Surgery with and without extracorporeal circulation in patients aged above 65 and kidney injury assessed by NGAL concentration

Operacje w krążeniu pozaustrojowym i bez krążenia pozaustrojowego u chorych powyżej 65. roku życia a uszkodzenie nerek oceniane na podstawie stężenia NGAL

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Abstract

Background: Human neutrophil gelatinase-associated lipocalin (NGAL) is one of the most sensitive predictive indices of acute kidney injury (AKI).

Aim: The aim of the work was to determine whether NGAL is a sensitive predictive index of AKI in elderly patients (> 65 years old) undergoing cardiac surgery, with and without extracorporeal circulation.

Material and methods: The study group encompassed 30 patients aged > 65 years, treated surgically, 18 with extracorporeal circulation (group I) and 12 without (group II). The serum concentrations of NGAL, cystatin C and the serum glomerular filtration rate (GFR) were assessed 24 h before surgery, and then 2 h and 24 h after surgery. The tests were carried out using immunochemical, nephelometric and standard clinical biochemical methods.

Results: In both groups, pre-operative cardiac, pulmonary and renal functions were normal. Hypertension was successfully treated in 16 patients, diabetes type 2 with normal baseline NGAL and no signs of nephropathy in 4 patients. In group I, the pre-operative levels of NGAL, cystatin C and GFR were normal. Two hours after surgery, there was a statistically significant increase in the level of NGAL, whilst GFR and cystatin C remained unchanged. Twenty-four hours after surgery, NGAL decreased slightly but was still statistically significantly higher than the baseline value. In group II, by contrast, there were no significant differences between pre- and post-operative levels of NGAL, cystatin C and GFR.

Conclusions: Neutrophil gelatinase-associated lipocalin is the most sensitive biomarker of transient renal ischemia related to the use of extracorporeal circulation in elderly patients with normal pre- and post-operative renal function. In elderly patients with normal renal function before and after cardiac surgery without extracorporeal circulation, NGAL levels are normal.

Key words: neutrophil gelatinase-associated lipocalin (NGAL), renal diseases, cardiac surgery, elderly patients

Streszczenie

Wstęp: Lipokalina związana z żelatynazą neutrofilów (*human neutrophil gelatinase associated lipocalin* – NGAL) jest jednym z najczulszych wskaźników predykcyjnych ostrej niewydolności nerek.

Cel: Ustalenie, czy u chorych powyżej 65. roku życia poddanych operacjom kardiochirurgicznym zarówno przy użyciu, jak i bez krążenia pozaustrojowego NGAL jest czułym wskaźnikiem predykcyjnym zagrażającej ostrej niewydolności nerek.

Materiał i metody: Grupę badaną stanowili chorzy powyżej 65 lat leczeni operacyjnie z zastosowaniem krążenia pozaustrojowego (n = 18) oraz bez jego zastosowania (*off pump coronary artery bypass* – OPCAB) (n = 12). Stężenie NGAL, cystatyny C i współczynnik przesączania kłębuszkowego (*glomerular filtration rate* – GFR) w surowicy oznaczano dobę przed operacją oraz 2 i 24 godziny po operacji. Badania wykonano przy użyciu metod immunochemicznych, nefelometrycznych oraz standardowych metod biochemii klinicznej.

Wyniki: W obu grupach przed leczeniem operacyjnym wydolność serca, płuc i nerek były prawidłowe. U 16 pacjentów skutecznie leczono nadciśnienie tętnicze, u 4 cukrzycę typu 2 z wyjściowo prawidłowym stężeniem NGAL, bez cech nefropatii. W grupie I przed operacją wartości NGAL, cystyny C i GFR były prawidłowe. Dwie godziny po operacji stwierdzono istotny statystycznie wzrost stęże-

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nia NGAL przy niezmienionej wartości GFR i cystatyny C. W kolejnej dobie po zabiegu wartość NGAL nieznacznie się zmniejszyła, ale nadal była statystycznie istotnie zwiększona względem wartości wyjściowej. W grupie II przed operacją i po niej wartości NGAL, cystatyny C i GFR istotnie się nie zmieniły.

Wnioski: Lipokalina związana z żelatynazą neutrofilów jest najczulszym biomarkerem przejściowego niedokrwienia nerek związanego z użyciem krążenia pozaustrojowego u pacjentów starszych, przy prawidłowej funkcji tego narządu zarówno przed operacją, jak i po niej. U pacjentów starszych z prawidłową funkcją nerek przed operacjami i po operacjach kardiochirurgicznych bez krążenia pozaustrojowego wartość NGAL była prawidłowa.

Słowa kluczowe: obojętnochłonna lipokalina związana z żelatynazą (NGAL), choroby nerek, operacje kardiochirurgiczne, starsi chorzy

Introduction

Current diagnostics of renal dysfunction based on creatinine levels, renal imaging and histological examinations often prove insufficient due to poor accuracy or excessive invasiveness. The most sensitive and specific markers are neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule-1 (KIM-1), and cystatin C [1-3]. Neutrophil gelatinase-associated lipocalin is a secretion protein, a member of the lipocalin family, present in neutrophil granulocytes. A common feature of this family of proteins, related to their structure, is the ability to bind and transport small lyophilic particles, i.e. free fatty acids, retinoids, arachidonic acids and steroids. The main ligands of NGAL are sideromacrophages, i.e. hemosiderin-containing cells synthesized by bacteria and papillary adenoma. The protein is also present in the trachea, stomach, colon and proximal renal tubules. Neutrophil gelatinase-associated lipocalin expression has been observed in numerous human cells but only at very low levels; however, it becomes considerably intensified in damaged epithelial cells, for example in the kidney, affecting cell survival and proliferation through the transcription factor NF-κB.

Neutrophil gelatinase-associated lipocalin activates nephron formation in the developing kidney, thereby displaying a protective action. Due to its small molecular mass and resistance to degradation, NGAL may be easily secreted by the cells of the thick ascending limb of the loop of Henle and the collecting duct system, and then excreted in the urine, both in the free form and complexed with matrix metalloproteinase-9 (MMP-9). Urinary levels correlate with serum levels; hence NGAL may become a useful diagnostic marker for renal diseases [4-6].

The incidence of acute kidney injury (AKI) following cardiac surgery ranges from 7.7% to 42%. According to the current definition, acute kidney injury (AKI) is a sudden loss of kidney function (within 48 h), fulfilling at least 1 of the 3 following conditions: increased creatinine concentration by ≥ 0.3 mg/dl (> 25 mmol/l), increased creatinine concentration by ≥ 50%, or decreased diuresis (< 0.5 ml/kg/h for > 6 h).

Renal function assessment using AKI markers, such as NGAL, cystatin C and glomelur filtration rate (GFR) in elderly patients undergoing cardiac surgery with and without extracorporeal circulation seems an interesting issue. Another challenging question is whether NGAL is the most sensitive biomarker of AKI and transient ischemia with no clinical signs of renal failure [1, 2].

Aim

The aim of the work was to determine whether NGAL is a sensitive predictive index for AKI in patients aged above 65 years, undergoing cardiac surgery, both with and without extracorporeal circulation.

Material and methods

The study group comprised only elderly patients, without concomitant diseases that could result in elevated baseline NGAL levels, such as chronic kidney disease, heart failure and chronic obstructive pulmonary disease. The concentrations of NGAL, cystatin C and GFR were assessed 24 h before the planned cardiac surgery (NGAL1, Cystatin C1, GFR1), then 2 h after surgery (NGAL2, Cystatin C2, GFR2) and finally 24 h after surgery (NGAL3, Cystatin C3, GFR3). GFR was assessed using the Cockcroft and Gault formula. The study encompassed 30 patients (8 women and 22 men) divided into two groups. Group I comprised 18 patients undergoing surgery with extracorporeal circulation, specifically: coronary artery bypass graft (CABG) (n = 9), CABG and mitral valve plasty (n = 3), mitral valve plasty (n = 1), mitral valve replacement with a biological valve (n = 1), aortic valve replacement with a biological valve (n = 1), replacement of mitral and aortic valves with biological valves (n = 2), and CABG and aortic valve replacement with a biological valve (n = 1). Group II encompassed 12 patients undergoing surgery without extracorporeal circulation (off-pump coronary artery bypass – OPCAB). The mean age was 73 ±3.8 years old and was comparable in both groups. All study participants had normal left ventricular ejection fraction, with a mean value of 50.2 ±6%.

Results

Pre-operative cardiac, pulmonary and renal functions were normal in both groups. Sixteen patients were successfully treated for hypertension, and 4 for diabetes type 2, with no signs of nephropathy and with normal NGAL concentration. It is worth emphasising that after the age of 40 years, the filtration surface and glomerular filtration

Table 1. Neutrophil gelatinase-associated lipocalin, cystatin C and GFR in the entire study population, and divided into group I and group II

Tabela 1. *Lipokalina związana z żelatynazą neutrofilów, cystatyna C i GFR bez podziału i z podziałem na grupę I i II*

	N	Mean	STDEV std	Minimum	10th percentile	Lower quartile	Median	Upper quartile	90th percentile	Maximum
Without division into groups										
NGAL1	30	133.5	63.5	64.3	66.25	96.5	115.15	137.4	234.8	285.6
NGAL2	30	163.9	62.2	75.4	81.8	116.4	153.65	205.4	253.2	292.3
NGAL3	30	158.3	73.9	69.2	90.25	100.2	134.5	185.7	270.95	346.2
GFR1	30	78.6	26.9	30	39.5	54.2	82.65	98.7	115.5	121.35
GFR2	30	75.6	33.5	38.7	42.22	50.51	68.265	86	108.28	188
GFR3	30	84.0	41.2	30.77	34.03	50.48	79.42	119	145	188
cyst1	30	0.99	0.33	0.65	0.685	0.8	0.895	1	1.505	1.94
cyst2	30	0.96	0.34	0.53	0.61	0.7	0.9	1.1	1.56	1.8
cyst3	30	1.01	0.42	0.52	0.62	0.66	0.89	1.2	1.77	1.9
Group I										
NGAL1	18	124.4	61.0	64.3	65.9	82.8	111.4	131.3	229.3	285.1
NGAL2	18	176.2	57.8	77.9	116.4	135.2	164.3	229.8	252.5	292.3
NGAL3	18	157.2	77.1	69.2	88.2	100.2	129.55	185.7	282.6	342.5
GFR1	18	82.5	23.1	32	49.2	70.1	87.15	99	112	119
GFR2	18	76.2	34.1	38.7	43.49	54.36	67.555	85	111	188
GFR3	18	84.1	40.2	31.28	32.37	58	79.42	95	145	188
cyst1	18	0.90	0.29	0.65	0.66	0.76	0.845	0.95	1.1	1.94
cyst2	18	0.87	0.28	0.53	0.57	0.67	0.885	0.9	1.2	1.78
cyst3	18	0.95	0.40	0.52	0.58	0.69	0.82	1.1	1.9	1.9
Group II										
NGAL1	12	147.2	67.5	66.6	79.9	111.25	125.8	185.5	236	285.6
NGAL2	12	145.6	66.6	75.4	77.5	92.55	125.55	189.3	253.9	267.2
NGAL3	12	160.0	72.2	79.6	92.3	110.25	146.05	189.45	214.5	346.2
GFR1	12	72.7	31.9	30	31	48.35	72.1	97.7	119	121.35
GFR2	12	74.9	34.0	40.97	41.7	43.37	72.21	93.53	102.83	154.43
GFR3	12	83.8	44.5	30.77	35.69	43.74	72.08	125.875	145	145
cyst1	12	1.12	0.37	0.66	0.8	0.885	0.95	1.355	1.6	1.9
cyst2	12	1.09	0.39	0.56	0.65	0.865	0.905	1.435	1.59	1.8
cyst3	12	1.10	0.44	0.61	0.63	0.65	1.05	1.46	1.67	1.87

decrease physiologically by 8-10 ml/min/decade; therefore in geriatric patients aged > 70 years, GFR > 70 ml/min/1.73 m^2 is considered normal.

In both groups, pre-operative GFR and concentrations of cystatin C and NGAL were normal. Two hours after surgery, a statistically significant increase in NGAL concentration was observed in group I, whilst the concentration of cystatin C and GFR did not change. In group II, the levels of NGAL, cystatin and GFR remained unchanged. On the first post-operative day, in group I the concentration of NGAL was still statistically significantly elevated compared to the baseline value. The concentration of cystatin C and GFR did not change significantly. In group II, 24 h after surgery, the concentration of NGAL, cystatin C and GFR were normal. No clinical signs of AKI occurred in either group. The results are presented in Table 1 and Figures 1 A, B; 2 A, B; 3 A, B.

Discussion

Serum and urinary NGAL concentration is a proven early index of AKI after cardiac surgery. The prospective study of Mishra *et al*. conducted in children after cardiac surgery who developed AKI shows a significant increase in serum and urinary NGAL concentration as early as 2 h after surgery [4, 7]. Acute kidney injury developed in 51% out of 196 children, with a 15-fold increase in NGAL concentration after 2 h, and a 25-fold increase after 4 and 6 h [4, 7].

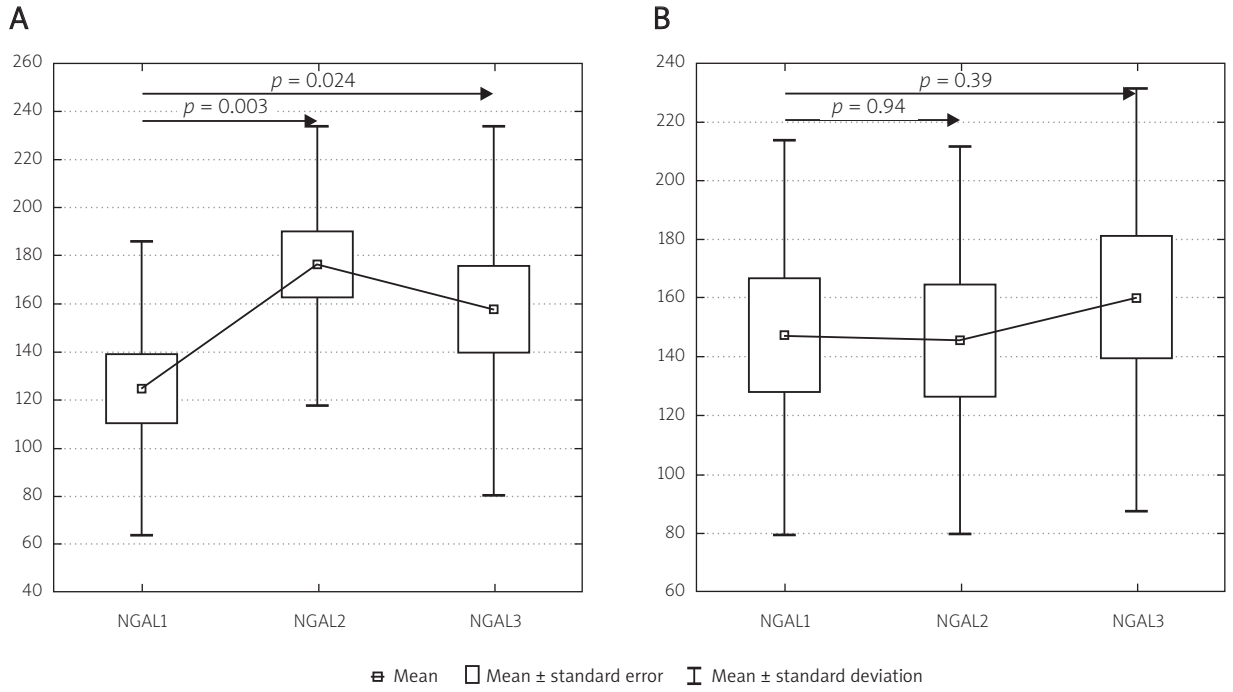

Fig. 1. Neutrophil gelatinase-associated lipocalin in group I (**A**) and group II (**B**)
Ryc. 1. *Lipokalina związana z żelatynazą neutrofilów w grupie I (**A**) i grupie II (**B**)*

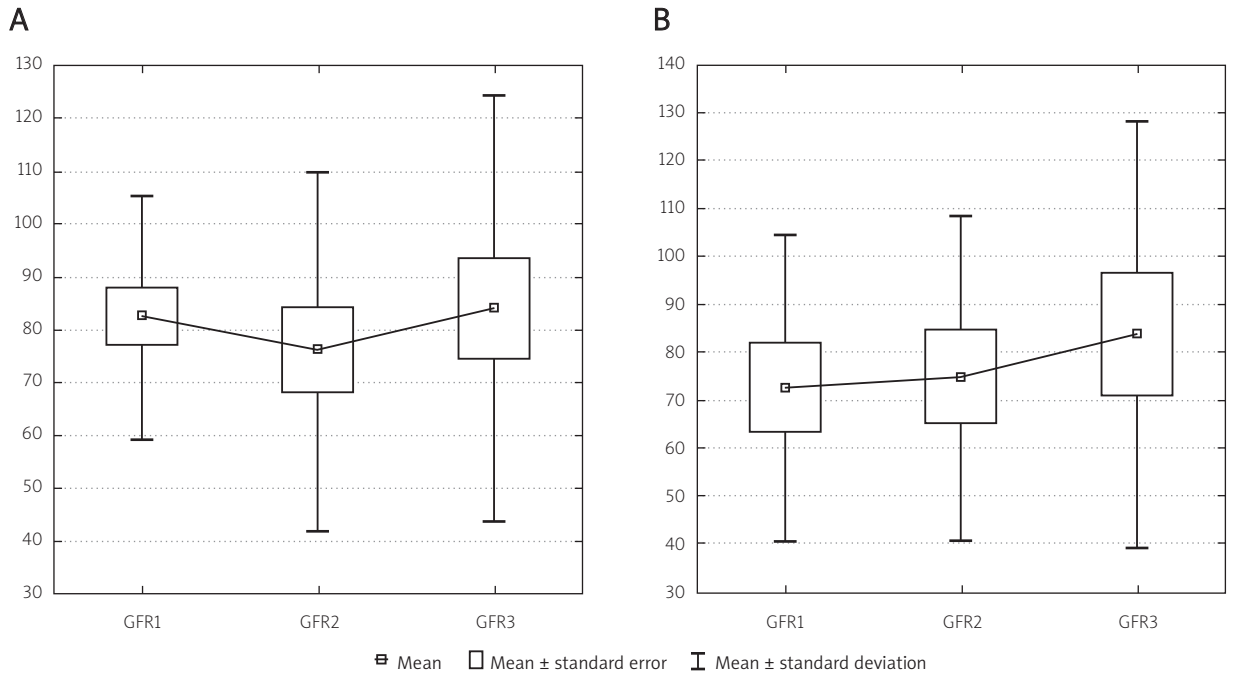

Fig. 2. Glomelural filtration rate in group I (**A**) and group II (**B**)
Ryc. 2. *Współczynnik przesączania kłębuszkowego w grupie I (**A**) i grupie II (**B**)*

According to Devarajan, also in adult patients who developed AKI, an increase in urinary NGAL concentration was observed as early as 1-3 h after cardiac surgery [8]. Moreover, numerous data indicate a relationship between early post-operative urinary and serum NGAL concentration and the severity of AKI, patient hospitalization, dialysis therapy and increased mortality [9-12]. Accordingly, urinary NGAL concentration after 2 h correlates with AKI intensification and duration [13, 14]. Neutrophil gelatinase-associated lipocalin is considered an independent risk factor for AKI

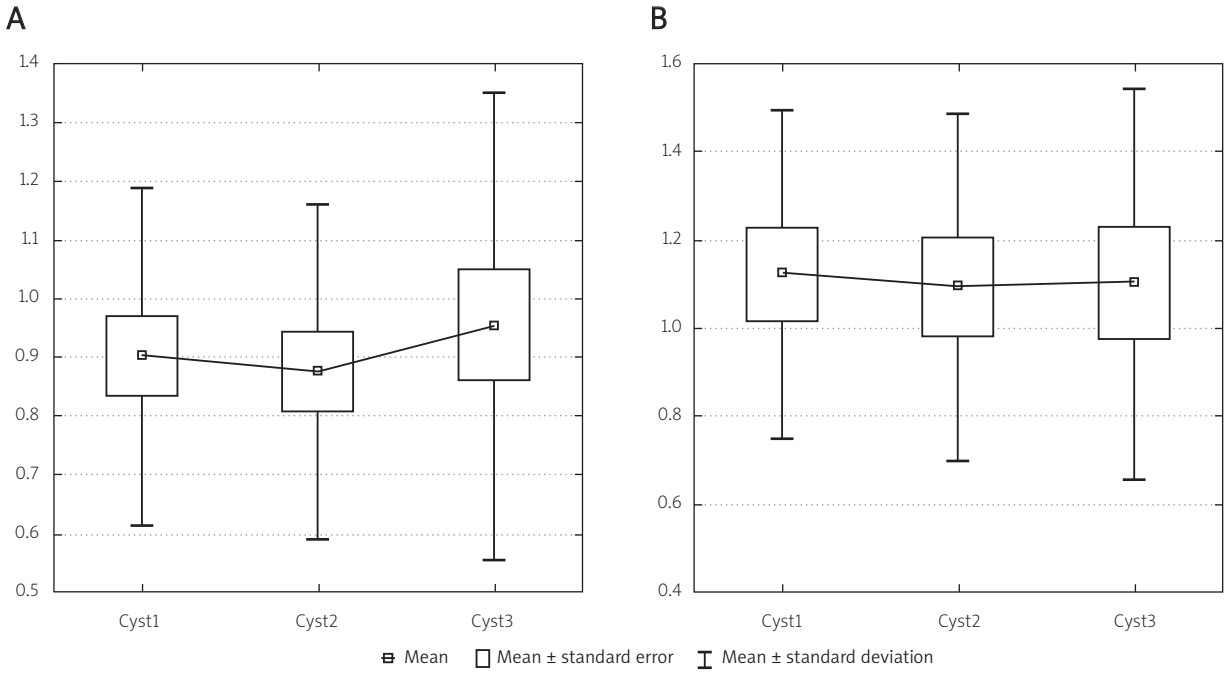

Fig. 3. Cystatin C in group I (**A**) and group II (**B**)
Ryc. 3. *Cystatyna C w grupie I (**A**) i grupie II (**B**)*

[13-15]. Its concentration has been demonstrated to correlate closely with the acute state; a significant increase in NGAL concentration is observed in elderly patients with ischemic renal failure, which frequently leads to AKI, tubular necrosis or tubulo-interstitial nephritis [16, 17]. Patients with ischemic heart disease frequently display various levels of kidney dysfunction resulting from concomitant diseases, i.e. diabetes, hypertension and congestive heart failure, despite normal serum creatinine levels [17].

To date, there are no scientific reports considering renal function assessment in elderly patients undergoing cardiac surgery with and without extracorporeal circulation. It is well known that at the age of approx. 70 years, the number of active nephrons decreases by 20-30%. Involution of the renal cortex takes place, the quantity of normal glomeruli decreases, whilst glomerulosclerosis increases, all of which makes the interpretation of renal biopsy results difficult. Focal or diffuse thickening of glomerular basement membrane associated with type IV collagen deposition occurs. The mesangial volume increases (both the number of mesangial cells and the extracellular matrix), whilst the number of epithelial cells decreases. This leads to a decrease in the filtration surface and glomerular filtration by 8-10 ml/min/decade [17]. Hence transient renal ischemia associated with the use of extracorporeal circulation in elderly patients with decreased baseline renal function may be dangerous and necessitate hemotherapy or dialysis therapy. Additionally, geriatric patients suffer from numerous chronic diseases, such as hypertension, congestive heart failure, ischemic heart disease and diabetes [17].

Conclusions

Neutrophil gelatinase-associated lipocalin is the most sensitive biomarker of transient renal ischemia related to the use of extracorporeal circulation in elderly patients with normal renal function both before and after surgery. In elderly patients with normal renal function before and after cardiac surgery without extracorporeal circulation, NGAL is normal.

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