VILNIUS UNIVERSITY

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THE ASSOCIATION BETWEEN CARDIOVASCULAR EVENTS AND MARKERS OF ENDOTHELIAL DAMAGE AFTER CORONARY ARTERY BYPASS GRAFTING SURGERY

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VILNIAUS UNIVERSITETAS

Mindaugas Balčiūnas

KARDIOVASKULINIŲ KOMPLIKACIJŲ SĄSAJOS SU ENDOTELIO PAŽEIDIMO ŽYMENIMIS PO AORTOS VAINIKINIŲ JUNGČIŲ SUFORMAVIMO OPERACIJŲ

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List of abbreviations

sVCAM-1	soluble vascular cell adhesion molecule - 1
sICAM-1	soluble intercellular adhesion molecule - 1
hs-CRP	high sensitivity C-reactive protein
CABG	coronary artery bypass grafting
CPB	cardiopulmonary bypass
ROC curve	receiver operator characteristic curve
NO	nitric oxide
NOS	nitric oxyde synthase
EuroSCORE	European system for cardiac operative risk evaluation

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1 Introduction

Identification of risk factors associated with an increased risk of developing complications after cardiac surgery is important for preoperative patient selection and consent, as well as postoperative management. Several systems such as EuroSCORE or Parsonnet have been shown to predict outcome after cardiac surgery however they can not accurately predict individual risk of postoperative complications. A growing body of evidence suggests that endothelial dysfunction is associated with future cardiovascular events including cardiac death, myocardial infarction and the need for revascularization procedures.

The endothelium is considered as a true organ with functions such as regulation of vascular growth, permeability, circulating cells interaction, modulation of coagulation, inflammation and vascular tone (Ranucci M, 2006). Exposition of endothelial cells to inflammatory stimuli such as cytokines and endotoxin, to physical injury or hemodynamic shear stress during cardiopulmonary bypass (CPB) result in endothelial cell damage/dysfunction, that is associated with increased expression of adhesion molecules, synthesis of proinflammatory, prothrombotic factors and abnormal modulation of vascular tone (Verrier ED et al., 1998).

Adhesion molecules are expressed on the surface of activated leukocytes, platelets and endothelial cells, and play a pivotal role in leukocyte–endothelial interactions (Drexler H, 1997). Four structural families of adhesion molecules including selectins, integrins, adressins and immunoglobulin superfamily have been described up to date to be responsible for the leukocytes adhesion, penetration of the vessel wall and transendothelial migration into the tissue. The immunoglobulin superfamily is largely found on the endothelium consisting of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Springer TA, 1990). An increase in circulating adhesion molecules results either from increased expression of activated endothelial cells or from increased proteolytic cleavage of endothelial-bound forms secondary to endothelial cells damage (Lei K, 1992).

Markers of inflammation including high sensitivity C-reactive protein (hs-CRP) (Fichtlscherer S et al., 2000), soluble vascular and intercellular adhesion molecules (VCAM-1 and ICAM-1) (Blake GJ et al., 2001) are known as surrogate markers of

endothelial damage and have been used in high risk patients with documented coronary artery disease to predict future cardiovascular events (Leu HB et al., 2004). Increased levels of soluble and membrane forms of VCAM-1 and ICAM-1 were used to demonstrate endothelial cells activation in vivo and vitro after cardiac surgery with extracorporeal circulation (Andresen TK et al., 2002).

The predictive value of soluble adhesion molecules, sVCAM-1 and sICAM-1, for the development of cardiovascular events has not been investigated in cardiac surgery. There are controversial studies evaluating the impact of the CRP for prediction of postoperative complications. Only few authors used high sensitivity CRP assay (Hedman A et al., 2007) in their studies. We performed ROC analysis to find the cut-off value of markers, hs-CRP, sVCAM-1 and sICAM-1, with the combination of the highest sensitivity and specificity for prediction of cardiovascular events that was not done before and recorded cardiovascular events exclusively for 30 days after on pump CABG surgery. Furthermore we included EuroSCORE in multivariate analysis to determine the value of hs-CRP and adhesion molecules for prediction of postoperative cardiovascular events.

There is also lack of data about impact of on-pump cardiac surgery on circulating markers of endothelial damage, sVCAM-1 and sICAM-1. We also looked for the correlation between postoperative level of hs-CRP, sVCAM-1 and sICAM-1 and cardiovascular events after coronary artery bypass grafting surgery.

In Lithuania we have no studies evaluating the association between endothelial damage and cardiovascular complications in patients undergoing coronary artery bypass grafting surgery.

2 The aim of the study

To evaluate the impact of markers of endothelial damage as predictors of cardiovascular events after on-pump coronary artery bypass grafting surgery.

3 Tasks of the study

1. To investigate the association between markers of endothelial damage preoperatively, hs-CRP, sVCAM-1 and sICAM-1, and cardiovascular events in patients after coronary artery bypass grafting surgery.
2. To evaluate the impact of on-pump coronary artery bypass grafting surgery on circulating levels of hs-CRP, sVCAM-1 and sICAM-1.
3. To investigate the correlation between concentration postoperatively of hs-CRP, sICAM-1 and sVCAM-1 and cardiovascular events in patients after coronary artery bypass grafting surgery.

4 Significance and novelty of research work

1. Perioperative concentrations of hs-CRP, sVCAM-1 and sICAM-1 were investigated in patients undergoing coronary artery bypass grafting surgery and results were compared with studies done by others.
2. The value of concentration preoperatively of hs-CRP, sICAM-1 and sVCAM-1 was estimated for the prediction of cardiovascular events in patients after coronary artery bypass grafting surgery.
3. Established risk factors of cardiovascular events after coronary artery bypass grafting surgery were evaluated in respect to the markers of endothelial damage.
4. The correlation between the concentration postoperatively of hs-CRP, sICAM-1 and sVCAM-1 and cardiovascular events were evaluated in patients after coronary artery bypass grafting surgery.

5. Materials and methods

5.1 Study population

This study conforms to the principles outlined in the Declaration of Helsinki and was approved by the Lithuanian Bioethics Committee (Reference number – 40, issued on September 18th, 2006).

66 patients were enrolled into the study after giving their written informed consent. The inclusion criteria were: patients scheduled for elective on-pump CABG surgery, aged less than 75 years, with left ventricle ejection fraction greater than 30%. Exclusion criteria included diabetes mellitus (non-insulin dependent and insulin dependent), chronic obstructive pulmonary disease (documented asthma, chronic bronchitis or pulmonary emphysema), myocardial infarction within 30 days of inclusion into the study, chronic renal disease (glomerular filtration rate less than 56 mL/min/m2 for male and 50 mL/min/m2 – for female patients), chronic liver disease (total bilirubin concentration greater than 17 μmol/l), treatment with intravenous nitrates or inotropes before surgery, re-do cardiac surgery, pulmonary hypertension, extra-cardiac arteriopathy or treatment with steroids in the previous 6 months.

The number, type and severity of diseased coronary arteries were determined based on angiography of the patient. According to Society of Thoracic Surgeons, left anterior descending, left circumflex, right coronary artery was considered to be diseased if the stenosis was equal or grater to than 50 % of the luminal diameter, the left main coronary artery was classified to be diseased if the stenosis equal to or greater than 50 % of luminal diameter was reported.

5.2 Anaesthesia and surgery

All patients underwent general anaesthesia according to our standardized protocol. The induction of anaesthesia was performed with midazolamum, fentanylum, and etomidatum. Rocuronium or cisatracurium were used to facilitate tracheal intubation and ensure muscle relaxation throughout the surgery. A mixture of volatile anaesthetics (Sevofluranum or Isofluranum), propofolum and remifentanilum were used for the maintenance of anaesthesia. No antifibrinolytic agents were administered.

Surgery was performed during mild hypothermia (32-34 °C) with standardized cardiopulmonary bypass technique. The extracorporeal circuit was primed with 1000 ml of ringer's lactate, 500 ml of hydroxyethylstarch 130/0.4 6%, 250 ml of mannitolum 15 % and 1 g. of cefazolinum was also added. Nonpulsatile pump flow was kept between 2.0-2.4 L min^{-1} m^{-2} to maintain mean arterial pressure between 50 and 70 mmHg. Hydroxyethylstarch 130/0.4 6 % and gelatine 4% were used for volume therapy during and after surgery. Activated clotting time (kaolin as activator) was kept greater than 480 seconds with unfractionated heparin during artificial blood circulation. The heart was arrested using antegrade/retrograde intermittent tepid blood cardioplegia. Following cessation of cardiopulmonary bypass heparin was neutralized with protamine sulphate, to correct the activated clotting time to less than 120 seconds. After skin closure, patients were transferred to the surgical intensive care unit (ICU). Donated red blood cells were transfused if hemoglobin level dropped below 80 g/L during extracorporeal circulation and below 90 g/L after. Transfusion of blood at higher hemoglobin levels as well as infusion of catecholamine was given at the discretion of the attending physician. Blood drained from the thoracic cavity was not re-transfused. Patients were sedated with morphinum and propofolum by infusion until they fulfilled ventilator weaning criteria according to our protocol. Infusion of inotropes was gradually discontinued and patients free of inotropic drugs were discharged from intensive care unit.

5.3 Laboratory assays

Blood for biochemical and complete blood count analysis was taken in the morning on the day of surgery and on the first postoperative day 12 hours after surgery in ICU from a peripheral vein using a tourniquet.

Creatinine, troponin I, white blood cells, platelets, red blood cell count and haemoglobin levels were measured immediately in the central biochemical and clinical laboratory. Serum for measurement of adhesion molecules was recovered instantly, divided into aliquots and frozen at -20 degrees C. High sensitivity CRP analysis was performed using the commercially available Nephelometer system (BN II (Dade Behring, USA). Soluble ICAM-1 and VCAM-1 concentrations were measured in blood serum using a solid phase sandwich enzyme linked immunosorbent assay (BioSourse reagents, Belgium). The recommended normal values by the manufacturer were used: sVCAM-1-394-812 ng/ml; sICAM-1-129.9-297.4 ng/ml. The minimum detectable concentration for sVCAM-1 is 0.5 ng/ml; for sICAM-1-0.33 ng/ml; for hs-CRP-0.5 mg/l.

5.4 Data collection

Demographic, pre- and intra-operative data were recorded prospectively, including aortic cross clamp time, duration of CPB and surgery, number of grafts, intraoperative red blood cell transfusion and lowest oesophageal temperature on CPB.

Patients were followed up for 30 days after surgery and events recorded included (1) death from cardiovascular causes, (2) ischemic stroke (defined as new neurological deficit lasting for at least 24 hours with definite image evidence of cerebrovascular accident by head computer tomography), (3) low output heart failure (defined as needing one of the following: intraoperative intra-aortic balloon pump, return to CPB after initial separation, or ≥ 2 inotropes at 48 hours postoperatively), (4) myocardial damage (defined as elevated troponin I (Tn I) > 10.0 μg/l at 12 hours after surgery), (5) myocardial infarction (defined as elevated troponin I (TnI) > 10.0 μg/l at 12 hours after surgery associated with characteristic electrocardiography changes or echocardiography documented new dyskinetic-akinetic segment, (6) combined cardiovascular event (a composite endpoint defined as any cardiovascular event listed above).

5.5 Statistical analysis

The primary outcome variables used for the sample size calculation for this study were the baseline levels of soluble vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. Based on the assumption of standard deviation for sVCAM-1 of 551 ng/ml and for sICAM-1 of 45.5 ng/ml, mean difference for sVCAM-1 of 193 ng/ml and for sICAM-1 17 ng/ml were considered as clinical significant. Taking power 0.8 and alpha error 0.05 a minimum sample size of 66 patients was calculated.

The normal distribution of continuous variables was checked with one-sample Kolmogorov-Smirnov test. Categorical data are expressed as number (%), continuous variables as mean and standard deviation (mean ± SD) if normally distributed or as median (range) otherwise (Me [25% and 75%.] The continuous variables and frequencies between the groups were compared by Mann-Whitney *U* test and χ^2 or Fisher exact test as appropriate.

In order to evaluate the predictive ability of baseline hs-CRP and sVCAM-1 on combined cardiovascular event, receiver operating characteristic curves were made and the optimum cut-off values, with the combination of the highest sensitivity and specificity, were calculated. Several univariate logistic models were built to see whether variables with respect to which patients' groups differed were significantly associated with adverse outcome and variables that had univariate probability value of < 0.05 to predict combined cardiovascular event were included in a multivariate logistic regression model with forward stepwise selection.

Differences were considered significant at $p < 0.05$. Data were analyzed with Statistical Package for the Social Sciences for Windows version 11.5 (SPSS Inc.,Chicago, IL, USA).

6 Results

6.1 Postoperative period and complications

During the first 30 days after surgery, 52 patients were event-free and 14 developed the following cardiovascular events: 10 (15 %) had myocardial damage, 4 (6 %) had low output heart failure and 2 (3 %) suffered stroke. No patients were diagnosed having myocardial infarction (Figure 1).

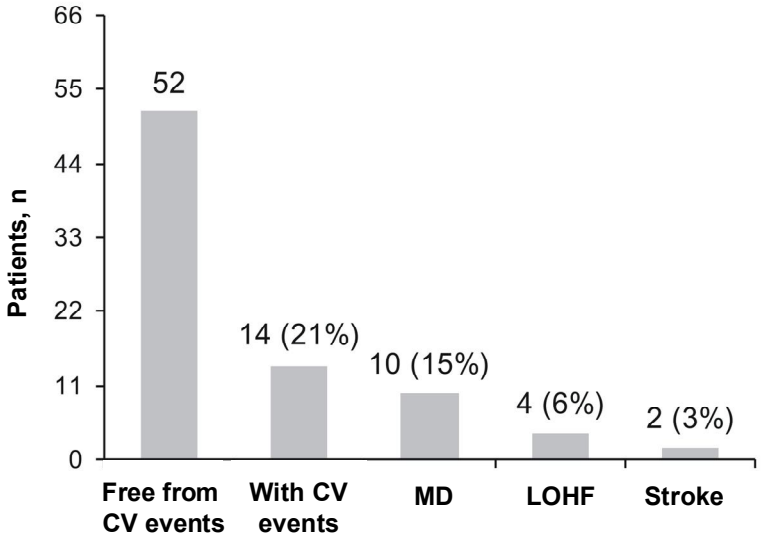

Figure 1. Postoperative cardiovascular events

CV events = cardiovascular events; MD = myocardial damage; LOHF = low output heart failure.

The univariate analysis of the impact of pre- and intraoperative variables on combined postoperative cardiovascular events is shown in tables 1 and 2.

Table 1. Distribution of demographic and preoperative clinical data according to the combined cardiovascular events

Variables	Patients free from events (n = 52)	Patients with events (n = 14)	*p* Value
Demographics			
Age, years	61.5±6.8	64.7±9.7	0.03
Female gender, n (%)	4 (8)	3 (21)	0.8
Body mass index, kg/m²	28.8±3.7	30.6±4.6	0.2
Weight, kg	85.5±14.5	85.5±19.4	0.8
Co-morbidities, n (%)			
Previous MI	29 (56)	11 (79)	0.1
Vessel disease, n (%)			
Left main disease	2 (4)	2 (14)	0.2
2-vessel disease	5 (10)	1 (7)	1.0
3-vessel disease	45 (86)	11 (79)	0.5
Echocardiography			
LV ejection fraction, %	50 (50; 60)	50 (44; 51)	0.08
Haematology			
White blood cells, 10^9/L	6.4±1.5	5.9±1.4	0.3
Red blood cells, 10^9/L	4.6±0.3	4.5±0.4	0.25
Haemoglobin, g/l	140.6±13.0	135.5±14.3	0.4
Platelets, 10^6/L	235.8±53.9	253.0±56.8	0.3
hs-CRP, mg/l	2.9 (1.6; 6.0)	6.7 (3.5; 9.7)	0.01
sVCAM-1, ng/ml	1079.3±620.2	1511.0±629.3	0.02
sICAM-1, ng/ml	283.4±134.6	285.3±96.9	0.7
Creatinine, µmol/l	89.8±19.0	98.0±21.6	0.3
Troponin I, µg/l	0.03 (0.01; 0.04)	0.03 (0.02; 0.06)	0.3
Medications, n (%)			
Beta blockers	49 (94)	14 (100)	0.4
Calcium blockers	11 (21)	0 (0)	0.06
ACE inhibitors	44 (85)	13 (93)	0.4
Nitrates	38 (73)	11 (79)	0.7
Heparin	22 (42)	10 (71)	0.05
Statins	10 (19)	5 (36)	0.2
Diuretics	17 (33)	1 (7)	0.06
Aspirin	22 (42)	6 (43)	0.9
Operative risk			
Standard EuroSCORE	1.54±1.5	3.14±1.03	< 0.001

Data are presented as mean ± SD or median [25% and 75%] unless otherwise indicated.

LV = left ventricle; MI = myocardial infarction; ACE = angiotensin-converting enzyme; n = number of patients.

Table 2. Distribution of operative clinical data according to the combined cardiovascular events

Variables	Patients free from events (n = 52)	Patients with events (n= 14)	*p* Value
Aortic cross-clamp time, min	63.8±16.4	61.6±13.4	0.6
CPB time, min	108.3±24.3	108.6±28.5	0.7
Duration of surgery, min	227.1±51.4	242.9±62.8	0.4
Number of grafts	4 (3; 4)	4 (3; 4.2)	0.9
Blood transfusion, n (%)	4 (8)	4 (29)	0.03

Data are presented as mean ± SD or median [25% and 75%] unless otherwise indicated.

n = number of patients.

The duration of mechanical lung ventilation ranged from 1 hour to 137 hours and 2 patients were ventilated longer than 24 hours. Patients having any cardiovascular event were ventilated longer compared to patients' group with uneventful course after on-pump coronary artery bypass grafting surgery (10 hours [6.7; 20.5] and 7 hours [5; 9] respectively; p = 0.04).

Thirty three patients needed inotropes infusion after the arrival to ICU, and 17 (51.5%) were dependent on inotropic drug support longer than 24 hours. An intra-aortic balloon pump was inserted for one patient intra-operatively because of initial unsuccessful separation from cardiopulmonary bypass. The duration of inotropes infusion was longer in patients with postoperative cardiovascular events compared to patients' group without events after on-pump coronary artery bypass grafting surgery (30 hours [1.75; 62.0] and 0 hours (0; 17.5] respectively; p = 0.001).

The length of stay in ICU and hospital was longer for patients having cardiovascular events compared to those without events and was respectively 2.5 days [1; 4] vs 1 day [1; 1.7] in ICU (p = 0.0001) and 14.5 days [10.7; 15.2] vs 10 days [9; 14] in hospital (p = 0.01). None of the patient died during hospitalization after surgery.

6.2 The investigation of cut-off values of the markers of endothelial damage

The cut-off value of the preoperative concentration of hs-CRP, sVCAM-1 and sICAM-1 giving the highest sensitivity and specificity for prediction of cardiovascular events after CABG surgery was found using ROC curves and calculating the area under the curve. Data are presented in figure 2 and table 3.

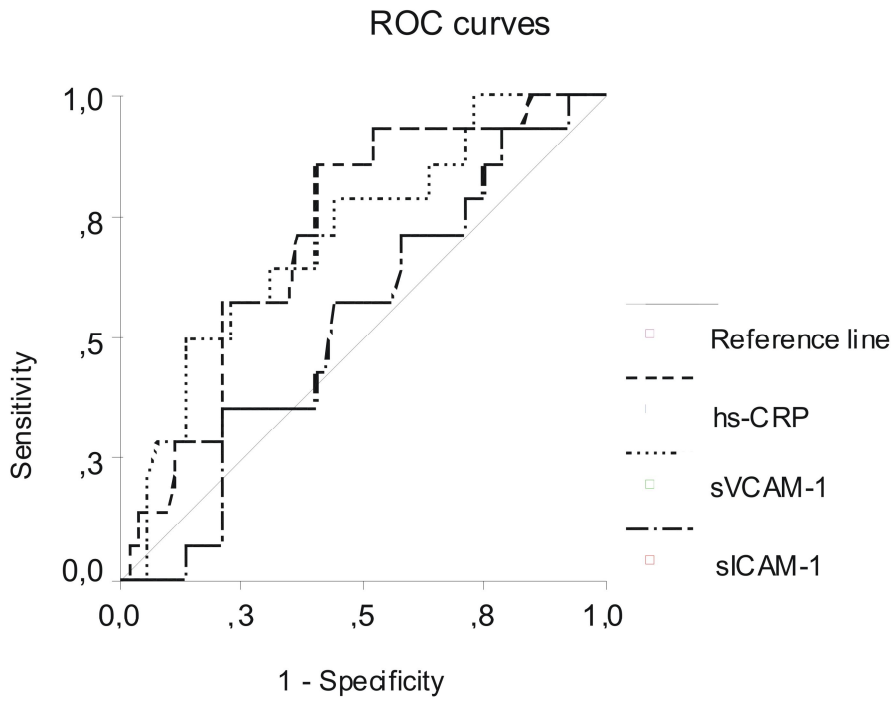

Figure 2. Preoperative hs-CRP, sVCAM-1 ir sICAM-1 ROC curves

Table 3. Area under the ROC curve

Variables	Area	P value	95% Confidence Interval	
			Lower bound	Upper bound
sICAM-1	0.531	0.724	0.372	0.690
sVCAM-1	0.707	0.018	0.559	0.855
hs-CRP	0.714	0.014	0.576	0.853

As the sICAM-1 area under the ROC curve was about 0.5 and p value > 0.05, we concluded that the sICAM-1 had not sufficient prognostic features. hs-CRP and sVCAM-1 p value was below the 0.05 and these markers were used for further analysis.

The highest sensitivity and specificity for the prediction of cardiovascular events was reached at the cut-off value of hs-CRP - 3.3 mg/l (sensitivity was 86% and specificity – 60%) and sVCAM-1 – 1261.75 ng/ml (sensitivity – 57% and specificity – 77%).

6.3 Association between preoperative level of hs-CRP and cardiovascular complications

All patients were divided into two groups according to the cut-off value of preoperative hs-CRP ≥ 3.3 mg/l or < 3.3 mg/l. ROC curve is presented in Figure 2.

Thirty three patients had elevated serum concentration preoperatively of high sensitivity C-reactive protein greater than or equal to 3.3 mg/l. With preoperative hs-CRP greater than or equal to 3.3 mg/l, the cumulative event incidence was 36 % compared to 6 % in patients with levels preoperatively of hs-CRP less than 3.3 mg/l (p = 0.01). Patients with concentration preoperatively of high sensitivity C-reactive protein greater than or equal to 3.3 mg/l had higher risk of myocardial damage (24 % vs 6 %, p = 0.04) and low output heart failure (12 % vs 0 %, p = 0.04) after surgery. Data are presented in table 4.

Table 4. Cardiovascular complications in regard to the cut-off value of *hs-CRP*

Cardiovascular events	Patients, n	hs-CRP, mg/L		P, value
		<3,3 n=33	≥3,3 n=33	
Stroke	2	0	2	0.2
Low output heart failure	4	0	4	0.04
Myocardial damage	10	2	8	0.04
Combined CV events	14	2	12	0.01

CV events = cardiovascular events; n = number of patients.

Patients with preoperative level of hs-CRP greater than or equal to 3.3 mg/l had higher concentration of preoperative soluble intercellular adhesion molecule-1 compared to group with hs-CRP less than 3.3 mg/l. Table 5 shows the distribution of other preoperative variables according to high sensitivity CRP less than 3.3 mg/l or greater than or equal to 3.3 mg/l.

Table 5. Distribution of variables according to the preoperative hs-CRP

Variables	hs-CRP < 3.3 mg/l (n = 33)	hs-CRP ≥ 3.3 mg/l (n = 33)	*P*, value
Demographics			
Age, years	61.1±6.0	63.2±8.8	0.07
Female gender, n (%)	3 (9)	4 (12)	0.7
Body mass index, kg/m²	28.3±3.8	30.0±4.0	0.1
Weight, kg	84.4±14.9	86.6±16.3	0.5
Co-morbidities, n (%)			
Previous MI	18 (54)	22 (67)	0.3
Vessel disease, n (%)			
Left main disease	3 (9)	1 (3)	0.6
2-vessel disease	3 (9)	3 (9)	1.0
3-vessel disease	27 (82)	29 (88)	0.5
Echocardiography			
LV ejection fraction, %	50 (50; 59)	50 (49; 57)	0.7
Haematology			
White blood cells, 10^9/L	6.1±1.7	6.5±1.3	0.08
Red blood cells, 10^9/L	4.6±0.3	4.5±0.4	0.4
Haemoglobin, g/l	141.7±10.9	137.2±15.1	0.6
Platelets, 10^6/L	239.8±57.7	239.1±52.0	0.9
sVCAM-1, ng/ml	1134.6±676	1207.1±615.2	0.3
sICAM-1, ng/ml	250±106	317.7±138.2	0.04
Creatinine, µmol/l	88.4±14.3	94.7±23.8	0.3
Troponin I, µg/l	0.03 (0.01; 0.04)	0.03 (0.02; 0.04)	0.2
Medications, n (%)			
Beta blockers	32 (97)	31 (94)	0.5
Calcium blockers	7 (21)	4 (12)	0.3
ACE inhibitors	28 (85)	29 (88)	0.7
Nitrates	25 (76)	24 (73)	0.8
Heparin	15 (45)	17 (51)	0.6
Statins	8 (24)	7 (21)	0.8
Diuretics	6 (18)	12 (36)	0.1
Aspirin	17 (51)	11 (33)	0.1

Data are presented as mean ± SD or median [25% and 75%] unless otherwise indicated.

LV = left ventricle; MI = myocardial infarction; ACE = angiotensin-converting enzyme; n = number of patients.

6.4 Association between preoperative level of sICAM-1 and cardiovascular complications

Patients were divided into two groups according to the cut-off value of the preoperative sVCAM-1 ≥ 1261.75 ng/ml or < 1261.75 ng/ml. ROC curve for preoperative level of sVCAM-1 is presented in Figure 2.

Twenty patients had preoperative serum concentration of soluble vascular cell adhesion molecule-1 greater than or equal to 1261.75 ng/ml. With preoperative sVCAM-1 greater than or equal to 1261.75 ng/ml, the cumulative event incidence was 40 % compared to 13 % in patients with levels preoperatively of sVCAM-1 less than 1261.75 ng/ml (p = 0.01). Patients with concentration preoperatively of soluble vascular cell adhesion molecule-1 greater than or equal to 1261.75 ng/ml had higher risk of myocardial damage (30 % vs 9 %, p = 0.03) (Table 6). Distributions of preoperative variables according to soluble VCAM-1 less than 1261.75 ng/ml or greater than or equal to 1261.75 ng/ml are presented in table 7.

Table 6. Cardiovascular complications in regard to the preoperative *sVCAM-1* value

Cardiovascular events	Patients, n.	sVCAM-1, ng/ml		P, value
		< 1261.75 n = 46	≥ 1261.75 n = 20	
Stroke	2	2	0	0.5
Low output heart failure	4	1	3	0.08
Myocardial damage	10	4	6	0.03
Combined CV events	14	6	8	0.014

CV events = cardiovascular events; n = number of patients.

Table 7. Distribution of variables according to the preoperative sVCAM-1

Variables	sVCAM-1 < 1261.75 ng/ml (n=46)	sVCAM-1 ≥ 1261.75 ng/ml (n=20)	P, value
Demographics			
Age, years	61.3±8.1	64.1±5.9	0.2
Female gender, n (%)	4 (9)	3 (15)	0.4
Body mass index, kg/m²	29.5±3.8	28.3±4.3	0.3
Weight, kg	87.6±15.1	80.7±15.9	0.08
Co-morbidities, n (%)			
Previous MI	26 (56)	14 (70)	0.3
Vessel disease, n (%)			
Left main disease	4 (9)	0 (0)	0.2
2-vessel disease	5 (11)	1 (5)	0.4
3-vessel disease	37 (80)	19 (95)	0.1
Echocardiography			
LV ejection fraction, %	50 (50; 60)	50 (42; 53.7)	0.07
Haematology			
White blood cells, 10^9/L	6.3±1.4	6.2±1.7	0.5
Red blood cells, 10^9/L	4.5±0.3	4.5±0.4	1.0
Haemoglobin, g/l	138.7±13.1	141.4±13.9	0.6
Platelets, 10^6/L	241.9±55.4	233.8±53.5	0.7
hs-CRP, mg/l	3.8 (1.8; 7.6)	3.2 (1.4; 6.5)	0.6
sICAM-1, ng/ml	293.2±136.1	262.4±102.6	0.45
Creatinine, µmol/l	89.8±19.3	95.6±20.5	0.4
Troponin I, µg/l	0.03 (0.01; 0.04)	0.025 (0.025; 0.04)	0.3
Medications, n (%)			
Beta blockers	43 (93)	20 (100)	0.5
Calcium blockers	9 (20)	2 (10)	0.3
ACE inhibitors	40 (87)	20 (100)	0.8
Nitrates	34 (74)	15 (75)	0.9
Heparin	21 (46)	11 (55)	0.5
Statins	9 (20)	6 (30)	0.35
Diuretics	15 (33)	3 (15)	0.1
Aspirin	19 (41)	9 (45)	0.8

Data are presented as mean ± SD or median [25% and 75%] unless otherwise indicated.

LV = left ventricle; MI = myocardial infarction; ACE = angiotensin-converting enzyme; n = number of patients.

6.5. Analysis of risk factors for cardiovascular events

Univariate logistic regression analysis was used in pursuance to determine the reliability of variables for prediction of cardiovascular events. Several univariate regression models were built in respect to demographic, preoperative clinical and operative data that differed with p value < 0.1 between patients' group with cardiovascular events and free from events patients'group.

Univariate logistic regression analysis was performed in respect to patient's age, left ventricle ejection fraction, hs-CRP, sVCAM-1, standard EuroSCORE, transfusion of packed red blood cells intraoperatively, treatment with calcium channel blockers, heparin and diuretics. Reliable markers for prediction of cardiovascular events after on-pump coronary artery bypass grafting surgery were following - hs-CRP, sVCAM-1, standard EuroSCORE and transfusion of packed red blood cells intraoperatively. Results of univariate logistic regression analysis for prediction of combined cardiovascular events are presented in table 8.

Table 8. Univariate analysis of risk factors for prediction of cardiovascular events

Risk factors	Odds ratio	P, value	95% Confidence Interval	
			Lower bound	Upper bound
Age	1.069	0.159	0.974	1.172
LV ejection fraction	0.927	0.061	0.857	1.003
hs-CRP ≥ 3.3 mg/l	8.857	0.007	1.795	43.701
sVCAM-1 ≥ 1261.75 ng/ml	4.444	0.018	1.287	15.352
Ca blockers	0.000	0.999	-	-
Heparin	3.409	0.061	0.945	12.303
Diuretics	0.158	0.088	0.019	1.313
Standard EuroSCORE	2.071	0.002	1.307	3.283
Blood transfusion	4.8	0.047	1.025	22.487

LV = left ventricle; Ca = calcium.

6.6 Independent risk factors for cardiovascular events

The independence of risk factors that significantly predicted combined cardiovascular events in univariate logistic regression analysis was assessed using multivariate logistic regression model. Standard EuroSCORE, concentration preoperatively of high sensitivity C-reactive protein and soluble vascular cell adhesion molecule-1 and intraoperative transfusion of packed red blood cells were included in multivariate logistic regression analysis. Preoperative values of hs-CRP greater than or equal to 3.3 mg/l and sVCAM-1 greater than or equal to 1261.75 ng/ml and standard EuroSCORE were independent predictors of combined cardiovascular event after on-pump coronary artery bypass grafting surgery. Results are presented in table 9.

Table 9. Independent risk factors for cardiovascular events

Risk factors	Odds ratio	P, value	95% Confidence Interval	
			Lower bound	Upper bound
hs-CRP ≥ 3.3 mg/l	7.387	0.035	1.154	47.307
sVCAM-1 ≥ 1261.75 ng/ml	7.111	0.017	1.430	35.348
EuroSCORE	1.824	0.038	1.034	3.217

6.7 Changes of hs-CRP, sVCAM-1 and sICAM-1 concentration after surgery

High sensitivity C-reactive protein concentration increased significantly after on-pump CABG surgery compared to preoperative levels in both patients‘ groups with and without cardiovascular events (from 6.7 mg/l [3.5; 9.7] up to 81 mg/l [58.4; 114.1]; p = 0.001 and from 2.9 mg/l [1.6; 6.0] up to 99.1 mg/l [71; 112.6]; p < 0.001 respectively).

Concentration of soluble vascular and intercellular adhesion molecules increased significantly after CABG surgery compared to preoperative value. Level of sVCAM-1 increased from 1079.3±620.2 ng/ml up to 1734.9±1114.1 ng/ml (p < 0.001) and from 1511.0±629.3 ng/ml up to 2093.5±824.9 ng/ml (p = 0,02) in patients' groups free from cardiovascular events and with cardiovascular events respectively. Concentration of sICAM-1 increased from 283.4±134.6 ng/nml up to 356.1±173.0 ng/ml (p < 0.001) in patients' group free from cardiovascular events and from 285.3±96.9 ng/ml up to 323.8±82.5 ng/ml (p = 0.048) in patients' group with postoperative cardiovascular events.

No correlation was found between postoperative levels of hs-CRP, sVCAM-1, sICAM-1 and the duration of the aorta cross-clamp, extracorporeal circulation or surgery. Results are presented in table 10.

Table 10. Correlation between postoperative markers of the endothelial damage and surgery

		Aortic cross-clamp time	Duration of CPB	Duration of surgery
sVCAM-1	Correlation coefficient	-0.064	-0.095	-0.077
	p value	0.611	0.453	0.541
sICAM-1	Correlation coefficient	0.047	-0.007	-0.092
	p value	0.705	0.956	0.460
hs-CRP	Correlation coefficient	0.079	0.066	0.078
	p value	0.529	0.596	0.536

6.8 Correlation between concentration postoperatively of hs-CRP, sVCAM-1, sICAM-1 and cardiovascular events

Concentrations postoperatively of hs-CRP didn,t differ between patients‘ groups with and without cardiovascular events after CABG surgery (81 mg/l [58.4; 114.1] and 99.1 mg/l [71; 112.6] respectively; p = 0.3).

Postoperative levels of sVCAM-1 and sICAM-1 didn’t reach statistical significance between both patients’ groups with and without cardiovascular events after on-pump CABG surgery (p = 0.08 and p = 0.9 respectively). Data are presented in figure 3 and 4.

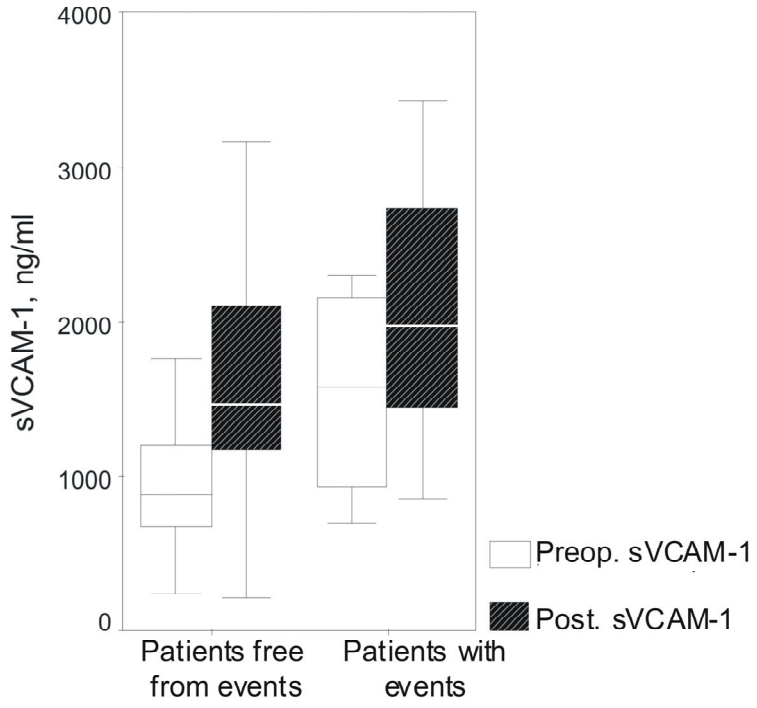

Figure 3. Changes of sVCAM-1 levels

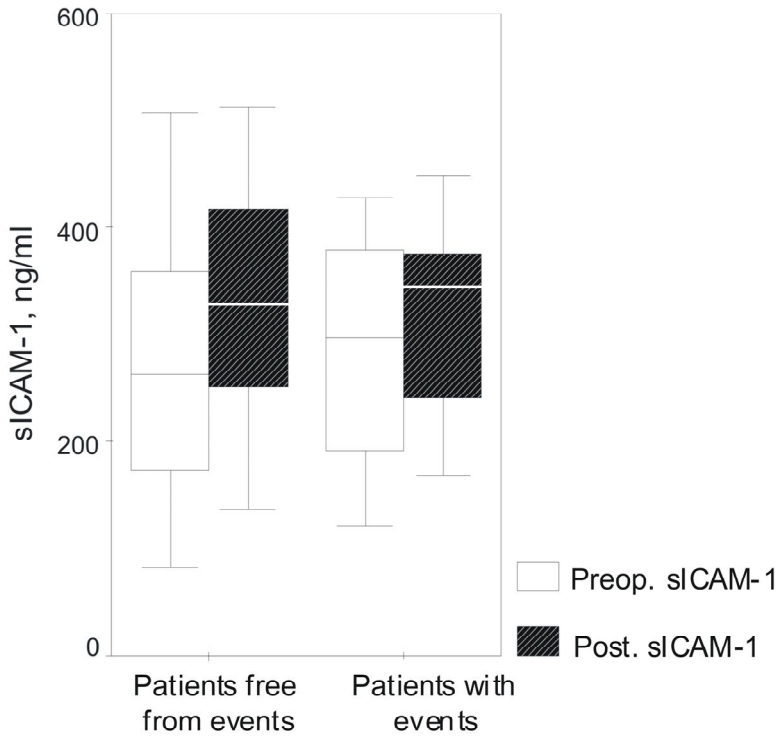

Figure 4. Changes of sICAM-1 levels

7 Conclusions

1. Higher concentrations preoperatively of hs-CRP and sVCAM-1 were independent markers for higher risk of cardiovascular events after coronary artery bypass grafting surgery.

2. Concentration of hs-CRP, sVCAM-1 and sICAM-1 increased significantly after on-pump coronary artery bypass grafting surgery compared to preoperative level. .Correlation between the duration of aortic cross-clamp, cardiopulmonary bypass or surgery and markers of endothelial damage was not found.

3. Correlation between postoperative concentration of hs-CRP, sVCAM-1 and sICAM-1 and risk for cardiovascular events after coronary artery bypass grafting surgery was not found.

8 List of publications

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3. Balčiūnas M, Bagdonaitė L, Samalavičius R, Baublys A. Markers of endothelial dysfunction after cardiac surgery: soluble forms of vascular-1 and intercellular-1 adhesion molecules. .Medicina (Kaunas). 2009;45(6):434-9.
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9. Reziumė

Kardiovaskulinių komplikacijų sąsajos su endotelio pažeidimo žymenimis po aortos vainikinių jungčių suformavimo operacijų

Įvadas. Širdies chirurgija yra pripažintas Išeminės širdies ligos, vožtuvų patologijos ir įgimtų širdies ydų gydymo būdas. Nors gerėja priešoperacinis ligonių paruošimas, tobulėja chirurgijos technika bei pacientų gydymas reanimacijos-intensyvios terapijos skyriuje, pooperacinės kardiovaskulinės komplikacijos sukelia daugiausiai problemų po širdies operacijų. Širdies ritmo sutrikimai (prieširdžių virpėjimas), miokardo infarktas, mažo minutinio tūrio širdies nepakankamumas (inotropinių medikamentų ar intraaortinės balioninės kontrapulsacijos poreikis) bei išeminis galvos smegenų insultas yra dažniausiai pasitaikančios kardiovaskulinės komplikacijos po širdies operacijų. Pooperacinės komplikacijos pailgina pacientų hospitalizacijos laikotarpį, padidina mirštamumą ir pacientų gydymo išlaidas. Priklausomai nuo pacientų amžiaus 30 dienų mirštamumas po aortos vainikinių jungčių suformavimo operacijų svyruoja nuo 1,3 iki 4,2 %. Pooperacinių komplikacijų išsivystymą lemia ne tik pacientų amžius, funkcinė būklė prieš operaciją, lydintys susirgimai, bet ir atliekama chirurginė intervencija.

Pastaruoju metu didelis dėmesys skiriamas kardiovaskulinių įvykių rizikos veiksnių ir pacientų su didele kardiovaskulinių įvykių rizika nustatymui bei kardiovaskulinių įvykių prevencijai.

Endotelio funkcijos sutrikimas (disfunkcija) - būklė, apibūdinama padidėjusia adhezijos molekulių ekspresija, padidėjusia prouždegiminių veiksnių ir protrombotinių faktorių sinteze bei sutrikusia kraujagyslių tono reguliacija - yra taip pat siejamas su kardiovaskuline rizika. Klinikiniais tyrimais nustatyta, kad endotelio disfunkcija yra mirties dėl kardiovaskulinės patologijos, miokardo infarkto bei poreikio revaskuliarizacijos procedūroms (perkutaninė transliuminalinė vainikinių arterijų angioplastika ar aortos vainikinių jungčių suformavimo operacija) išsivystymo rizikos veiksnys.

Endotelio pažeidimo įvertinimas pacientams prieš širdies operaciją, leistų nustatyti pacientus su didele pooperacinių kardiovaskulinių komplikacijų rizika ir ateityje jiems taikyti gydymą, sumažinantį šių komplikacijų dažnį.

Tyrimo tikslas. Nustatyti endotelio pažeidimą atspindinčių žymenų reikšmę, nuspėjant kardiovaskulines komplikacijas po aortos vainikinių jungčių suformavimo operacijos, atliktos dirbtinės kraujo apytakos sąlygomis.

Tyrimo uždaviniai:

1. Ištirti priešoperacinį endotelio pažeidimą atspindinčių žymenų, *hs-CRP*, *sVCAM-1* ir *sICAM-1*, sąryšį su pooperacinėmis kardiovaskulinėmis komplikacijomis pacientams po aortos vainikinių jungčių suformavimo operacijų.
2. Įvertinti aortos vainikinių jungčių suformavimo operacijos, atliktos dirbtinės kraujo apytakos sąlygomis, įtaką *hs-CRP, sICAM-1 ir sVCAM-1* koncentracijos pokyčiams.
3. Ištirti pooperacinį *hs-CRP*, *sVCAM-1* ir *sICAM-1*, koncentracijos ryšį su pooperacinėmis kardiovaskulinėmis komplikacijomis pacientams po aortos vainikinių jungčių suformavimo operacijos.

Mokslinė darbo reikšmė ir naujumas:

1. Ištirtos pacientų, kuriems atliekama aortos vainikinių jungčių suformavimo operacija, *hs-CRP*, *sVCAM-1* ir *sICAM-1* perioperacinės koncentracijos ir gauti rezultatai palyginti su kitų autorių duomenimis.
2. Įvertinta priešoperacinės *hs-CRP*, *sVCAM-1 ir sICAM-1* koncentracijos prognostinė reikšmė nuspėjant kardiovaskulines komplikacijas pacientams po aortos vainikinių jungčių suformavimo operacijų.
3. Atsižvelgiant į endotelio pažeidimo žymenis, įvertinti pripažinti kardiovaskulinių komplikacijų po aortos vainikinių jungčių suformavimo operacijos rizikos veiksniai.
4. Įvertinta pooperacinės *hs-CRP*, *sICAM-1* ir *sVCAM-1* koncentracijos koreliacija su pooperacinėmis kardiovaskulinėmis komplikacijomis pacientams, kuriems atlikta aortos vainikinių jungčių suformavimo operacija.

Tiriamieji. Į tyrimą įtraukti 66 pacientai, kuriems atlikta aortos vainikinių jungčių suformavimo operacija dirbtinės kraujo apytakos sąlygomis.

Įtraukimo kriterijai: planinė širdies vainikinių arterijų apeinamųjų jungčių operacija atliekama su dirbtine kraujo apytaka, pacientai jaunesni nei 75 metai, kairio skilvelio išstūmimo frakcija daugiau kaip 30 procentų.

Atmetimo kriterijai: cukrinis diabetas (nuo insulino priklausomas ar nepriklausomas cukrinis diabetas), lėtinė obstrukcinė plaučių liga (dokumentuota astma, lėtinis obstrukcinis bronchitas ar plaučių emfizema), naujas miokardo infarktas (miokardo infarktas laike 30 dienų paciento į studiją įtraukimo metu), lėtinė inkstų liga (glomerulų filtracijos greitis mažesnis nei 56 mL/min/m^2 vyrams ir 50 mL/min/m^2 moterims), lėtinė kepenų liga (bendras bilirubinas daugiau nei 17 μmol/l), gydymas su intraveniniais nitratais ar inotropais prieš operaciją, pakartotina širdies operacija, plautinė hipertenzija (vidutinis spaudimas plaučių arterijoje > 25 mmHg ramybėje ir > 30 mmHg fizinio krūvio metu), periferinių kraujagyslių aterosklerozė (protarpinis šlūbčiojimas, miego arterijų okliuzija ar stenozė > 50 %, buvusi ar planuojama pilvo aortos, miego ar galūnių arterijų intervencija), gydymas steroidiniais preparatais per paskutinius 6 mėnesius.

Duomenų rinkimas. Demografiniai, priešoperaciniai ir operaciniai duomenys buvo renkami perspektyviai. Ligoniai buvo stebimi 30 dienų laike po operacijos ir registruojamos žemiau pateiktos kardiovaskulinės komplikacijos:

- mirtis dėl kardiovaskulinės patologijos;
- išeminis insultas (apibūdintas kaip naujas neurologinis deficitas, trunkantis ilgiau nei 24 valandas su aiškiais kraujotakos sutrikimo požymiais, stebimais atlikus galvos kompiuterinę tomografiją);
- širdies nepakankamumas (ŠN) dėl mažo širdies išmetimo tūrio sindromo (apibūdinamas poreikiu bent vieno iš pateiktų: pakartotina dirbtinė kraujo apytaka po nesėkmingo atjungimo, intra-aortinės balioninės kontrapulsacijos (IABK) taikymas intra ar pooperaciniame laikotarpyje, 2 ir daugiau inotropinių vaistų infuzija, trunkanti daugiau kaip 48 val., skaičiuojant nuo dirbtinės kraujo apytakos atjungimo);
- miokardo pažeidimas (jei troponino I (Tn I) koncentracija nustatyta daugiau kaip 10,0 μg/l praėjus 12 val. nuo operacijos pabaigos);

- miokardo infarktas (patvirtintas, jei troponino koncentracija nustatyta daugiau kaip 10,0 µg/l praėjus 12 val. nuo operacijos pabaigos ir yra miokardo infarktui būdingi pokyčiai elektrokardiogramoje ar širdies echoskopijos metu nustatyti akinetiniai-dikinetiniai segmentai);
- jungtinė kardiovaskulinė komplikacija (nustatytas bent viena iš aukščiau pateiktų kardiovaskulinių pooperacinių komplikacijų).

Anestezijos ir operacijos metodika. Taikant bendrą endotrachėjinę nejautrą ir naudojant standartizuotą dirbtinės kraujo apytakos metodiką, nedidelės hipotermijos sąlygomis (32-34 ºC) buvo atlikta neplakančios, bekraujės širdies operacija

Laboratorinių tyrimų medžiaga ir metodai. Kad būtų atlikti laboratoriniai tyrimai, prieš operaciją (ryte 12 val. nevalgius) ir pirmą pooperacinę parą (praėjus 12 val. po operacijos) reanimacijos-intensyvios terapijos skyriuje iš periferinės venos buvo imamas kraujas.

Bendras kraujo tyrimas (leukocitų ir eritrocitų skaičius, hemoglobino koncentracija, hematokritas ir trombocitų skaičius), kreatinino ir troponino I koncentracija buvo nustatomi įprastine metodika valandos laikotarpiu nuo kraujo paėmimo.

Kraujo serumas tirpių adhezijos molekulių (*sICAM-1* ir *sVCAM-1*) koncentracijos nustatymui iki tyrimo atlikimo buvo užšaldytas -20 ºC temperatūroje.

Didelio jautrumo C-reaktyvusis baltymas buvo nustatytas naudojant nefelometrinį metodą (BN II (Dade Behring, JAV). *sICAM-1* ir *sVCAM-1* koncentracija kraujo serume nustatyta kietos fazės „sumuštinio“ tipo imunofermentinės analizės metodu (Belgijos „BioSource“ reagentai, Belgija).

Rezultatai. Per 30 dienų po operacijos 52 pacientams pooperacinis periodas buvo be komplikacijų. Keturiolikai pacientų nustatytos šios kardiovaskulinės komplikacijos: 10 (15 %) ligonių nustatytas miokardo pažeidimas, 4 (6 %) - ligoniams mažo širdies išmetimo tūrio sindromas ir 2 (3 %) ligoniams - išeminis galvos smegenų insultas (7 paveikslas). Nei vienam pacientui nediagnozuotas ūminis miokardo infarktas.

Ligoniai, kuriems pooperaciniame laikotarpyje nustatyta bent viena kardiovaskulinė komplikacija, buvo vyresni, jiems nustatytos didesnės priešoperacinės koncentracijos *hs-*

CRP ir *sVCAM-1* bei didesniam pacientų skaičiui buvo perpilta eritrocitų masės operacijos metu. Dirbtinės plaučių ventiliacijos ir inotropinių vaistų infuzijos trukmės buvo ilgesnės pacientams su kardiovaskulinėmis komplikacijomis, palyginus su pacientais, kuriems nenustatytos kardiovaskulinės komplikacijos po širdies operacijos. Gulėjimo laikas reanimacijos ir intensyvios terapijos skyriuje bei ligoninėje po širdies operacijos taip pat buvo ilgesnis ligonių tarpe su kardiovaskulinėmis komplikacijomis, lyginant su pacientais be šių komplikacijų.

Iš ROC kreivių surastos *sVCAM-1* ir *hs-CRP* reikšmės, kurios patikimiausiai nuspėjo jungtinę kardiovaskulinę komplikaciją. Didžiausias *hs-CRP* ir *sVCAM-1* tyrimo jautrumas ir specifiškumas nuspėjant kardiovaskulines komplikacijas buvo pasiekiamas, kai ribinė ***hs-CRP*** vertė buvo **3,3 mg/l** (jautrumas - 86%, specifiškumas - 60%), o ***sVCAM-1*** – **1261,75 ng/ml** (jautrumas - 57%, specifiškumas - 77%).

Jungtinė kardiovaskulinė komplikacija dažniau pasitaikė pacientams, turintiems priešoperacinę *hs-CRP* koncentraciją didesnę ar lygią 3,3 mg/l, palyginus su pacientais, kuriems priešoperacinė *hs-CRP* koncentracija buvo mažesnė nei 3,3 mg/l (atitinkamai 36 % ir 6 %; p = 0,01). Miokardo pažeidimas (24 % ir 6 %, p = 0,04) ir mažo širdies išmetimo tūrio sindromas (12 % ir 0 %, p = 0,04) taip pat dažniau diagnozuotas pacientams, kurių priešoperacinis *hs-CRP* koncentracijos lygis buvo didesnis ar lygus 3,3 mg/l.

Pacientams, kurių priešoperacinė *sVCAM-1* koncentracija buvo didesnė ar lygi 1261,75 ng/ml, nustatyta daugiau pooperacinių kardiovaskulinių komplikacijų, palyginus su pacientais, kurių priešoperacinis *sVCAM-1* koncentracijos lygis buvo mažesnis nei 1261,75 ng/ml (40 % ir 13 %, p = 0,01). Didesnę miokardo pažeidimo riziką taip pat turėjo pacientai, kuriems nustatyta priešoperacinė *sVCAM-1* koncentracija buvo didesnė ar lygi 1261,75 ng/ml (30 % ir 9 %, p = 0,03).

Atlikta amžiaus, kairio skilvelio išstūmimo frakcijos, *hs-CRP*, *sVCAM-1*, standartinio EuroSCORE, eritrocitų masės transfuzijos poreikio, gydymo kalcio kanalų blokatoriais, heparinu bei diuretikais univariacinė logistinė regresinė analizė. Tačiau tik *hs-CRP*, *sVCAM-1*, standartinis EuroSCORE (angl. *European system for cardiac operative risk evaluation*; Europinė širdies operacijos rizikos įvertinimo sistema) ir eritrocitų masės transfuzijos poreikis patikimai nuspėjo kardiovaskulines komplikacijas pacientams po aortos vainikinių jungčių suformavimo operacijų.

Multivariacinės regresinės analizės modelis sukurtas naudojant *hs-CRP*, *sVCAM-1*, standartinį EuroSCORE ir eritrocitų masės transfuzijos poreikį. Nustatyta, kad priešoperacinė *hs-CRP* koncentracija didesnė ar lygi 3,3 mg/l, *sVCAM-1* koncentracija didesnė ar lygi 1261,75 ng/ml ir EuroSCORE buvo nepriklausomi rizikos veiksniai nuspėjant pacientams po aortos vainikinių jungčių suformavimo operacijų jungtinę kardiovaskulinę komplikaciją.

Didelio jautrumo C reaktyviojo baltymo koncentracija pacientams be komplikacijų padidėjo nuo 2,9 mg/l [1,6; 6,0] iki 99,1 mg/l [71; 112,6] ($p < 0,0001$), pacientams su pooperacinėmis komplikacijomis aptiktas koncentracijos padidėjimas nuo 6,7 mg/l [3,5; 9,7] iki 81 mg/l [58,4; 114,1] ($p = 0,001$) po operacijos.

Po operacijos pacientų grupėje be kardiovaskulinių komplikacijų *sVCAM-1* koncentracija padidėjo nuo 1079,3±620,2 ng/ml iki 1734,9±1114,1 ng/ml ($p < 0,0001$). Pacientams, kuriems per stebėjimo laikotarpį nustatyta bent viena kardiovaskulinė komplikacija, pooperacinė *sVCAM-1* koncentracija taip pat buvo reikšmingai didesnė palyginus su priešoperacine koncentracija (atitinkamai 2093,5±824,9 ng/ml ir 1511,0±629,3 ng/ml; $p = 0,02$). Įvertinus pooperacinę *hs-CRP*, *sICAM-1* bei *sVCAM-1* koncentraciją, patikimos koreliacijos tarp endotelio pažeidimą atspindinčių žymenų ir aortos užspaudimo, dirbtinės kraujo apytakos bei operacijos trukmės nenustatyta

Pacientų, kurie patyrė kardiovaskulines komplikacijas, pooperacinė *hs-CRP* koncentracija nesiskyrė nuo pacientų, kuriems šių komplikacijų nebuvo (atitinkamai 81 mg/l [58,4; 114,1] ir 99,1 mg/l [71; 112,6]; $p = 0,3$).

Ženklaus skirtumo tarp pooperacinės *sVCAM-1* ir *sICAM-1* koncentracijos lyginant šias pacientų grupes taip pat nerasta ($p = 0,08$ ir $p = 0,9$).

Išvados:

1. Didesnės priešoperacinės *hs-CRP* ir *sVCAM-1* koncentracijos buvo nepriklausomi didesnės kardiovaskulinių komplikacijų po aortos vainikinių jungčių suformavimo operacijų rizikos žymenys.

2. Po aortos vainikinių jungčių suformavimo operacijos nustatyta reikšmingai didesnė *hs-CRP*, *sVCAM-1* ir *sICAM-1* koncentracija, palyginus su priešoperaciniu koncentracijos lygiu. Patikimos žymenų koreliacijos su aortos užspaudimo, dirbtinės kraujo apytakos bei operacijos trukme neradome.

3. Pacientams po aortos vainikinių jungčių suformavimo operacijos koreliacijos tarp pooperacinio *sICAM-1*, *sVCAM-1* bei *hs-CRP* koncentracijos lygio ir kardiovaskulinių komplikacijų išsivystymo rizikos nenustatyta.

10 Curriculum vitae

Mindaugas Balčiūnas was born in Biržai, Lithuania on September 13, 1975

Working place

Vilnius University Hospital Santariškių klinikos, Centre of Anaesthesiology, Intensive Therapy and pain Treatment, Santariškių str. 2, Vilnius 08661, Lithuania.
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Medical education

1982/09-1993/06	Biržai secondary school
1993/09-1999/06	Vilnius university Medical faculty
1999/08-2000/06	First year internalship study in Antakalnio university hospital
2000/09-2003/07	Resident of anaesthesiology and intensive care in Vilnius University Hospital "Santariskiu klinikos"
2004-2009	Doctoral (Ph. D.) studies in Vilnius university Medical faculty.

Languages

Lithuanian	mother tongue
Russian	excellent
Englisch	excellent

Professional Experience:

2008/02	Dortmund University Clinics, Germany	Training in minimally invasive cardiac surgery
2005/11-2006/06	Papworth Hospital NHS, Cambridge, UK	Anesthetist specialist registrar in Cardiothoracic and Critical Care
2005/03-2005/05	Carolinas Medical Centre	Fellow in the Cardiovascular

	Charlotte, North Carolina, US.	surgery department
2003 - present	Vilnius University Hospital Santariskiu Clinics	Consultant anesthetist in Cardiac surgery department

Professional certification, membership:

- European Association of Cardiothoracic Anaesthesiologists (Board member; since 2007);
- European Society of Cardiology (Board member; since 2005);
- Accreditation in TEE endorsed by European Society of Echocardiography Association (since 2007).

Research interests:

Heart failure, TEE, endothelial dysfunction.

Research grants:

1. *Investigator:* Lithuanian State Science and Studies Foundation Grant No T-07098 Investigation - Impact of Perioperative Endothelial Dysfunction on Inflammatory Respond and Cardiovascular Complications after on Pump Cardiac Surgery. 2007-2008
2. *Investigator:* Lithuanian Science Foundation Grant No U-04001 , Integration, survival and functional efficiency of stem cells in the pathological lesion. Preclinical study", 2004-2006;

Selected publications: (of last 5 yers)

- Laucevicius A, Sirvydis V, Celutkiene J, Marcinkute A, Zurauskas E, Geboes K, Malickaite R, Cibiras S, **Balciunas M**, et al. Heart failure in a young woman due to toxoplasmic myocarditis. Seminars in Cardiology 2004;10:217–224.
- Bukelskiene V, Baltriukiene D, Imbrasaite I, Sirmenis R, **Balciunas M**, Zurauskas E, et al. Muscle-derived primary stem cell lines for heart repair. Seminars in Cardiology. 2005; 11(3): 99-105.

- **Balciunas M**, Rucinskas K, Celutkiene J, Zurauskas E, Malickaite R, Valentinaviciene G, et al. Successful treatment of multiple organ dysfunction after doxorubicin-induced congestive heart failure with left ventricle assist devize. Seminars in cardiology. - ISSN 1648-7966. – 2005;11(4):172-176.
- **Balciunas M**, Rucinskas K, Miniauskas S, Zemaitytė G, Bubulis R, Stankevic S, et al. Levosimendan on top of an intra-aortic ballon pump in the treatment of deteriorated congestive heart failure after mitral valve repair. Seminars in cardiology. - ISSN 1648-7966. – 2006;12(4):159-162.
- Sirmenis R, Baltriukiene D, Kalvelyte A, **Balciunas M**, Malickaite R, Zurauskas E, Bukelskiene V. Cellular cardiomyoplasty using autologous myogenic celės. Lietuvos chirurgija. ISSN 1392-0995. 2007;5(3):260-267.
- **Balciunas M**, Bagdonaitė L, Baublys A, Griskevicius L. Impact of perioperative endothelial function on cardiovascular complications after on pump coronary artery bypass grafting surgery. Laboratorinė medicina. ISSN 1392-6470. 2007;9(4):180-185
- **Mindaugas Balčiūnas**, Loreta Bagdonaitė, Robertas Samalavičius, Laimonas Griskevičius. Evaluation of the impact of coronary artery bypass grafting surgery on soluble markers of endothelial activation, vascular and intercellular adhesion molecules. Seminars in Cardiovascular Medicine 2009; 15: 4
- **Balčiūnas M**, Bagdonaitė L, Samalavičius R, Baublys A. Markers of endothelial dysfunction after cardiac surgery: soluble forms of vascular-1 and intercellular-1 adhesion molecules. .Medicina (Kaunas). 2009;45(6):434-9.
- **Balciunas M,** Bagdonaite L, Samalavicius R, Griskevicius L, Vuylsteke A. Pre-operative high sensitive C-reactive protein predicts cardiovascular events after coronary artery bypass grafting surgery: a prospective observational study. Ann Card Anaesth. 2009 Jul-Dec;12(2):127-32.

Poster presentations:

- **Balciunas M**, Bubulis R, Baublys A. Impact of shed mediastinal blood reinfusion on patients outcome and reduction of homologous blood trasfusion. EACTA Book of Abstracts 2003;168.
- Bukelskiene V, Baltriukiene D, Bironaite D, Sirmenis R, **Balciunas M,** Kalvelyte A. Development of muscle – derived primary cell lines for heart repair. J Cardiovasc Surg 2005;46(1):S85.
- **Balciunas M,** Bubulis R, Stankevicus S, Jurkuvenas V, Baublys A. Procalcitonin as an early prognostic marker of adverse outcome in patients with acute heart failure after complicated cardiac surgery. European J Anaesthesiology 2005;22(34):S164.
- **Balciunas M**, Skutaite R, Jurkuvenas V, Baublys A. $\Delta PCO_2/C_{(a-v)}O_2$ ratio to predict anaerobic metabolism in patients with hyperlactatemia after complicated coronary artery bypass grafting surgery. J Critical Care 2005;22(1):S127.
- **Balciunas M**, Bagdonaite L, Griskevicius L, Samalavicius R, Baublys A, Vuylsteke A. Preoperative endothelial function predicts cardiovascular morbidity after coronary artery bypass grafting. Heart surgery forum 2008;11(1):S335-336.
- **Balciunas M**, Bagdonaite L, Griskevicius L, Samalavicius R, Baublys A, Vuylsteke A. Preoperative high sensitivity C-reactive protein predicts cardiovascular morbidity after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2008;22(3):S44-45. 3rd prize of the poster presentations at the 2008 EACTA Annual Meeting in Antalya.

Oral presentations:

1. 2008. 12.12 – Impact of perioperative transoesophageal echocardiography in making clinical decision in cardiac surgery. The 4th International Baltic Congress of Anaesthesiology and Intensive Care in Latvia