

# INFLUENCE OF THE ACUTE INFLAMMATION AND ENDOTHELIAL DYSFUNCTION ON THE RETINAL VEIN OCCLUSION FORMATION AFTER CARDIO-SURGICAL INTERFERENCES WITH THE USE OF CARDIOPULMONARY BYPASS

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## Abstract

Acute inflammation and endothelial dysfunction (EDF) are typical pathological processes, which determine the development of retinal vein occlusion (RVO) during cardio-surgery with the use of cardiopulmonary bypass (CB), but the connection of seromarkers according to the terms of occlusion appearance remains undefined.

**The aim** – to determine the influence of the acute inflammation and EDF for RVO formation after cardio-surgical interferences with the use of CB according to the terms of occlusion appearance.

**Material and methods.** There were selected for the research the data of 137 eyes (126 patients, the main group) with RVO after the surgery with CB. The comparison group contains the data about examination of 86 eyes (43 patients), who had not any occlusion during all term of examination. The control group consisted of 10 eyes (5 patients) without occlusion, which were examined before surgery. An ophthalmologist 2, 7, 30, 60, 90 and 180 days after cardio-surgical interference, examined patients. The content of IL-6, IL-8 and VE-cadherin in blood serum was determined by immunoenzyme technique (Bender Medsystems, Austria). Statistical data processing was performed with the use of Statistica 10 program (StatSoft, Inc., USA), regression analysis – with the use of the program package GLZ.

**Results.** The conduction of cardio-surgeries with the use of CB caused an increase of the interleukins content in the early period (IL-6 on the 2<sup>nd</sup> and 7<sup>th</sup> days, and IL-8 up to 30 days), while the content of VE-cadherin (VE-C) was slightly increased during almost all period of monitoring. With the availability of RVO, the content of IL-6 during all terms of occlusion appearance was significantly higher, the content of IL-6 was up to 30 days, and the content of VE-C in a greater degree was after the 7<sup>th</sup> day.

The regression analysis showed that after 1–2 days RVO appearance was directly related with the content of IL-6 and IL-8 in the blood, on the 3<sup>rd</sup> and 7<sup>th</sup> days – only with the content of IL-8, on the 8<sup>th</sup> and 30<sup>th</sup> days – with the content of all markers, and then with the content of IL-6 and VE-C. The accuracy of the prediction of the presence or absence of RVO at the appropriate period according to the calculated regression model is at least 78 % ( $p < 0.001$ ), what proves the influence of markers on the development of RVO.

**Conclusions.** The undertaken study shows the meaning of the acute inflammation and EDF by appearance of RVO with the use of CB, what justifies the application of the preventive measures – at the early stages the restriction of activity of the inflammatory process, at the later stages – prevention of EDF development.

**Keywords:** retinal vein occlusion, cardiopulmonary bypass, IL-6, IL-8, VE-cadherin.

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## 1. Introduction

The retinal vein occlusion, according to population studies in the countries of the world, occurs with a frequency of 5.2 per 1000 of population [1]. The study of Huttenberh showed that the prevalence of RVO composes 0.40 % [2]. There is a definite relationship between RVO and cardiovascular diseases – ischemic heart disease and brain [3, 4]. It has been shown that RVO is associated with arterial hypertension and atrial fibrillation [2]. Cardio-surgeries, accompanied by artificial circulation (IC) may be accompanied by perioperative complications on the part of the visual organ, which are related to retinal ischemia and development of ischemic optical neuropathy and vascular occlusion of retina [5, 6]. Their occurrence factors are prolonged hypothermia, hemodilution and decrease of hemoglobin concentration, hypovolemia, blood circulation redistribution, prolonged hypotension during CB surgery, secondary vasospasm [7, 8].

When using CB, inflammation and endothelial dysfunction (EDF) are activated during the surgery, what leads to damage of internal organs [9], and serumal levels of pro-inflammatory cytokines – interleukin-6 (IL-6), intercellular adhesion molecules (ICAM-1) in three hours after the surgery determined 30-day and 5-year mortality of such patients [10]. The application of CB increases the penetrance of the microcirculation vessels of lungs, neutrophilous emigration, the content of IL-6 and other inflammatory markers, including, – a protein of cell-cell adhesion of vasculoendothelial cadherin (VE-C) [11].

The patients after CB had a content increase in the blood of VE-C [12].

The last one can be considered as the marker of EDF, as it regulates the connection of endothelial adhesives and vascular permeability [13, 14].

In such a way, the acute inflammation and EDF can be considered as typical pathological processes, which determine the development of RVO during cardiac surgery and the use of CB, but the relation of serum markers by the terms of occlusion appearance remains undefined.

**The aim of the research.** To determine the influence of acute inflammation and EDF on the formation of RVO after cardio-surgical interferences with the use of CB by the terms of occlusion appearance.

## 2. Material and methods

The recruitment of patients was conducted from 2013 to 2019. The cardio-surgeries were made in the specialized cardio-surgical institutions of Kyiv city, where there is an opportunity to make interferences using an artificial blood circulation apparatus. The ophthalmological studies were carried out based on City Scientific and Practical Center for “Laser Methods of Eye Treatment” of the Kiev City Clinical Ophthalmological Hospital “Centre of eye microsurgery”, which is the clinical base of the Ophthalmology Department of the National Medical Academy of Postgraduate Education named after Shupyk P. L.

Totally, there were examined 233 eyes (174 patients), which were divided on three groups. The main group included 137 eyes (126 patients), which were diagnosed with RVO after cardio-surgery with cardiopulmonary bypass. According to the term of occlusion appearance, the distribution of cases was the following: in 2 days after the surgery, the RVO was found on 14 (10.2 %) eyes, in 7 days – on 23 (16.8 %), in 30 days – on 15 (10.9 %), in 60 days – on 29 (21.2 %), in 90 days – on 39 (28.5 %) and in 180 days – on 17 (12.4 %).

As a comparison group, there was examined the data of 86 eyes (43 patients), which during all period of examination had not any vascular occlusion of retina. The distribution of observations according to the time was the following: 2 days – 14 (16.3 %) patients, 7 days – 15 (17.4 %), 30 days – 15 (17.4 %), 60 days – 17 (19.8 %); 90 days – 12 (14.0 %), 180 days – 13 (15.1 %).

For the control was attracted the data of examination of 10 eyes (5 patients), which had the same degree and duration of the main disease, the indications to surgery with CB, but were examined before the surgery. During 180 days after surgery, these patients had not any vascular occlusion of retina.

The age of the main group was  $64.6 \pm 10.2$  years, in the comparison group –  $65.2 \pm 9.1$  years and by the control –  $69.6 \pm 6.0$  years ( $p=0.318$ ). The groups of patients by gender did not differ: the correlation of men/women was equal to 1:1.

The study design was considered by Ethics Committee of the National Medical Academy of Postgraduate Education named after Shupyk P.L. at the planning stage of the study and found to be in conformity with the principles of the Helsinki Declaration of General Assembly of the World Medical Association (1964–2000), the Council of Europe Convention on Human Rights and Bio-medicine (1997), the relevant provisions of WHO, the International Council of Medical Scientific Societies, the International Code medical ethics (1983) and the laws of Ukraine.

All patients gave written consent to participate in the study and processing of personal data.

The patients were examined in 2, 7, 30, 60, 90 and 180 days after the cardio-surgical interference. All patients had standard ophthalmological examinations and spectral domain optical coherence tomography (OCT), OCT-angiography.

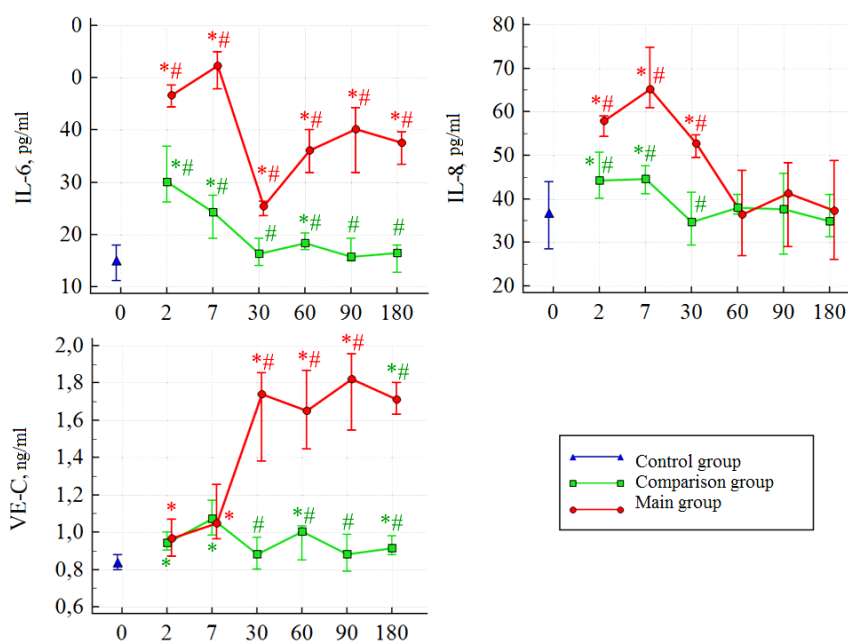
The content of IL-6, IL-8 and VE-C in the blood serum was determined by the immunoenzyme technique: Bender Medsystems reagent kits (Austria). Laboratory studies were conducted at the Research and Development Establishment of the experimental and clinical medicine of the National medical university named after O.O. Bohomolets (director – Doctor of Medicine, professor Natrus L. V.).

The statistical data processing was conducted with the use of Statistica 10 program (StatSoft, Inc., USA). It was evaluated the character of data distribution according to tests of Kolmogorov-Smirnov and x-square ( $\chi^2$ ). The normality of the distribution is confirmed at  $p < 0.05$ . Two independent sets of data were compared with the use of Mann–Whitney criterion (U) and Kruskal-Wallis criterion (H), - the dependent – of Wilcoxon criterion (W).

To compare the frequencies of categorical variables, the Pearson's non-parametric tests  $\chi^2$  in the Yeits's modification. The predictive models were constructed with the use of multivariable logistic regression with systematic involvement of independent variables from GLZ Statistics 10 software package (generalized linear and non-linear models). The received model is designated for calculation of prediction of RVO development in patients within 180 days after surgery. There were used, as independent variables, the indicators of content of pro-inflammatory markers in the blood (IL-6, IL-8 i VE-C).

### 3. Results of research

The content of interleukins and VE-C in terms of observation in patient groups is shown in Fig. 1.



**Fig. 1.** The content of markers by the observation time (by the horizontal axis, days). It is shown, by the vertical axis, the medians, the 1<sup>st</sup> and the 3<sup>rd</sup> quartiles; the statistical significance of comparisons: \* – with control, # – indicators of the main group with the comparison group at the corresponding term

The content of IL-6 in the patients' blood of the comparison group was higher than the control on the 2<sup>nd</sup> and 7<sup>th</sup> days after the surgery (accordingly in 2.0 and 1.6 times more;  $p < 0.001$ ). The patients of the main group had a significantly increased content of IL-6 than in controlled group at all terms (in 1.7–3.5 times;  $p < 0.001$ ) and for such one in the comparison group (in 1.6–2.5 times;  $p < 0.001$ ).

The content of IL-8 in the comparison group did not statistically differ from the control, but on the 2<sup>nd</sup> and 7<sup>th</sup> days it was higher than that, which was at the other periods of observation

( $p < 0.05$ ). The content of IL-8 in the main group exceeded the content in the control and comparison groups only on the 2-30 days (in 1.5–1.8 times;  $p < 0.01$ ).

The content of VE-C in the comparison group exceeded the control on the 2<sup>nd</sup>, 7<sup>th</sup>, 60<sup>th</sup> and 180<sup>th</sup> days ( $p < 0.05$ ), but such increase was insignificant (in 1.1–1.3 times). Instead of it the content of VE-C in the main group significantly exceeded the control, and such one in the comparison group, especially from the period of 30 days (in 1.6–2.2 times;  $p < 0.001$ ).

In such a way, by comparison of content of the studied markers of inflammation and EDF showed certain differences. The cardio-surgery with the use of CB promoted the increase of the content of interleukins only in the early period (IL 6 on the 2<sup>nd</sup> and 7<sup>th</sup> days, and IL-8 up to 30 days), while the content of VE-C was slightly increased during almost the entire observation period. In the presence of RVO, the content of IL-6 at all periods of occlusion occurrence was significantly higher, the content of IL-8 up to 30 days, and the content of VE-C in a greater degree after 7 days.

So, considering interleukins as the markers of acute inflammation, and VE-C as the marker of EDF, the succession of these pathological processes can be established.

In the early terms after CB, it was expressed the acute inflammation, which was later regressed and was inferior to the development of EDF. With RVO, the dynamics of the process was the same; however, its intensity was significantly higher. Such results had the necessity of evidence-based scientific determination of the relation between the increased blood levels of the studied markers with RVO development.

To solve this task, we used the multivariate logistic regression analysis with systematic involvement of independent variables (Table 1).

**Table 1**

Independent variables of the regression equations by the terms of RVO appearance (selected in the process of regression analysis)

Term (days)	Marker	$\beta$	$\pm SE$	Wald	95 % BI	p
1–2	IL-6	0.286	0.045	39.64	0.197–0.375	<0.001
	IL-8	0.163	0.035	21.69	0.095–0.232	<0.001
	FI	–19.007	2.825	45.27	–(24.544–13.471)	<0.001
3–7	IL-8	0.277	0.035	61.13	0.208–0.346	<0.001
	FI	–16.342	2.067	62.51	–(20.393–12.291)	<0.001
	IL-6	0.580	0.163	12.70	0.261–0.899	<0.001
8–30	IL-8	0.190	0.063	9.08	0.066–0.313	0.002
	VE-C	11.660	2.589	20.28	6.585–16.735	<0.001
	FI	–35.452	6.678	28.182	–(45.542–22.364)	<0.001
31–60	IL-6	–0.299	0.042	50.96	–(0.381–0.217)	<0.001
	VE-C	5.757	0.765	56.57	4.257–7.258	<0.001
61–90	IL-6	0.206	0.028	52.37	0.150–0.262	<0.001
	VE-C	–3.966	0.581	46.63	–(5.105–2.828)	<0.001
91–180	IL6	0.493	0.059	70.47	0.378–0.609	<0.001
	VE-C	–8.786	1.068	67.61	–(10.880–6.691)	<0.001

Note: FI – a free indicator;  $\beta \pm SE$  – beta coefficients of independent variables of the regression equation; Wald – the criterion of Wald statistics; 95 % BI – 95 % possible interval for  $\beta$  coefficients; p – probability of difference from the null hypothesis ( $p < 0.05$ )

At a period of 1–2 days, the appearance of RVO was directly related with the content of both interleukins in the blood, at the 3<sup>rd</sup>–7<sup>th</sup> days - only with the content of IL-8, for 8<sup>th</sup>–30<sup>th</sup> days – with the content of all markers, at 31<sup>st</sup>–60<sup>th</sup>, 61<sup>st</sup>–90<sup>th</sup> and on 91<sup>st</sup>–180<sup>th</sup> days – with the content of IL-6 and VE-C. The regression equations of the probability prediction of RVO development by the terms after the surgery are as follows:

– for 1–2 days:

$$P_{(1-2)} = 1 / \left( 1 + e^{-(-19.007 + 0.286 * IL6 + 0.163 * IL8)} \right); \quad (1)$$

– for 3–7 days:

$$P_{(3-7)} = 1 / \left( 1 + e^{-(16.342 + 0.277 * IL8)} \right); \quad (2)$$

– for 8–30 days:

$$P_{(8-30)} = 1 / \left( 1 + e^{-(-35.452 + 0.580 * IL6 + 0.190 * IL8 + 11.660 * VEK)} \right); \quad (3)$$

– for 31–60 days:

$$P_{(31-60)} = 1 / \left( 1 + e^{-(-0.299 * IL6 + 5.757 * VEK)} \right); \quad (4)$$

– for 61–90 days:

$$P_{(61-90)} = 1 / \left( 1 + e^{-(0.206 * IL6 - 3.966 * VEK)} \right); \quad (5)$$

– for 91–180 day:

$$P_{(91-180)} = 1 / \left( 1 + e^{-(0.493 * IL6 - 8.786 * VEK)} \right); \quad (6)$$

where  $P_{(1-2)}$ ,  $P_{(3-7)}$ ,  $P_{(8-30)}$ ,  $P_{(31-60)}$ ,  $P_{(61-90)}$ ,  $P_{(91-180)}$  – the possibility of RVO development according to the correspondent terms; IL6 – blood content of IL-6, pg/ml; IL-8 – blood content of IL-8, pg/ml; VE-C – blood content of VE-C, ng/ml.

The quality of the calculated models was characterized by the parameters, which were indicated in **Table 2**. The presented data testifies about their satisfactory operational characteristics.

**Table 2**

Quality indicators of regression models of the projected RVO development by the terms of its occurrence

Formula	Term (days)	AUC	-2*log	$\chi^2$	p
1	1–2	0.960	102.2	175.1	<0.001
2	3–7	0.954	131.4	205.1	<0.001
3	8–30	0.950	138.2	377.7	<0.001
4	31–60	0.856	145.8	256.1	<0.001
5	61–90	0.869	139.4	222.8	<0.001
6	91–180	0.922	165.1	333.5	<0.001

Note: AUC – area under the diagram of the operating characteristic of the model (ROC) –2 log – maximum likelihood coefficient;  $\chi^2$  – Pearson's chi-squared test; p – probability of differences from the null hypothesis

It was accepted, as a threshold value for the probability of RVO development, the standard value, accepted for binary classification models – more than 0.5. All probability values, obtained during calculation according to the developed formulas, established a positive prediction for RVO

development in the corresponding term of the postoperative period. The quantitative characteristics of the classification of regression models properties are given in **Table 3**.

**Table 3**

Classification characteristics of regression models for the projected RVO development by the terms of its occurrence

Formula	The number of results in fact		The number of projected results		Sensibility, %	Specificity, %	Accuracy, %
	+	-	+	-			
1	14	14	13	12	92.9	85.7	89.3
2	23	15	19	14	82.6	93.3	86.6
3	15	15	14	12	93.3	80.0	86.7
4	29	18	26	11	89.7	61.1	78.7
5	39	12	33	8	84.6	66.7	80.4
6	17	13	15	10	88.2	76.9	83.3

Note: + – RVO availability, – – its absence

In such a way, the accuracy of prediction of RVO availability or absence at the corresponding term according to the proposed technology is at least 78 %, what together with the quality indicators of regression models (**Table 2**) proves the influence of certain markers on the development of RVO.

#### 4. Discussion of research results

Our results were agreed with the available data in the literature [12, 15]. The increase of the content of pro-inflammatory cytokines after CB in the blood reflects acute inflammation, which develops during and immediately after surgery [11, 16]. Interleukins increase vascular permeability, activate neutrophil migration, and the activity of proteinases [10]. According to our data, the content of IL-6 and IL-8 in patients without RVO was increased at the 2<sup>nd</sup> and 7<sup>th</sup> days of observation. There exists an opinion that immediately after the use of CB with the increase the content of pro-inflammatory cytokines in the blood, there was no reaction from intercellular adhesion molecules, including VE-C [17].

We have shown the defining role of inflammation and blood content of IL-6 and IL-8 in the case of RVO appearance when using CB, especially at the early terms. The Regression analysis showed the significance of IL-6, the content of which was directly related to RVO development at the 1<sup>st</sup>–2<sup>nd</sup> and after the 8<sup>th</sup> days of observation (almost the entire time of observation). The content of IL-8 was directly related to the development of RVO only up to 30 days.

The result of inflammation activation is tissue damage and development of EDF, which, in our opinion, has the secondary origin. The cascade of inflammatory reactions leads to damage of the vascular endothelium and contributes to the progression of ischemia, thrombosis, macrophages activation [18]. The regression analysis shows that the content of VE-C after 8 days is important for the development of RVO, what is compliant with the literature data and reflects the development and pathogenetic value of EDF [19, 20].

So, it can be considered as proved, that the use of CB starts an acute inflammation, which later causes EDF, and the severity of this process has significance for RVO development. In our opinion, this fact is a pathogenetic justification of the use of prophylactic agents after cardiosurgical interventions with the use of CB – at the early terms of restriction of the inflammatory process activity, at the later – prevention of the development of EDF.

**Study limitations.** This study included the relationship of proinflammatory factors (IL-6 and IL-8) and factors of endothelial dysfunction to the occurrence of retinal vein occlusion after cardiac surgery using cardiopulmonary bypass at different times after surgery, but did not include a study of the relationship between preoperative or postoperative patient preparation, type and course of operation, parameters of artificial blood circulation on the occurrence of retinal vein occlusion.

**Perspective of further research** of this problem are presented in the further study of new links in the pathogenesis of retinal vein occlusions after cardiac surgery using cardiopulmonary bypass and on the basis of this development of new methods for their prevention and treatment.

## 5. Conclusions

The execution of cardio-surgeries with the use of CB caused an increase of the content of interleukins at the early term (IL-6 on the 2<sup>nd</sup> and 7<sup>th</sup> days, and IL-8 – up to 30 days), while the content of VE-C was slightly increased during almost all observation period. With the availability of RVO, the content of IL-6 at all terms of occlusion occurrence was significantly higher, the content of IL-8 up to 30 days, and the content of VE-C to in a greater degree after the 7<sup>th</sup> day.

The regression analysis showed that after 1–2 days, RVO appearance was directly related to the blood content of IL-6 and IL-8, on the 3<sup>rd</sup>–7<sup>th</sup> days – only with the content of IL-8, on the 8<sup>th</sup>–30<sup>th</sup> days – with the content of all markers, and then with the content of IL-6 and VE-C. The accuracy of the prediction of RVO availability or absence at the correspondent term according to the calculated regression models is not less than 78 % ( $p < 0.001$ ), what proves the influence of markers on the RVO development.

## Conflict of interest

The author declare that they have no conflicts of interest.

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