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PRACA ORYGINALNA
ORIGINAL PAPER

Endothelial function/damage markers and NGAL – intraoperative assessment in blood specimens obtained from different sampling sites during open repair of abdominal aortic aneurysm

Śródoperacyjne stężenia wskaźników czynności/uszkodzenia śródbłonka oraz NGAL oznaczanych w próbkach krwi pochodzących z różnych źródeł naczyniowych w trakcie zabiegu naprawczego tętniaka aorty brzusznej metodą otwartą

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ABSTRACT

INTRODUCTION: The aim of the study was to investigate the dynamics of changes in the concentrations of neutrophil gelatinase-associated lipocalin (NGAL), an acute kidney injury biomarker, as well as endothelial function/damage markers including P-selectin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and the von Willebrand factor (vWf) in blood specimens obtained from different sampling sites during open abdominal aortic aneurysm (AAA) repair.

MATERIAL AND METHODS: Thirty-three patients qualified for elective open repair (ORe) were enrolled in the study. All the mentioned parameters were determined in blood samples drawn from: 1) the cubital vein prior to surgery, and then intraoperatively, 2) the renal vein before aortic cross-clamping, 3) renal vein immediately before aortic cross-clamp removal, 4) cubital vein immediately before aortic cross-clamp removal, 5) inferior vena cava immediately before aortic cross-clamp removal, 6) renal vein at 5 minutes after aortic cross-clamp removal and 7) cubital vein at 5 minutes after aortic cross-clamp removal.

RESULTS: The P-selectin, ICAM-1 and VCAM-1 concentrations were found to have decreased in the cubital samples drawn immediately before aortic clamp removal and at 5 minutes after aortic clamp removal vs the pre-surgery cubital samples. Rapid changes during surgery were also found in the NGAL, vWf and VCAM-1 concentrations.

CONCLUSIONS: The obtained results seem to evidence the development of an inflammatory response while open AAA repair is still in progress.

KEYWORDS

abdominal aortic aneurysm, P-selectin, ICAM-1, VCAM-1, NGAL

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STRESZCZENIE

WPROWADZENIE: Celem pracy było zbadanie dynamiki zmian stężenia lipokainy związanej z żelatynazą neutrofilów (*neutrophil gelatinase-associated lipocalin* – NGAL), która jest wskaźnikiem ostrego uszkodzenia nerek, oraz wskaźników czynności/uszkodzenia śródbłonka: selektyny P, cząsteczki adhezji międzykomórkowej 1 (*intercellular adhesion molecule 1* – ICAM-1), cząstki adhezyjnej śródbłonka naczyniowego 1 (*vascular cell adhesion molecule 1* – VCAM-1) i czynnika von Willebranda (*von Willebrand factor* – vWf) w próbkach krwi pobieranych z różnych obszarów naczyniowych podczas elektywnej operacji naprawczej tętniaka aorty brzusznej (*abdominal aortic aneurysm* – AAA) metodą otwartą.

MATERIAŁ I METODY: Badanie objęło grupę 33 chorych zakwalifikowanych do planowego zabiegu metodą otwartą (*open repair* – ORe). Wszystkie wymienione parametry oznaczono w próbkach krwi pobranych: 1) przed zabiegiem z żyły łokciowej oraz w trakcie zabiegu; 2) z żyły nerkowej przed założeniem zacisku aorty; 3) z żyły nerkowej bezpośrednio przed zwolnieniem zacisku aorty; 4) z żyły łokciowej bezpośrednio przed zwolnieniem zacisku aorty; 5) z żyły głównej dolnej bezpośrednio przed zwolnieniem zacisku aorty; 6) z żyły nerkowej w 5 minucie po zwolnieniu zacisku aorty; 7) z żyły łokciowej w 5 minucie po zwolnieniu zacisku aorty.

WYNIKI: Stwierdzono zmniejszenie stężenia selektyny P, ICAM-1 i VCAM-1 w próbkach pobranych z żyły łokciowej bezpośrednio przed zdjęciem zacisku aorty oraz 5 minut po zdjęciu zacisku aorty w porównaniu z wartościami przed zabiegiem. Ponadto obserwowano nagłe zmiany stężenia NGAL, vWf i VCAM-1 podczas zabiegu.

WNIOSKI: Uzyskane wyniki wydają się przemawiać za rozwojem stanu zapalnego już w trakcie zabiegu operacyjnego AAA metodą otwartą.

SŁOWA KLUCZOWE

tętniak aorty brzusznej, selektyna P, ICAM-1, VCAM-1, NGAL

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a major complication of atherosclerosis – a civilization disease. AAA is defined as an enlargement of the abdominal aorta such that its diameter exceeds 3 cm [1,2].

There are two primary methods of AAA management. The first consists in replacement of the diseased segment of the aorta with a vascular prosthesis accessing the aorta through a transperitoneal incision (open repair – ORe). The other is endovascular aneurysm repair (EVAR) with an endoluminal stent-graft [3]. Takagi et al. [4] analyzed the 5-year survival curves of EVAR and ORe. They concluded that up to 1.8 years, survival was better after EVAR. Afterwards, post-EVAR survival was worse compared to that observed for ORe. The meta-analysis of Powell et al. [5] also showed that although early mortality (0––6 months of the intervention) was lower in the EVAR groups, the survival curves of both management methods later converged, and beyond 3 years, aneurysm-related mortality was lower in the ORe patients. These results indicate that while ORe might be more traumatic and not as modern as EVAR, it still remains a valuable treatment option for AAA.

Renal injury is a serious complication of both ORe and EVAR and remains independently associated with mortality [6]. Neutrophil gelatinase-associated lipocalin (NGAL) has recently emerged as an early biomarker of acute kidney injury (AKI) as well as has been used to monitor AKI in pediatric and adult patients after cardiac surgery, critically ill patients in addition to those who had received iodinated contrast media [7,8,9,10,11,12]. It is believed inflammation plays a major role in AKI [13]. Inflammatory processes are also important in the pathophysiology of AAA [14] and can be induced by AAA repair itself [15]. Vascular endothelial cells (ECs) are both an active participant and "victim" of the inflammatory process [16,17]. ECs are important components of the renal histological structure. Inflammation is a common cause of AKI as well as EC injury. The markers used to determine endothelial function/damage are, among others, P-selectin [18], intercellular adhesion molecule 1 (ICAM-1) [19], vascular cell adhesion molecule 1 (VCAM-1) [20] and the von Willebrand factor (vWf) [21].

Little is known about the earliest stages of AKI and ORe-induced inflammatory responses. In particular, it seems important to determine the dynamics of changes in AKI biomarkers as well as the dynamics of inflammatory responses within vessels other than peripheral veins.

The aim of the study was to investigate changes in the concentrations of NGAL, an AKI biomarker, as well as endothelial function/damage markers including P-selectin, ICAM-1, VCAM-1 and vWf in blood specimens obtained from different sampling sites during open AAA repair. These changes reflect the earliest stages of kidney and endothelial injury.

MATERIAL AND METHODS

Basic information

This was a prospective, observational, non-randomized study.

Thirty-three patients diagnosed with AAA were admitted to the department of general and vascular

surgery for elective AAA repair. After being provided with pertinent information, all the patients gave informed consent to participate in the study, which was approved by the Bioethics Committee of the Medical University of Silesia (KNW/0022/KB1/130/I/09 and KNW/0022/KB1/130/IV/09/11).

Inclusion criteria

(1) The diagnosis of an infrarenal aortic aneurysm confirmed by ultrasound and CT angiography. (2) Age between 50 and 90 years. (3) Informed consent to participate in the study. (4) Eligibility for open AAA repair (ORe). (5) eGFR > 30 ml/min/1.73 m^2. (6) Discontinuation of nephrotoxic drugs (including metformin and nonsteroidal anti-inflammatory agents) 24 hours before the intervention.

Exclusion criteria

(1) Lack of informed consent. (2) Patients with one kidney. (3) > 60% reduction in the diameter of the renal artery. (4) Patients with a kidney transplant. (5) Hematuria defined as > 3 red blood cells and/or leukocyturia > 5 white blood cells per high powered field (400 × magnification; sediment obtained by centrifugation of a 10 ml fresh urine sample for 15 minutes). (6) Treatment with aminoglycoside antibiotics in the previous month. (7) History of treatment with cyclosporine A. (8) History of, or active neoplastic disease. (9) Surgical treatment in the previous month. (10) Recent stroke (in 2 months preceding the study). (11) Recent myocardial infarction (in 3 months preceding the study). (12) Clinically relevant disorders of the internal organs, metabolism, as well as blood, neurological or psychiatric disease. (13) History of AKI in 6 months preceding the study. (14) Acute inflammatory disease. (15) Urinary tract obstruction.

AAA diagnosis

An abdominal aortic aneurysm was diagnosed based on previously performed CT angiography.

Patient eligibility for ORe

The following patients were found eligible for ORe: (a) men with AAA diameter ≥ 55 mm, (b) women with AAA diameter ≥ 50 mm, (c) patients in whom the AAA diameter increased by 10 mm in the preceding 12 months, (d) patients with symptomatic AAA.

Course of ORe

Nephrotoxic drugs including metformin and nonsteroidal anti-inflammatory agents (except for antithrombotic prophylaxis with acetylsalicylic acid – AsA) were discontinued 24 hours before AAA repair. Diuretic therapy was continued if considered indispensable for blood pressure control. During 48 hours preceding the intervention the patients received adequate amounts of oral fluids while solid foods were eliminated. Six hours prior to anesthesia, the patients were instructed to abstain from fluid intake. Intravenous infusion was started before ORe (normal saline, multi-electrolyte concentrate, Ringer's solution) – on average 2500–3000 ml/procedure. All the patients received antithrombotic prophylaxis. If no contraindications were found, they were administered 75–150 mg AsA per day. The drug was discontinued on the day of the procedure, and if there was no bleeding, re-instituted 48 hours after the intervention.

The repair was performed under general anesthesia. The transperitoneal approach was adopted with subrenal aortic clamping. A Dallon Uni-Graft collagen--coated vascular prosthesis was implanted. During the operation all the patients were given 1250–2500 units of unfractionated heparin (the activated clotting time was not determined). The heparin infusions were continued for 24 hours after surgery in a dose calculated to maintain an APTT ratio greater than 1.5 times the baseline. On day 2, prophylactic enoxaparin (40 mg/day) was started and continued for 14 days. Prophylactic pantoprazole (20 mg twice daily) was started on the day of surgery.

Study protocol

A. Data collection: (1) age; (2) sex; (3) body weight and height – calculation of body mass index (BMI); (4) smoking history; (5) evaluation for concomitant disease (diabetes mellitus, ischemic heart disease, history of myocardial infarction, arterial hypertension, obliterating atherosclerosis of lower limb arteries, chronic kidney disease); (6) medication history.

B. Preliminary investigations: (1) ultrasound AAA measurement; aneurysm location in relation to the renal arteries; (2) echocardiography with determination of ejection fraction (EF); (3) renal ultrasound to obtain longitudinal (long axis) view and rule out urinary tract obstruction; (4) renal artery Doppler ultrasound.

C. Pre-surgery tests: (1) serum levels of total and high-density lipoprotein (HDL) cholesterol (the low-density lipoprotein (LDL) fraction was calculated), triglycerides, glucose, Na^+, K^+, creatinine, C-reactive protein (CRP); (2); HbA_{1C} test; (3) complete blood count; (4) serum NGAL, ICAM-1, VCAM-1, P-selectin and vWF level in plasma expressed as a percentage of the normal pooled plasma standard (NPP).

D. Intra-procedural determinations: (1) procedure duration, aortic cross-clamping time, moment of clamp removal; (2) volume of i.v. infusions administered during the surgical procedure; (3) number of units of packed red blood cells transfused during surgery; (4) intraoperative blood loss; (5) intraoperative blood pressure measurements – every 5 minutes; (6) blood sample collections for NGAL, ICAM-1, VCAM-1, P-selectin and vWf from: a) the (left) renal vein

immediately before aortic cross-clamping, b) renal vein immediately before aortic cross-clamp removal, c) peripheral vein immediately before aortic cross--clamp removal (upper limb), d) inferior vena cava immediately before aortic cross-clamp removal, e) renal vein at 5 minutes after aortic cross-clamp removal and f) peripheral vein at 5 minutes after aortic cross-clamp removal (upper limb).

Laboratory investigations

Blood samples were collected in Vacutainer plastic tubes (the blood vessels were selected according to the study protocol; upper limb – cubital vein). After clotting (or anticoagulant treatment with 3.2% sodium citrate), the blood was centrifuged for 15 minutes (3000 g, 4000 rpm). The obtained serum or plasma as well as urine samples were frozen and stored at -80°C until assay. NGAL, ICAM-1, VCAM-1, P-selectin concentrations and the vWf level were determined using an ELISA SIRIO-S microplate reader with an automatic plate washer.

The following laboratory kits were utilised according to the manufacturers' instructions: 1. NGAL: Human LIPOCALIN-2/NGAL ELISA Kit BioVendor – Laboratorni medicina a.s., Czech Republic; 2. ICAM-1: Quantikine Human sICAM-1/CD54 ELISA Kit, R&D Systems, Inc., Minneapolis, United States of America; 3. VCAM-1: Quantikine Human sVCAM-1 ELISA Kit, R&D Systems, Inc., Minneapolis, United States of America; 4. P-selectin: Human soluble P-Selectin/CD62P ELISA Kit, R&D Systems, Inc., Minneapolis, United States of America; 5. vWf: von Willebrand Factor Antigen ELISA Kit, Helena BioSciences Europe, Gateshead, United Kingdom.

We measured the serum concentrations of NGAL, P-selectin, ICAM-1 and VCAM-1, while the plasma vWF level was expressed as a percentage of NPP. The creatinine concentrations were determined by means of the colorimetric Jaffe method, the remaining parameters with routine tests used in our Department. eGFR was calculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) and, additionally, with the MDRD (Modification of Diet in Renal Disease Study) equations [22,23]. LDL was evaluated utilising the Friedewald formula [24] and BMI with the standard BMI calculator (weight [kg]/height^2 [m^2]. Systolic and diastolic pressure was quoted in mm Hg. The mean arterial blood pressure (MAP) was calculated as (systolic blood pressure + 2 × diastolic blood pressure)/3 [mm Hg].

Statistical analysis

MAP was calculated based on intraoperative measurements of the systolic and diastolic pressure. Wesselink et al. [25] used MAP = 60 mm Hg as a threshold between normal arterial pressure and arterial hypotension. The area under the curve (AUC) for this MAP threshold (expressed in mm Hg × min) represented the effect of MAP on the biological parameters. In our study the rectangle method was used to estimate the AUCs separately for MAP > 60 mm Hg and MAP < 60 mm Hg for all the patients. The whole-group sum total of AUCs separately for MAP > 60 mm Hg and for MAP < 60 mm Hg were calculated and compared.

Statistical analysis was carried out by means of Statistica v. 12 (StatSoft). Numerical data are presented as the mean (± SD) or median (with the maximum and minimum). The Shapiro-Wilk test was employed to test data distribution. If normal distribution was not confirmed, the Mann-Whitney U test and the Wilcoxon test were used for independent and dependent variables, respectively. When the data distribution was normal, independent and dependent t-tests were applied. The level of significance was set at $p < 0.05$.

RESULTS

Clinical and biochemical characteristics of patients (Table I)

Table I. Group characteristics (x ± SD or number: n)

Study population {including women} (n)	33 {2}
Age (years)	69.20 ± 7.98
BMI (kg/m^2)	26.50 ± 3.50
Kidney ultrasound	
Right kidney – long axis (mm)	97.55 ± 7.96
Left kidney – long axis (mm)	99.30 ^{ns} ± 7.81
Doppler ultrasound – renal arteries	
Peak systolic velocity: right kidney (cm/s)	61.27 ± 14.22
Peak systolic velocity: left kidney (cm/s)	60.85 ^{ns} ± 14.23
End diastolic velocity: right kidney (cm/s)	20.50 ± 6.73
End diastolic velocity : left kidney (cm/s)	21.23 ^{ns} ± 7.30
Echocardiography	
Posterior wall thickness (mm)	10.65 ± 2.37
Interventricular septal thickness (mm)	13.16 ± 3.95
EF (%)	57.05 ± 6.96
LV EDD (mm)	49.72 ± 4.69
LV ESD (mm)	33.26 ± 5.60
RV EDD (mm)	25.59 ± 5.42174
Dimension of aortic bulb (mm)	35.87 ± 7.28
Aortic aneurysm	
AAA neck length (mm)	25.80 ± 8.17
AAA neck diameter (mm)	24.22 ± 5.62
AAA diameter (mm)	57.72 ± 11.52
Laboratory tests – prior to surgery	
Total serum cholesterol (mg/dl)	200.00 ± 53.32
HDL (mg/dl)	39.26 ± 8.73

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LDL (mg/dl)	130.66 ± 48.81
Serum triglycerides (mg/dl)	156.97 ± 78.13
Blood glucose (mg/dl)	106.53 ± 52.36
HbA1c (%)	5.96 ± 0.70
Serum Na^+ (mmol/l)	139.85 ± 2.36
Serum K^+ (mmol/l)	4.25 ± 0.34
Hemoglobin concentration (g/dl)	14.60 ± 1.10
RBC (× 10^6/µl)	4.76 ± 0.37
Hematocrit (%)	43.20 ± 3.18
PLT (× 10^3/µl)	209.91 ± 61.60
PDW (fl)	13.64 ± 2.30
MPV (fl)	9.95 ± 1.36
CRP (mg/l)	19.17 ± 28.40
Estimated glomerular filtration rate – prior to surgery	
eGFR-CKD-EPI (ml/min/1.73 m^2)	74.21 ± 21.42
eGFR-MDRD (ml/min/1.73 m^2)	83.65 ± 32.80

ns – no statistically significant differences between long axes of left and right kidneys and Doppler ultrasound parameters measured in left and right renal arteries (independent variables); BMI – body mass index; EF – ejection fraction; LV EDD – left ventricular end diastolic diameter; LV ESD – left ventricular end systolic diameter; RV EDD – right ventricular end diastolic diameter; AAA – abdominal aortic aneurysm; HDL – high-density lipoproteins; LDL – low-density lipoproteins; HbA1c – glycated haemoglobin; RBC – red blood count; PLT – platelets; PDW – platelet distribution width; MPV – mean platelet volume; CRP – C-reactive protein.

The study group included 13 smokers. The numbers of participants suffering from concomitant diseases were as follows: diabetes – 4, ischemic heart disease – 15, arterial hypertension – 21, obliterating atherosclerosis of lower limb arteries – 19. The following medications had been used: statins – 12 patients, convertase inhibitors – 14, angiotensin receptor blockers – 3, nonsteroidal anti-inflammatory drugs – 6, β-blocker – 16, calcium channel blocker – 7, nitrates – 8 and diuretics – 5 patients. Twelve patients had symptomatic AAA; none had a dissecting aneurysm. CT angiography of the abdominal aorta was performed between days 204 and 2 before surgery (median 4 days).

Surgery data (Table II)

Table II. Surgery details (x ± SD or number: n)

Duration (min)	117.27 ± 33.05
Aortic cross-clamping time (min)	37.28 ± 15.33
Intraoperative blood loss (ml)	826.56 ± 627.59
Parenteral fluids (ml)	3493.75 ± 868.61
RBC units (n) {(ml)}	5 {1120; 560; 560; 560; 560}
Plasma units (n) {(ml)}	1 {1020}

n – number of patients who received RBC or plasma transfusion {RBC concentrate / plasma volumes (ml) in particular patients}; RBC – red blood count.

NGAL, endothelial function/damage markers and vWF in serum as well as plasma samples obtained from different sampling sites during ORe of AAA (Tables III–VII)

Table III. Neutrophil gelatinase-associated lipocalin concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

		1	2	3	4	5	6	7
	C	**0 h**	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		60.47 ± 56.09	60.76 ± 49.34	58.29 ± 42.82	62.10 ± 51.41	68.72 ± 55.98	92.12 ± 77.96	67.50 ± 50.52
A	1 of 4	p = 0.635859						
	1 of 7	p = 0.16073						
	2 of 3		p = 0.859006					
	2 of 6		**p = 0.002773**					
	3 of 6			**p = 0.009329**				
	4 of 7				p = 0.264107			
B	1 of 2	p = 0.479059						
	1 of 3	p = 0.908112						
	1 of 6	p = 0.152739						
	1 of 5	p = 0.156454						
	5 of 2		p = 0.073397					
	5 of 3			p = 0.284241				
	5 of 6					p = 0.434043		
	5 of 4				p = 0.386682			
	5 of 7					p = 0.925926		

0 h: concentration before surgery in peripheral vein (1). **Pre-AC(-)-rv**: concentration in renal vein immediately before aortic clamping (AC) (2). **Pre-CR(+)-rv**: concentration in renal vein immediately before aortic cross-clamp removal (CR) (3). **Pre-CR(+)-pv**: concentration in peripheral vein immediately before aortic

cross-clamp removal (4). **Pre-CR(+)-ivc**: concentration in inferior vena cava immediately before aortic cross-clamp removal (5). **Post-CR(-)-rv**: concentration in renal vein at 5 minutes after aortic cross-clamp removal (6). **Post-CR(-)-pv**: concentration in peripheral vein at 5 minutes after aortic cross-clamp removal (7). **A**: Level of significance – difference between paired means (test for dependent variables). **B**: Level of significance – difference between paired means (test for independent variables). **C**: Pairs of means used in A or B determinations.

Table IV. P-selectin concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		126.88 ± 41.94	123.92 ± 44.82	89.89 ± 39.10	79.19 ± 37.88	84.52 ± 43.18	91.44 ± 41.16	87.42 ± 41.88
A	1 of 4	**p = 0.000002**						
	1 of 7	**p = 0.000038**						
	2 of 3		**p = 0.000007**					
	2 of 6		**p = 0.000076**					
	3 of 6			p = 0.781818				
	4 of 7				p = 0.105871			
B	1 of 2	p = 0.984645						
	1 of 3	**p = 0.000343**						
	1 of 6	**p = 0.000794**						
	1 of 5	**p = 0.000121**						
	5 of 2		**p = 0.000286**					
	5 of 3			p = 0.352489				
	5 of 6				p = 0.386682			
	5 of 4				p = 0.797573			
	5 of 7					p = 0.78286		

Legend same as in Table III.

Table V. Intercellular adhesion molecule 1 concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		237.25 ± 123.07	265.10 ± 141.60	207.36 ± 111.56	204.51 ± 129.86	195.03 ± 85.11	202.61 ± 103.86	185.69 ± 97.91
A	1 of 4	**p = 0.008402**						
	1 of 7	**p = 0.000095**						
	2 of 3		**p = 0.00005**					
	2 of 6		**p = 0.000136**					
	3 of 6			p = 0.714149				
	4 of 7				p = 0.14992			
B	1 of 2	p = 0.378383						
	1 of 3	p = 0.174						
	1 of 6	p = 0.123817						
	1 of 5	p = 0.147288						
	5 of 2		**p = 0.016388**					
	5 of 3			p = 0.892881				
	5 of 6					p = 0.933565		
	5 of 4				p = 0.594573			
	5 of 7					p = 0.680528		

Legend same as in Table III.

Table VI. Vascular cell adhesion molecule 1 concentrations in serum samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (ng/ml, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**Pre-AC(-)-rv**	**Pre-CR(+)-rv**	**Pre-CR(+)-pv**	**Pre-CR(+)-ivc**	**Post-CR(-)-rv**	**Post-CR(-)-pv**
		402.94 ± 174.05	392.97 ± 180.36	377.35 ± 193.18	347.76 ± 185.07	325.75 ± 143.04	316.92 ± 167.36	307.96 ± 158.57
A	1 of 4	**p = 0.020675**						
	1 of 7	**p = 0.000757**						
	2 of 3		p = 0.287721					
	2 of 6		**p = 0.009329**					
	3 of 6			**p = 0.000545**				
	4 of 7				**p = 0.007558**			
B	1 of 2	p = 0.695689						
	1 of 3	p = 0.700435						
	1 of 6	**p = 0.041442**						
	1 of 5	p = 0.08571						
	5 of 2		p = 0.195228					
	5 of 3			p = 0.278513				
	5 of 6					p = 0.827417		
	5 of 4				p = 0.882752			
	5 of 7					p = 0.633855		

Legend same as in Table III.

Table VII. von Willebrand factor levels expressed as percentage of normal pooled plasma in samples obtained from different sampling sites before and during open repair of abdominal aortic aneurysm (%, x ± SD)

	C	1	2	3	4	5	6	7
		0 h	**pre-AC(-)-rv**	**pre-CR(+)-rv**	**pre-CR(+)-pv**	**pre-CR(+)-ivc**	**post-CR(-)-rv**	**post-CR(-)-pv**
		99.32 ± 52.53	135.24 ± 75.65	139.17 ± 72.10	110.90 ± 59.12	114.08 ± 57.52	124.80 ± 66.83	113.62 ± 58.56
A	1 of 4	p = 0.275741						
	1 of 7	p = 0.207785						
	2 of 3		p = 0.256541					
	2 of 6		p = 0.783815					
	3 of 6			**p = 0.025483**				
	4 of 7				p = 0.714149			
B	1 of 2	**p = 0.046836**						
	1 of 3	**p = 0.009061**						
	1 of 6	p = 0.083399						
	1 of 5	p = 0.133496						
	5 of 2		p = 0.426546					
	5 of 3			p = 0.154588				
	5 of 6					p = 0.555241		
	5 of 4				p = 0.662814			
	5 of 7					p = 0.377213		

Legend same as in Table III

Intraoperative hypotension

The whole-group AUC generated for MAP < 60 mm Hg amounted to 0.6% of the whole-group AUC for MAP > 60 mm Hg. We therefore assumed that the effect of hypotension on NGAL and endothelial function/damage markers was insignificant and no analysis was carried out.

DISCUSSION

We studied the serum (plasma) concentrations of endothelial function/damage markers and NGAL in blood specimens obtained from different sampling sites during open AAA repair. The material sampling is specified in the *Material and Methods Section*.

Since only one renal vein could be accessed during surgery, preliminary investigations had been performed to measure the long axis of the left and right kidneys and the basic parameters of renal arterial blood flow. As shown in Table II, no statistically significant differences were found between the long axes of the left and right kidneys and the Doppler ultrasound parameters measured in the left and right renal arteries. We therefore assumed that the left and right kidneys functions did not differ significantly, and hence the determinations carried out using blood specimens collected from the left renal vein would likely represent the status of both kidneys.

Serum NGAL in renal vein blood was found to have increased significantly at 5 min after aortic cross--clamp removal compared to the pre-clamping, and importantly, immediate pre-clamp-removal concentrations (Table III). This indicates a massive clamp-removal associated effect, resulting in a rapid, i.e. occurring within minutes, change in this lipocalin concentration in the renal vein. NGAL, determined in the serum and urine, has been used as a novel AKI biomarker [26,27]. It should be mentioned though, that upregulated NGAL expression has been found in injured epithelial cells of the kidney, liver and lung, and not only in AKI but also in other diseases [28,29,30]. Also, NGAL is an acute phase protein and can be produced by innate immune cells including neutrophils and macrophages [31,32]. Any of the above mechanisms might lead to high serum NGAL concentrations. Increases in urinary NGAL are primarily attributable to the local dysfunction of kidney tissue [33]. Hence, it seems that in AKI patients serum NGAL reflects a larger number of simultaneously occurring events compared to urinary NGAL levels, consequently, the latter might be more AKI-specific. As already mentioned, AKI is a systemic inflammatory response [13]. On the other hand, it has been shown that some inflammatory markers might act as non-classical indicators of AKI development [34]. All these data indicate a rather complex relationship between serum NGAL and the development of AKI, the severity of inflammatory processes and maybe also endothelial dysfunction, a key component of the inflammatory process [16,17].

P-selectin, one of the three known selectins, is secreted by platelets and ECs; its expression might increase following surgical trauma. P-selectin mediates leukocyte rolling on activated endothelium that occurs after the initiation of inflammatory responses [35,36].

The serum P-selectin concentrations in the pre-surgery cubital vein samples and those collected from the renal vein prior to aortic cross-clamping were almost identical (Table IV), while the subsequent determinations turned out to be significantly lower with no significant differences in-between. No significant effect of aortic cross-clamp removal was found. However, a 10% rise in serum P-selectin was seen in the cubital samples at 5 minutes after clamp removal compared to the pre-clamp-removal concentrations in the same vessel ($p = 0.105871$). A larger population might reveal statistical significance as well as some effect of aortic clamp removal on serum P-selectin. Further research is therefore fully warranted.

ICAM-1 and VCAM-1 are adhesive molecules of a similar structure that belong to the immunoglobulin superfamily. Following the P-selectin stage of an inflammatory response, they are both expressed on the EC surface and contribute to leukocyte adhesion and transendothelial migration through the endothelium [20,37,38].

The serum ICAM-1 levels in the pre-clamp-removal and post-clamp-removal cubital vein samples were significantly lower compared to the pre-surgery determinations (Table V). The pre-clamp-removal and post-clamp-removal renal vein concentrations were also lower than those revealed at the start of surgery. These results indicate a reduction in the ICAM-1 (and P-selectin) levels during surgery (Table IV).

The serum VCAM-1 levels in the pre-clamp-removal and post-clamp-removal cubital vein samples were significantly lower compared to the pre-surgery concentrations (Table VI). The post-clamp-removal renal vein concentrations were also significantly lower than those determined at the start of surgery. The pre--clamp-removal renal vein concentrations were lower compared to the pre-clamping levels but the difference did not reach the level of statistical significance. All these results evidence an intra-surgical decrease in serum P-selectin, ICAM-1, and VCAM-1 concentrations.

It should be emphasized that a rapid, i.e. occurring within minutes, decrease in serum VCAM-1 was found in the post-clamp-removal cubital and renal vein samples compared to the concentrations determined in both vessels immediately before clamp removal. This indicates a clamp-removal associated effect, which is opposite to that for NGAL.

vWf is synthesized in megakaryocytes and ECs, while pre-formed vWf is released by platelets [39,40]. This plasma protein participates in the development of the inflammatory process by supporting platelet aggregation and adhesion at sites of vascular injury [41]. It is believed vWf is the most important marker of endothelial damage [21].

No differences were found with respect to the vWf levels in the pre-clamping and pre-clamp-removal renal vein samples; nevertheless, the levels were significantly higher than the pre-surgery determinations in the cubital samples (Table VII). The post-clamp-removal vWf levels in the renal vein samples were significantly decreased compared to the pre-clamp-removal values. The cubital sample levels gradually increased but the rise did not reach the level of statistical significance. The difference in the vWf levels measured in the pre-surgery cubital vein and pre-clamping renal vein samples is worth noting. A hypothesis that, under physiological conditions, the renal vein vWf might be higher than in the cubital vein samples is quite unlikely. Experimental studies revealed that even a relatively slight injury to the vessel wall like catheterization might lead to vWf elevation [42]. The plasma vWf concentrations increased within minutes of a perturbation factor [43]. The increase in renal vein vWf observed in our study might have resulted from the surgery-related interventions performed to obtain access to this vessel. Nonetheless, if this was the case, the renal vein vWf levels should continue to increase; the cubital vein increases should be more dynamic as well. Neither of these were observed though. Gamulin et al. [44] and Colson et al. [45] found that infrarenal aortic cross-clamping produced profound impairment in renal hemodynamics. Hence, it might be hypothesized that vWf increases in the renal vein were a consequence of clamping-induced intrarenal endothelial injury. A decrease noted at 5 minutes after clamp removal would then reflect improvement in renal hemodynamics. Nevertheless, high pre-clamping vWf concentrations in the renal vein speak against this hypothesis. Further studies are needed to elucidate this issue.

Changes in NGAL, VCAM-1 and vWf are highly indicative of a clamp-removal associated effect consisting of a rapid (occurring within minutes) increase or decrease in parameter concentrations in the renal and/or cubital vein samples. It might also encompass the P-selectin levels. Following clamp removal, normal circulation is restored in tissues supplied by arteries located distally to the clamp site, and an ischemia-reperfusion injury might result. P-selectin, VCAM-1, their receptors [46,47], and probably also vWf [48], are ischemia-reperfusion injury suspected culprits.

As the average resting cardiac output is about 5 L/min (which is about equal to the total blood volume) [49], it was assumed that at 5 minutes after aortic clamp removal, blood from different areas (including ischemic lower limb regions) would have mixed. Consequently, a peripheral blood sample should be representative of the entire circulatory system.

During those five minutes, rapid molecular interactions (ligand-receptor) may occur between active substances that had originated in the ischemic areas leading to abrupt changes in the concentrations of various molecules. Theoretically, if the observed ligand is delivered in excess during reperfusion from the ischemic area then its concentration increases, whereas if the soluble form of its receptor is delivered, its concentration decreases. However, our results indicate that the causes underlying the above phenomenon may be much more complex. The post-clamp-removal associated effect in the case of VCAM-1 was observed in both the cubital and renal veins, which might be well explained by the sudden wash-out effect of the VCAM-1 and/or VCAM-1-binding molecules from the ischemic area. Nonetheless, the NGAL and vWf concentrations only increased in the renal vein, which is difficult to account for. Considering the short, i.e. 5-minute time span between the pre- and post-clamp removal blood sampling, aortic clamp removal and the associated lower limb reperfusion seems the only factor that might possibly trigger the above mentioned concentration changes. Again, this issue requires further investigations.

Another observation was the intraoperative decrease in P-selectin, ICAM-1 and VCAM-1. These molecules play an active role in the inflammatory process; soluble forms were determined in the samples [50,51]. The concentration decrease seems therefore to evidence continuous depletion of these molecules in circulation, thus confirming the dynamic development of an inflammatory response already during surgical intervention. The absence of comparable decreases in the vWf levels indicates some other course of vWf-mediated inflammatory processes.

The limitations of our study include the small number of participants. Failure to consider the post-clamp--removal blood sampling from the interior vena cava should also be mentioned as a shortcoming since such data might have allowed a more accurate interpretation of the rapid changes in the endothelial function/damage markers.

The novel contribution of this study is the determination of marker concentrations in blood samples obtained from different intraabdominal blood vessels during ORe of AAA.

CONCLUSIONS

1. The obtained results seem to evidence the development of the inflammatory response already during open AAA repair.
2. The rapid changes in the serum NGAL and VCAM-1 concentrations and vWf levels revealed in the course of open AAA repair indicate that these markers, expressed in the lower body as a result of aortic cross-clamping associated ischemia, massively enter systemic circulation following aortic clamp removal.

Authors' contribution

Study design – M. Kokot, J. Duława
Data collection – M. Kokot, G. Biolik, L. Kędzierski, T. Fojt, D. Ziaja, K. Ziaja
Data interpretation – M. Kokot, K. Ziaja, J. Duława
Statistical analysis – A. Kokot, M. Kokot
Manuscript preparation – M. Kokot, J. Duława
Literature research – M. Kokot, L. Kędzierski, A. Kokot
Final approval of the version to be published – M. Kokot, J. Duława

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