ORIGINAL ARTICLE

Acute kidney injury after abdominal aortic aneurysm surgery: detailed assessment of early effects using novel markers

Michał Kokot[1], Grzegorz Biolik[2], Damian Ziaja[2], Tadeusz Fojt[1], Kamila Cisak[1], Katarzyna Antoniak[1], Teresa Kowalewska-Twardela[2], Krzysztof Pawlicki[3], Krzysztof Ziaja[2], Jan Duława[1]

1 Department of Internal Medicine and Metabolic Diseases, Clinical Hospital No. 7, Medical University of Silesia, Upper Silesian Medical Center, Katowice, Poland
2 Department of General Surgery, Vascular Surgery and Angiology, Clinical Hospital No. 7, Medical University of Silesia, Upper Silesian Medical Center, Katowice, Poland
3 Department of Biophysics, Medical University of Silesia, Katowice, Poland

KEY WORDS

abdominal aortic aneurysm surgery, acute kidney injury, interleukin 18, liver-type fatty acid-binding protein, neutrophil gelatinase-associated lipocalin

ABSTRACT

INTRODUCTION One of the most severe complications of repair surgery for abdominal aortic aneurysms (AAA) is acute kidney injury (AKI). Even small rises in serum creatinine after surgery are associated with increased mortality.

OBJECTIVES The aim of the study was to assess the dynamics of AKI after elective AAA surgery using novel markers.

PATIENTS AND METHODS The study group consisted of 14 patients with AAA. We measured serum neutrophil gelatinase-associated lipocalin (NGAL) before, during (including intra-abdominal vein levels before and after removal of aortic clamp), and within 2 days after surgery. Moreover, we assessed urinary NGAL, interleukin 18 (IL-18), and liver-type fatty acid-binding protein (L-FABP) before, during, and within 3 days after surgery.

RESULTS We observed a marked but nonsignificant increase in serum NGAL directly after clamp removal (75.21 ±55.83 vs. 46.37 ±21.60 ng/ml baseline value, $P > 0.05$) and significantly elevated plasma NGAL at 2 hours (91.54 ±76.54 vs. baseline, $P < 0.05$), 12 hours (100.78 ±44.92 vs. baseline, $P < 0.05$) and 24 hours (89.46 ±94.18 vs. baseline, $P < 0.05$) after clamp release. There was also significant elevation of urinary IL-18 at 2 hours (51.60 [12.12–527.16] vs. 25.99 [9.34–187.80] pg/ml at baseline, $P < 0.05$); L-FABP at 2 hours (47.10 [5.40–500.00] vs. 5.50 (2.20–27.20) ng/ml at baseline, $P < 0.05$) and 12 hours (39.00 [5.20–500.00] vs. baseline, $P < 0.05$); NGAL at 12 hours (20.75 [5.00–176.10] vs. 5.85 [1.40–16.00] ng/ml at baseline, $P < 0.05$) and 24 hours (13.95 [3.90–163.30] vs. baseline, $P < 0.05$) after clamp release.

CONCLUSIONS Elective AAA surgery may induce AKI. Novel markers can facilitate early detection of AKI, thus allowing to start therapy at an appropriate time point.

Correspondence to:
Michał Kokot, MD, PhD, Oddział Chorób Wewnętrznych i Metabolicznych, Samodzielny Publiczny Szpital Kliniczny nr 7, Śląski Uniwersytet Medyczny, Górnośląskie Centrum Medyczne, ul. Ziołowa 47, 40-635 Katowice, Poland, phone/fax: +48-32-252-35-93, e-mail: metabol@gcm.pl
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INTRODUCTION Acute kidney injury (AKI) is one of the most serious complications after major surgical interventions and develops in 1% to 30% of the patients after cardiac surgery. Approximately 1% of the patients with AKI require dialysis and subsequent mortality rate reaches from 60% to 70%.[1,2] Even slight rises in serum creatinine predict increased mortality.[3-5]

Currently, no efficacious preventive therapy is available except appropriate preoperative hydration.[6-8] Serum creatinine (or the estimated glomerular filtration rate [eGFR]), the commonly used indicator of kidney function, however simple and low-priced, has major drawbacks. First of all, it fails to reveal early or mild stages of AKI. Furthermore, the rise of serum creatinine is delayed a few hours or even days in relation to the actual

TABLE 1 Patients' characteristics

demographic characteristics	
number of patients	14
sex, men/women	12/4
age, y	66.39 ±6.31
body mass index, kg/m^2	26.41 ±3.86
comorbidities, n	
current smokers	7
diabetes	3
coronary artery disease	5
hypertension	8
peripheral vascular disease	6
aneurysm characteristics, mm	
neck diameter	24.43 ±6.54
neck length	25.67 ±8.02
aneurysm diameter	59.21 ±10.97
kidney long axis, mm	
right kidney	93.50 ±9.30
left kidney	96.79 ±8.59
kidney Doppler examination	
right kidney pulsation index	0.90 ±0.17
left kidney pulsation index	0.88 ±0.21
right kidney resistance index	0.61 ±0.08
left kidney resistance index	0.60 ±0.10
biochemical parameters	
total cholesterol, mg/dl	218.43 ±64.24
high-density cholesterol, mg/dl	38.46 ±7.70
low-density cholesterol, mg/dl	145.83 ±58.76
triglycerides, mg/dl	178.36 ±88.21
fasting glucose, mg/dl	94.07 ±15.60
sodium, mmol/l	140 ±2.18
potassium, mmol/l	4.26 ±0.40
glycated hemoglobin, %	6.14 ±0.71
blood count parameters	
erythrocyte count before surgery, $\times 10^{12}$/l	4.84 ±0.46
erythrocyte count 4 h after surgery, $\times 10^{12}$/l	3.91 ±0.48
hemoglobin level before surgery, mmol/l	14.67 ±1.30
hemoglobin level 4 h after surgery, mmol/l	11.69 ±1.45
hematocrit before operation, %	43.66 ±3.57
hematocrit 4 h after operation, %	35.48 ±4.15
platelet count before surgery, $\times 10^9$/l	228.07 ±57.15
platelet count after surgery, $\times 10^9$/l	185.43 ±50.55[a]
C-reactive protein, mg/l	
before surgery	10.38 ±14.63
72 h after surgery	214.95 ±63.68[a]

Data are presented as number or mean ± SD.

a $P < 0.05$ vs. prior to surgery

Abbreviations: SD – standard deviation

onset of AKI.[9] Since the time period when therapy can be effective is relatively short (about 48 to 72 hours), timely recognition of AKI is of uppermost importance.[10] Currently, more reliable indicators of renal function are available. The most promising are cistatin C, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin (NGAL), sodium/hydrogen exchanger isoform 3, interleukin 18 (IL-18), N-acetyl-β-glucosaminidase, matrix metalloproteinase[9,11-13] liver-type fatty acid-binding protein (L-FABP),[14,15] and possibly also meprin A β-subunit.[16]

Up till now, the investigators have predominantly focused on the detailed analysis of AKI associated with cardiac interventions, as reflected in a number of publications.[17]

In the last years, following the introduction of advanced imaging techniques including magnetic resonance angiography and computed tomography (CT), the number of surgical interventions for aortic aneurysms has substantially increased, particularly in the elderly who tend to develop chronic kidney disease or overt chronic kidney insufficiency more frequently than the general population. It is a well known fact that abdominal aortic aneurysm (AAA) surgery, similarly to cardiac surgery, constitutes a serious risk factor for AKI.[18] Thus, AAA-associated AKI deserves much more attention. Moreover, since AAA surgery facilitates the detection of the onset of kidney injury, it might serve as a very useful clinical model of AKI.

The aim of this pilot study was to assess the dynamics of AKI triggered by AAA surgery using several novel sensitive AKI indicators. Furthermore, as this kind of intervention enables easy access to intra-abdominal blood vessels and particularly to the left renal vein and vena cava inferior, we decided to scrutinize and compare the early signs of AKI already during AAA surgery at different time points and in blood samples drawn from different blood sources with regard to aorta cross-clamping time point.

PATIENTS AND METHODS

Patients The study comprised 14 consecutive patients admitted to the Department of General Surgery, Vascular Surgery and Angiology, Medical University of Silesia, Katowice, Poland, for elective operative treatment of AAA, who signed informed consent and did not meet any of the following exclusion criteria: 1) the use of aminoglycoside antibiotics within 1 month before surgery; 2) treatment with cyclosporine A; 3) neoplastic disease; 4) another surgical procedure during 1 month prior to enrollment; 5) stroke during the preceding 2 months; 6) myocardial infarction during the preceding 3 months; 7) essential psychiatric, metabolic, neurological, blood or major internal organ disorders; 8) incident of acute renal failure or renal replacement therapy during the preceding 6 months; 9) an ongoing acute inflammatory response; 10) urinary tract obstruction. The study was approved by the Bioethics Committee of the Medical University of Silesia. Patient characteristics, comorbidities, and basic laboratory data are shown in TABLE 1. Before enrollment, 4 patients were treated with statins, 6 with angiotensin-converting

TABLE 2 Surgery details

operative time, min	121.79 ±36.30
aorta cross-clamping time, min	35.71 ±11.91
blood loss during surgery, ml (14)	928.57 ±849.82
intravenous fluid supplementation during surgery, ml (14)	3496.43 ±1018.76
red blood cell mass transfused during surgery, ml (2)	1120; 560
blood plasma transfused during surgery, ml (1)	1020

Data are presented as mean ± SD or amount; the number of patients is given in brackets.

Abbreviations: see TABLE 1

enzyme inhibitors, 1 with angiotensin receptor blockers, 2 with nonsteroidal anti-inflammatory drugs, 8 with β-blockers, 3 with calcium channel blockers, 2 with nitrates, 1 with diuretics, but none with spironolactone or pentoxyphylline. No patients received nephrotoxic drugs 2 weeks before and during the study.

Methods **Abdominal aortic aneurysm surgery** Between days 2 and 108 before surgery, the subjects underwent contrast-enhanced CT angiography. After infrarenal cross-clamping, the aortic aneurysm was excised and the aorta was reconstructed using a polytetrafluoroethylene graft. The surgery was performed under general anesthesia; details are given in TABLE 2.

Design The protocol of the study was as follows. All admitted patients underwent AAA and kidney ultrasound as well as renal artery Doppler examination. The following blood samples were obtained: (aB) before surgery (day –1) from a vein in the upper extremity; (bB) during surgery (day 0) from the accessible (left) renal vein prior to aorta clamping; (cB) from the renal vein; (dB) from the vena cava inferior; (eB) from a vein in the upper extremity: (cB), (dB), and (eB) just before the removal of aortic clamp; (fB) from the renal vein; (gB) from a vein in the upper extremity: (fB) and (gB) 5 minutes after removal of the aortic clamp. The successive blood samples were drawn from a vein in the upper extremity: (hB) 2 hours (day 0), (iB) 4 hours (day 0), (jB) 12 hours (day 0), (kB) 24 hours (day 1), (lB) 48 hours (day 2), (mB) 72 hours (day 3), (nB) 96 hours (day 4), and (oB) 120 hours (day 5) following aortic clamp removal. Urine samples were taken from the urinary catheter: (aU) before the surgery (day –1); (bU) just before the removal of aortic clamp; (cU) 2 hours; (dU) 4 hours; (eU) 12 hours (bU–eU: day 0); (fU) 24 hours (day 1); (gU) 48 hours (day 2); and (hU) 72 hours (day 3) after the removal of aortic clamp. The duration of the surgery and aortic clamping, total volume of intravenous infusions, and blood loss during surgery were all considered. Complete blood count (4 hours after the termination of surgery) and C-reactive protein (CRP; 72 hours after surgery) were also assessed. Based on the literature on the subject, we have chosen serum NGAL and urine NGAL, L-FABP and IL-18 as potential indicators of renal function. NGAL concentrations were determined in aB–lB blood samples, while creatinine concentrations in aB, kB, lB, mB, nB, and oB samples. NGAL, L-FABP, IL-18, and creatinine concentrations were determined in all urine samples (i.e., aU–hU). eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation and, alternatively, by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study formula.[19]

Laboratory methods Immediately after clotting, blood samples were centrifuged for 15 minutes at 3000 g, (rotation 4000 × min^{-1}); frozen serum and urine were stored at –80°C. Serum and urine creatinine concentrations were determined by the Jaffe colorimetric method. Serum and urine NGAL, IL-18, and L-FABP were assessed using commercially available enzyme-linked immunosorbent assays (Human LIPOCALIN-2/NGAL ELISA Kit BioVendor – Laboratorní medicína a.s., Czech Republic; Human IL-18 Platinum ELISA Kit eBioscence, Bender MedSystems GmbH, Austria; Human L-FABP ELISA Kit Hycult-Biotech, The Netherlands) according to manufacturers' instructions. Other laboratory parameters were determined using routine tests.

Statistical analysis Data were analyzed using the Statistica 8.0. computer software. All variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Statistical analysis was conducted using the nonparametric Kruskal-Wallis/Mann-Whitney test for independent samples and the Wilcoxon test for paired samples. The analysis of variance was used for parametric data. The correlation rate was calculated using the Spearman's test. The Spearman rank correlation coefficient (R_s) was determined. All results were expressed as mean ± standard deviation or median with ranges. Statistical significance was set at a P value less than 0.05.

RESULTS There were no differences in blood count parameters, except platelet count (TABLE 1). These results indicate that blood loss and

TABLE 3 Serum creatinine levels on successive days

	Day –1	Day 1	Day 2	Day 3	Day 4	Day 5
mean ± SD, mg/dl	1.10 ±0.29	1.33 ±0.47	1.34 ±0.66	1.31 ±0.87	1.28 ±0.65	1.33 ±1.05
P vs. day (–1)		0.127	0.223	0.393	0.339	0.454

Abbreviations: see TABLE 1

TABLE 4 Serum concentrations of neutrophil gelatinase-associated lipocalin (ng/ml) in different blood samples and successive time points

(aB)	(bB)	(cB)	(dB)	(eB)	(fB)	(gB)	(hB)	(iB)	(jB)	(kB)	(lB)
46.37 ±21.60	47.01 ±17.49	52.63 ±26.23	58.24 ±21.36	52.63 ±27.22	73.91 ±47.30	75.21 ±55.83	74.25 ±34.12	91.54 ±76.54	72.32 ±31.62	100.78 ±44.92	89.46 ±94.18
P vs. (aB)	0.971	0.727	0.727	0.508	0.126	0.109	0.121	0.013	0.149	0.003	0.017
	P vs. (bB)	0.676	0.405	0.676	0.048	0.039					
		P vs. (cB)	0.698	1.000	0.144	0.121					
			P vs. (dB)	0.549							
					P vs. (fB)	0.947					

Values are expressed as means ±SD.

Abbreviations: (aB) – before surgery (day –1) from a vein in the upper extremity, (bB) – during surgery (day 0) from the accessible (left) renal vein before clamping of aorta, (cB) – from the renal vein (day 0) just before aortic clamp removal, (dB) – from the vena cava inferior (day 0) just before aortic clamp removal, (eB) – from a vein in the upper extremity (day 0) just before aortic clamp removal, (fB) – from the renal vein 5 minutes (day 0) after aortic clamp removal, (gB) – from a vein in the upper extremity 5 minutes (day 0) after aortic clamp removal, (hB) – from a vein in the upper extremity 2 hours (day 0) after aortic clamp removal, (iB) – from a vein in the upper extremity 4 hours (day 0) after aortic clamp removal, (jB) – from a vein in the upper extremity 12 hours (day 0) after aortic clamp removal, (kB) – from a vein in the upper extremity 24 hours (day 1) after aortic clamp removal, (lB) – from a vein in the upper extremity 48 hours (day 2) after aortic clamp removal, others – see **TABLE 1**

supplementation were balanced during the operation, and, consequently, the blood supply to the kidneys was satisfactory. After surgery, serum creatinine concentration (**TABLE 3**) increased, though not significantly. The eGFRs according to the MDRD Study and CKD-EPI Study equations before surgery were 74.39 ±25.65 and 88.84 ±23.47 ml/min/1.73 m^2, respectively. Serum NGAL values were compared as follows: 1) between peripheral vein samples obtained before surgery and all samples taken from different blood vessels at successive time points; 2) between samples taken from the renal vein at the start of surgery and samples taken just before aortic clamp release from the renal and peripheral veins and vena cava inferior as well as those obtained 5 minutes after clamp release from renal and peripheral veins; 3) between samples taken from the renal vein just before aortic clamp release and samples obtained from peripheral veins and vena cava inferior as well as samples obtained 5 minutes after clamp release from renal and peripheral veins; 4) between samples taken from a peripheral vein and vena cava inferior just before aortic clamp release; 5) between samples taken from a peripheral vein and renal vein 5 minutes after clamp release. Significant serum NGAL elevation was found at 4, 24, and 48 hours after aortic clamp removal as compared to day –1. Mean NGAL concentrations and all the above comparisons are shown in **TABLE 4**. Urine NGAL on day 0 at 12 hours after clamp release and on day 1, IL-18 on day 2, and L-FABP on day 0 at 2 and 12 hours after clamp release were significantly elevated compared with their concentrations on day –1. However, when expressed as a marker/creatinine ratio, the number of significant differences was diminished (**TABLE 5**). We also correlated serum creatinine on days –1, 1, and 2 with serum NGAL. A significant correlation ($P < 0.05$) was observed only on day –1 ($R_s = 0.586$). An analysis of correlations between serum creatinine and urinary NGAL, IL-18, and L-FABP on days –1, 1, 2, and 3 revealed that only on day 1 L-FABP (rs = 0.580) and L-FABP converted to 1 mg of creatinine ($R_s = 0.579$) correlated significantly with serum creatinine.

Correlations between serum and urinary NGAL at the same time points: a) day –1, b) at the moment of clamp removal (NGAL in a peripheral vein 5 minutes after removal), c) 24 hours, and d) 48 hours after clamp removal were significant at time point "b", surprisingly only with NGAL in urine converted to 1 mg of creatinine ($R_s = 0.666$), and at time point "c" with NGAL in urine ($R_s = 0.717$) and NGAL converted to 1 mg of creatinine ($R_s = 0.582$). We also correlated time of aorta clamping with serum creatinine, serum NGAL, and urinary NGAL, IL-18, L-FABP on all days and time points; however, the only significant correlation was revealed between the time of aorta clamping and urinary IL-18 at the moment of clamp removal ($R_s = 0.664$).

TABLE 5 Urine concentrations of neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), liver-type fatty acid-binding protein (L-FABP) and their urinary excretion expressed per 1 mg of creatinine (Cr): NGAL/Cr, IL-18/Cr, L-FABP/Cr at successive time points

(aU)	(bU)	(cU)	(dU)	(eU)	(fU)	(gU)	(hU)	(iU)
NGAL, ng/ml	5.85 (1.40–16.00)	9.90 (3.00–80.30)	10.30 (4.30–44.90)	14.95 (4.60–63.50)	20.75 (5.00–176.10)	13.95 (3.90–163.30)	8.05 (2.00–128.20)	6.70 (4.40–91.00)
P vs. (aU)		0.441	0.380	0.312	0.002	0.028	0.321	0.309
IL-18, pg/ml	25.99 (9.34–187.80)	39.36 (11.03–146.99)	51.60 (12.12–527.16)	43.57 (6.42–426.12)	48.93 (15.67–2402.50)	35.30 (20.40–2342.40)	42.63 (13.83–3107.00)	37.06 (16.96–365.49)
P vs. (aU)		0.989	0.006	0.217	0.119	0.273	0.316	0.920
L-FABP, ng/ml	5.50 (2.20–27.20)	9.30 (4.20–227.20)	47.10 (5.40–500.00)	16.30 (3.60–198.40)	39.00 (5.20–500.00)	29.90 (3.40–194.80)	33.10 (4.20–341.00)	35.60 (5.40–500.00)
P vs. (aU)		0.429	0.005	0.378	0.018	0.197	0.206	0.064
NGAL/Cr, ng/mg	7.87 (1.71–25.00)	19.83 (4.44–92.83)	33.44 (13.25–130.14)	35.18 (11.02–352.77)	22.41 (10.39–718.77)	15.12 (3.25–418.71)	17.33 (8.61–149.06)	17.44 (6.14–559.16)
P vs. (aU)		0.639	0.323	0.214	0.046	0.278	0.683	0.071
IL-18/Cr, pg/mg	37.85 (9.48–262.65)	99.56 (12.97–452.27)	222.18 (47.52–124.48)	115.89 (30.57–1374.58)	76.23 (28.10–9806.12)	47.12 (20.38–6006.15)	105.68 (44.5–3612.79)	93.93 (30.93–1066.58)
P vs. (aU)		0.875	0.556	0.636	0.080	0.332	0.513	0.753
L-FABP/Cr, ng/mg	10.42 (2.70–22.60)	27.71 (7.89–667.12)	131.88 (9.68–1449.28)	30.62 (7.44–1102.22)	54.35 (9.62–2040.81)	34.41 (5.00–499.49)	44.32 (13.80–396.51)	69.56 (16.25–1117.55)
P vs. (aU)		0.493	0.002	0.212	0.051	0.516	0.425	0.142

Values are expressed as medians (ranges).

Abbreviations: (aU) – before surgery (day –1), (bU) – just before aortic clamp removal (day – 1), (cU) – 2 hours (day 0) after aortic clamp removal, (dU) – 4 hours (day 0) after aortic clamp removal, (eU) – 12 hours (day 0) after aortic clamp removal, (fU) – 24 hours (day 1) after aortic clamp removal, (gU) – 48 hours (day 2) after aortic clamp removal, (hU) – 72 hours (day 3) after aortic clamp removal

DISCUSSION

Due to ethical and organizational imperatives, it was impossible to avoid the deleterious effect of preoperatively administered contrast medium during AAA CT. It should also be emphasized that our aging population was burdened with several risk factors, i.e., age-related physiological impairment of renal function, type 2 diabetes, arterial hypertension, peripheral arterial disease, or coronary artery disease,[18] which could not be eliminated. Thus, all examinations were conducted in a group with potential adverse reactions associated with contrast-induced nephropathy and AAA-surgery-induced AKI. Hence, our study has the advantage of mirroring the events occurring worldwide in everyday clinical practice. We investigated successive stages of perioperative kidney function deterioration commonly observed in vascular surgery departments during and after AAA surgery. Contrast nephropathy might represent the first stage.

During surgery, we only had access to the left renal vein; thus, the sample obtained from this vein had to represent the condition of both kidneys. Therefore, in the course of the qualification process, we performed the Doppler examination of both renal arteries to exclude renal artery stricture, ultrasound measurements of long axis dimensions of both kidneys to exclude any possible differences, and ultrasound scanning of the urinary tract to exclude obstruction. No significant differences were observed in the study population.

It is difficult to define all potential AAA-surgery-related risk factors for renal damage. Aorta cross-clamping is performed below renal veins and blood supply to the kidneys does not become compromised. However, AAA surgery evokes a potent inflammatory response.[20-22] An inflammatory process along with toxic metabolic waste flowing through the vena cava inferior from ischemic lower extremities as well as oxidative stress associated with surgical trauma could contribute to the development of AKI.

NGAL is a well-recognized and reliable early indicator and predictor of AKI.[13,23] We found that an increase of NGAL serum concentration and urinary output, although considerable, is significant only at isolated time points. NGAL performs excellently as an AKI marker in homogenous populations, such as children, but in adults with comorbidities and, possibly, a preexisting chronic kidney disease it is far less efficacious.[24] We suspect that some of our patients had contrast nephropathy with superimposed AAA-surgery-induced AKI. This makes our population still less homogenous. The discriminatory power of NGAL for AKI decreases with diminishing severity of kidney injury, which is consistent with our results.[25]

No distinct differences were found between baseline NGAL and blood samples drawn during surgery before clamp removal regardless of their source. However, 5 minutes after clamp release, NGAL concentration rose abruptly; the rise was only significant compared with NGAL

concentration in the samples drawn from the renal vein before aorta clamping, which was almost the same as at 2 and 12 hours following clamp release. This brings us to the question of the cause of increased NGAL production. During aneurysm repair, the lower extremities become ischemic. Before clamp release, there were no differences in NGAL concentration in the renal vein, upper extremity vein, and vena cava inferior. One of the possible explanations of increased NGAL concentrations following clamp removal might be its washing out from the lower extremities following normal circulation being restored, since 5 minutes are sufficient for thorough mixture of all the blood in the body. Although NGAL has been claimed to be "a troponin-like biomarker for human acute kidney injury",[13] this analogy seems to have its weak points. Troponin is released from cardiomyocytes and directly indicates their injury, while the origin of serum NGAL during AKI is not so clearly defined. It is mainly delivered by the liver and lungs, but not kidneys. NGAL is also an acute-phase reactant produced by some immune cells.[26] As mentioned above, AAA surgery triggers the inflammatory reaction. After the surgery, an impressive increase (above 20 times) of other "classical" acute inflammatory phase reactant, namely CRP, was observed (TABLE 1). This confirms the great intensity of postoperative inflammatory response and, consequently, supports the idea that serum NGAL could rather be a bystander (merely acute-phase reactant) than direct indicator of kidney tissue damage. Additionally, a substantial increase of CRP suggests that postoperative inflammatory process could be one of the main reasons for the development of AKI in this clinical setting. The reason for the seemingly strict parallelism between the development of AKI and increase in serum lipocalin remains unclear. Evidence has recently emerged that AKI is a multiorgan disease.[27,28] Whether the decreased GFR with subsequent clearance impairment per se is sufficient for the impressive rise of NGAL during AKI seems doubtful. We would tend to believe that the AKI-associated rise in serum NGAL might reflect a nonrenal response. Such an indirect relationship between kidney injury and serum NGAL questions its value as an AKI indicator. Our results seem to confirm these doubts. The abrupt rise of serum NGAL after clamp removal probably depends on some other cause than ongoing AKI.

Urinary NGAL in AKI seems to have 2 sources, i.e., glomerular ultrafiltration with resultant impairment of reabsorption from the proximal tubulus and augmented synthesis in distal nephron segments;[13,29] however, GFR reduction during AKI could decrease NGAL delivery from circulation to the nephron lumen. Urinary lipocalin really depends on several kidney processes such as filtration, reabsorption, and tubular secretion; therefore, it could mirror numerous kidney functions. Thus, in this case, a term "troponin-like indicator" appears more adequate. Moreover, the different significance of urinary and serum NGAL as suggested by the poor correlation between these markers at the same time points implies some kind of dissociation between them.

IL-18 has been regarded as a marker of the proximal tubule. It is induced during AKI and, after cleavage by caspase-1, is detected in urine.[10] Our observation revealed a significant rise in urinary IL-18 at 2 hours and a tendency to reach the level of significance between 2 and 48 hours. Its usefulness as a marker of AKI has been demonstrated in different studies and clinical settings.[30-34] IL-18 is an important mediator of inflammation, and AKI itself is an inflammatory process. But the study on sepsis and AKI has shown that this systemic inflammatory process will not largely contribute to urinary IL-18 excretion. The time dynamics of urinary IL-18 excretion in our patients is consistent with the results of a study on AKI after cardiac surgery.[33]

L-FABP is a marker of proximal tubule damage. It is primarily expressed in the liver, pancreas, and small intestine and plays an important role in the metabolism of free fatty acids.[35] It might be filtered at the glomeruli and reabsorbed in the tubules. In our study, L-FABP in urine showed a significant rise at 2 and 12 hours. However, its concentrations during the study were more variable than those of IL-18. It was tested as a marker of AKI in different clinical settings with good results.[36] The rise in urinary L-FABP excretion in our patients (hour 2) is consistent with a study on AKI after cardiac surgery.[37] The peak value of urinary excretion was found at 4 hours after cardiopulmonary bypass. The authors also addressed the issue of serum L-FABP concentrations during AKI. Liver secretion of L-FABP during AKI could be intensified and through glomerular filtration could contribute to its urinary secretion. Serum L-FABP concentration in the study increased 12 hours after cardiopulmonary bypass, i.e., several hours later than the peak of urinary L-FABP. It could be a potential explanation for a second significant L-FABP elevation in our population at 12 hours.

Urinary NGAL, IL-18, and L-FABP are usually expressed as the markers/creatinine ratio, which, however, does not always seem adequate. After converting to creatinine, the number of significant values diminished (TABLE 5).

Study limitations The limitation of our analysis is a relatively small number of participants; however, this report presents the results of a pilot study, a part of our ongoing research. The heterogeneity of our population should also be considered, but, as hypothesized above, it might also constitute an advantage. The strength of this study is the determination of the levels of AKI indicators in peripheral and intra-abdominal veins during surgery.

Conclusions In common clinical settings, elective AAA surgery may induce "mild form" of AKI,

which could not be detected by determination of serum creatinine levels. Novel markers could facilitate early diagnosis of AKI and, what follows, a timely and effective therapeutic intervention. Serum NGAL concentration after AAA surgery can also be affected by some phenomena other than AKI; therefore, it cannot be deemed a reliable indicator of AKI. Urine NGAL seems to be a more reliable AKI indicator than serum NGAL. AKI markers measured in urine perform better when not converted to creatinine excreted in urine.

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ARTYKUŁ ORYGINALNY

Ostre uszkodzenie nerek po operacjach naprawczych tętniaków aorty brzusznej – szczegółowa ocena wczesnych skutków uszkodzenia przy użyciu nowych wskaźników

Michał Kokot[1], Grzegorz Biolik[2], Damian Ziaja[2], Tadeusz Fojt[1], Kamila Cisak[1], Katarzyna Antoniak[1], Teresa Kowalewska-Twardela[2], Krzysztof Pawlicki[3], Krzysztof Ziaja[2], Jan Duława[1]

1 Oddział Chorób Wewnętrznych i Metabolicznych, Samodzielny Publiczny Szpital Kliniczny Nr 7, Śląski Uniwersytet Medyczny, Górnośląskie Centrum Medyczne, Katowice
2 Oddział Chirurgii Ogólnej, Naczyniowej i Angiologii, Samodzielny Publiczny Szpital Kliniczny Nr 7, Śląski Uniwersytet Medyczny, Górnośląskie Centrum Medyczne, Katowice
3 Zakład Biofizyki, Śląski Uniwersytet Medyczny, Katowice

SŁOWA KLUCZOWE

interleukina 18, lipokalina związana z żelatynazą neutrofili, operacja tętniaka aorty brzusznej, ostre uszkodzenie nerek, białko wiążące kwasy tłuszczowe typu wątrobowego

STRESZCZENIE

WPROWADZENIE Jednym z poważnych powikłań operacji naprawczych tętniaków aorty brzusznej (*abdominal aortic aneurysms* – AAA) jest ostre uszkodzenie nerek (*acute kidney injury* – AKI). Nawet niewielkie wzrosty stężenia kreatyniny w surowicy po zabiegu związane są ze zwiększoną śmiertelnością.

CELE Celem badania była ocena dynamiki AKI po planowych operacjach naprawczych AAA przy użyciu nowych wskaźników.

PACJENCI I METODY Grupę badaną stanowiło 14 chorych z AAA. Oceniano stężenie w surowicy lipokaliny związanej z żelatynazą neutrofili (*neutrophil gelatinase-associated lipocalin* – NGAL) w surowicy krwi obwodowej przed, w czasie (śródoperacyjnie także w surowicy krwi naczyń wewnątrzbrzusznych przed i po usunięciu zacisku aorty) a także w ciągu 2 dni po operacji. Ponadto oceniano stężenie NGAL, interleukiny 18 (*interleukin 18* – IL-18) i białka wiążącego kwasy tłuszczowe typu wątrobowego (*liver-type fatty acid-binding protein* – L-FABP) w moczu przed, w czasie oraz w ciągu 3 dni po operacji.

WYNIKI Stwierdzono wyraźny, ale nieznamienny wzrost stężenia NGAL w surowicy bezpośrednio po usunięciu zacisku aorty (75,21 ±55,83 *vs* 46,37 ±21,60 ng/ml przed zabiegiem, p >0,05) oraz znamiennie podwyższone stężenia NGAL w 2 h (91,54 ±76,54 ng/ml *vs* przed zabiegiem, p <0,05), 12 h (100,78 ±44,92 ng/ml *vs* przed zabiegiem, p <0,05) i 24 h (89,46 ±94,18 ng/ml *vs* przed zabiegiem, p <0,05) po usunięciu zacisku aorty. Po usunięciu zacisku aorty obserwowano także znamienny wzrost stężenia w moczu IL-18 w 2 h (51,60 [12,12–527,16] *vs* 25,99 [9,34–187,80] pg/ml przed zabiegiem, p <0,05); L-FABP w 2h (47,10 [5,40–500,00] *vs* 5,50 [2,20–27,20] ng/ml przed zabiegiem, p <0,05) i w 12 h (39,00 [5,20–500,00] *vs* przed zabiegiem, p <0,05); NGAL w 12 h (20,75 [5,00–176,10] *vs* 5,85 [1,40–16,00] ng/ml przed zabiegiem, p <0,05) i w 24 h (13,95 [3,90–163,30] *vs* przed zabiegiem, p <0,05).

WNIOSKI Planowa operacja AAA może wywoływać AKI. Nowoczesne wskaźniki dają możliwość wczesnego rozpoznania AKI i tym samym pozwalają na rozpoczęcie terapii we właściwym momencie.

Adres do korespondencji:
dr med. Michał Kokot, Oddział Chorób Wewnętrznych i Metabolicznych, Samodzielny Publiczny Szpital Kliniczny nr 7, Śląski Uniwersytet Medyczny, Górnośląskie Centrum Medyczne, ul. Ziolowa 47, 40-635 Katowice, Poland, phone/fax: +48-32-252-35-93, e-mail: metabol@gcm.pl
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