in ICU	1 (6.6 %)	2 (13.3 %)	0.35
Chest tube drainage, mL/kg/24 h	3.58 ± 1.3	4.4 ± 2.8	0.12
Time to extubation, min.	456 ± 138	643 ± 248	0.03
Length of ICU stay, days	5 ± 1.7	5.9 ± 1.5	0.05

*Note: * — Measurements are presented as the mean ± SD. The p values are unadjusted for multiple comparisons*

Baseline levels of white blood cell count in the ultrafiltration and control groups were similar ($5.7 \pm 1.5 \cdot 10^9$/L (CUF) and $6.8 \pm 2.1 \cdot 10^9$/L (control); p = 0.39). In blood samples taken after 30 min. after CPB, marked leukocytosis, ($16.04 \pm 4.7 \cdot 10^9$/L (CUF) and $16.9 \pm 6.3 \cdot 10^9$/L (control); p = 0.3), which was maintained until the end of the study. In both groups, 2 stage, the value of this index was significantly higher than baseline levels (p = 0.012). 24 hours after the end of cardiopulmonary bypass intergroup differences number of leukocytes reach statistical significance ($11.7 \pm 3{,}2 \cdot 10^9$/L (CUF) and $14.4 \pm 3.25 \cdot 10^9$/L (control); p = 0.03).

Baseline levels of TNF-α were similar in both groups. (CUF, 11.63 ± 3.17 pg/ml vs. control 10.63 ± 1.18 pg/ml; p = 0.3). Statistically significant intragroup changes and differences between the groups on the stages of the study of this indicator has not been revealed. The mean value of the concentration of TNF-α at the second stage 11.34 ± 6.03 pg/ml (CUF) vs. 17.05 ± 18 pg/ml (control); p = 0.18. Cytokine concentration for 3 phase 9.28 ± 4.07 pg/ml (SUF) vs. 9.29 ± 3.94 pg/ml (control); p = 0.39.

Baseline levels of IL 6 were similar in both groups. (CUF, 1.65 ± 0.32 pg/ml vs. control 1.1 ± 0.62 pg/ml; p = 0.12). Thirty minutes after the end of cardiopulmonary bypass level of IL 6 significantly increased in both groups. The maximum average value in the control group amounted to ultrafiltration and 61.35 ± 47 pg/ml (p = 0.005 compared to baseline) and 104.1 ± 65.4 pg/ml (p = 0.001 compared to baseline). Between-group differences also reached statistical significance (p = 0.022). After 24 hours, there was a gradual decrease in the concentration of IL 6 (CUF, 48.95 ± 30.1 pg/ml vs. control 69.9 ± 44 pg/ml; p = 0.066). Intra-group differences were also statistically significant (p = 0.008 compared to baseline group ultrafiltration) and (p = 0.004 compared to baseline control group). It should be noted that at stage 3 between-group differences in the content of this cytokine were on the threshold of statistical significance.

Conclusion

Our study showed that the use of conventional ultrafiltration during cardiopulmonary bypass reduces the intensity of the inflammatory response in cardiac surgical patients.

This is manifested in:

1. Twenty-four hours after the cardiopulmonary bypass white blood cell count in patients with ultrafiltration was significantly lower compared with controls.
2. Conduct ultrafiltration significantly reduces the concentration of IL-6 in thirty minutes after the end of cardiopulmonary bypass.
3. In our study, we were unable to determine the impact of ultrafiltration on TNF α.
4. In the ultrafiltration's group reduced length of stay in intensive care and duration of mechanical ventilation.

References:

1. Boodram S., Evans E. J. Use of leukocyte-depleting filters during cardiac surgery with cardiopulmonary bypass: a review. J Extra Corpor Technol – 2008, – 40: 1: 27–42.
2. De Somer F., Francois K., van Oeveren W., Poelaert J., De Wolf D., Ebels T., et al. Phosphorylcholine coating of extracorporeal circuits provides natural protection against blood activation by the material surface. Eur J Cardiothorac Surg – 2000, – 18: 602–6.
3. Hess P. J. Jr. Systemic inflammatory response to coronary artery bypass graft surgery. Am J Health Syst Pharm – 2005, – 62: 18: 4: 6–9.
4. Hoel T. N., Videm V., Baksaas S. T., Mollnes T. E., Brosstad F., Svennevig J. L. Comparison of a Duraflo II-coated cardiopulmonary bypass circuit and a trillium-coated oxygenator during open-heart surgery. Perfusion – 2004, – 19: 177–84.
5. Immer F. F., Ackermann A., Gygax E. et al. Minimal extracorporeal circulation is a promising technique for coronary artery bypass grafting. Ann Thorac Surg – 2007, – 84: 5: 1515–1520.
6. Kotani T., Kotake Y., Morisaki H. et al. Activation of a neutrophilderived inflammatory response in the airways during cardiopulmonary bypass. Anesth Analg – 2006, – 103: 1394–1399.
7. Landis C. Why the inflammatory response is important to the cardiac surgical patient. J Extra Corpor Technol – 2007, – 39: 4: 281–284.
8. Landis C. Pharmacologic strategies for combating the inflammatory response. J Extra Corpor Technol – 2007. – 39: 4: 291–295.
9. Lim H. K., Anderson J., Leong J. Y. et al. What is the role of leukocyte depletion in cardiac surgery? Heart Lung Circ – 2007. – 16: 4: 243–253.
10. Menasche P., Edmunds L. H. Jr. Extracorporeal circulation: the inflammatory response. Cardiac surgery in the adult. – New York: McGraw-Hill – 2003, – P. 349–360.
11. Pérez-Vela J., Ruiz-Alonso E., Guillén-Ramírez F. et al. ICU outcomes in adult cardiac surgery patients in relation to ultrafiltration type. Perfusion – 2008, – 23: 2: 79–87.
12. Rubens F. D., Mesana T. The inflammatory response to cardiopulmonary bypass: a therapeutic overview. Perfusion – 2004,– 19 (Suppl 1): S5–12.
13. Zamora E., Delgado L., Castro M. A. et al. Coronary artery bypass surgery using the mini-extracorporeal circulation system: a Spanish unit's experience. Rev Esp Cardiol – 2008; 61: 4: 376–381.
14. Warren O. J., Smith A. J., Alexiou C., Rogers P. L., Jawad N., Vincent C., et al. The inflammatory response to cardiopulmonary bypass: part 1— mechanisms of pathogenesis. J Cardiothorac Vasc Anesth. – 2009. – 23 (2): 223–31.
15. Otania S., Kuinoseb M., Murakamic T. et al. Preoperative Oral Administration of Pentoxifylline Ameliorates Respiratory Index after Cardiopulmonary Bypass Through Decreased Production of IL-6. Acta Med. Okayama, – 2008, – Vol. 62, No. 2, – P. 69–74.