



Remote Ischemic Preconditioning and Contrast-Induced Acute Kidney Injury in Patients Undergoing Elective Percutaneous Coronary Intervention: A Randomized Clinical Trial

Karolina Stokfisz, MD*, Anna Ledakowicz-Polak, MD, PhD, Michal Kidawa, MD, PhD, Marzenna Zielinska, MD, PhD

Intensive Cardiac Therapy Clinic, Department of Invasive Cardiology and Electrocardiology, Medical University of Lodz, Lodz, Poland

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ABSTRACT

Background: Contrast-induced acute kidney injury (CI-AKI) is a common cause of hospital-acquired AKI and a serious complication of percutaneous coronary intervention.

Objective: The aim of the present study was to assess whether remote ischemic preconditioning (RIPC) reduces the incidence of CI-AKI.

Methods: We conducted a prospective, randomized, sham-controlled clinical study. The study included 101 patients admitted to the Intensive Cardiac Therapy Clinic of Medical University of Lodz for elective percutaneous coronary intervention. The participants were randomly assigned in a 1:1 ratio to either a control group (n=51) or an RIPC group (n=50). In the latter, RIPC was achieved before percutaneous coronary intervention by 4 cycles of 5-minute inflation of a cuff on the left upper arm to 200 mm Hg followed by 5-minute deflation. In the control group, a deflated cuff was placed on the left arm for 40 minutes. Serum creatinine concentration was measured to check for the presence of CI-AKI within 48 to 72 hours of percutaneous coronary intervention. Serum neutrophil gelatinase-associated lipocalin level was also measured within 3 hours.

Results: CI-AKI occurred in 2 patients from the RIPC group (4%) and 3 patients from the control group (5.9%), but the difference was not significant ($P=0.98$). The patients who developed CI-AKI also demonstrated increased serum neutrophil gelatinase-associated lipocalin concentrations (the area under the receiver operator characteristic curve=0.97; 95% CI, 0.938–1.00; $P < 0.00$) and the optimal cutoff point value was 118.9 ng/mL.

Conclusions: The use of RIPC before elective percutaneous coronary intervention was not found to prevent CI-AKI. ClinicalTrials.gov identifier: NCT03761368. (*Curr Ther Res Clin Exp.* 2020; 81:XXX–XXX)

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Introduction

The use of contrast medium in diagnostic and therapeutic procedures has grown in popularity, and now represents a leading cause of hospital-acquired acute kidney injury (AKI), known as contrast-induced AKI (CI-AKI).¹ In addition to pre-existing kidney disease with renal function impairment, a number of risk factors for developing CI-AKI have been identified: diabetes, hypertension, chronic heart failure, advanced age, volume depletion, hemody-

namic instability, use of concurrent nephrotoxic medications, and large volume or high osmolality of the contrast agent.² Although high-osmolar, iodine-containing contrast media has been replaced by low-osmolar agents and hydration protocols are improving, in approximately 12% of all patients undergoing percutaneous coronary intervention (PCI) experience CI-AKI, and the condition is closely associated with higher morbidity and mortality.³ CI-AKI is currently defined as either an absolute rise ≥ 0.5 mg/dL (44 μ mol/L) serum creatinine (SCr) concentration and/or a relative increase of 25% in SCr concentration compared with baseline within 48 to 72 hours after contrast administration.⁴ However, this definition of CI-AKI is of a limited value when working with ambulatory procedures or short-term hospitalizations because it does not allow CI-AKI to be diagnosed within 2 days of nephrotoxic

* Address correspondence to: Karolina Stokfisz, Intensive Cardiac Therapy Clinic, Department of Invasive Cardiology and Electrocardiology, Medical University of Lodz, Pomorska 251, 92-213 Lodz, Poland.

E-mail address: stokfisz.karolina@gmail.com (K. Stokfisz).

agent application. In addition, hydration status may modulate SCr concentration and further complicate the diagnosis of CI-AKI. There is a need to identify more effective AKI biomarkers that can register kidney injury much earlier, ideally within a few hours of treatment or even identify subclinical AKI, where structural kidney injury is not related with increase in SCr concentration. Over the past decades, several novel biomarkers of AKI have been studied, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule 1, liver-type fatty acid-binding protein, interleukin 18, insulin-like growth factor-binding protein 7, calprotectin, urine angiotensinogen, or urine microRNA.^{5,6} Of these, the most investigated and most promising, is NGAL. NGAL is almost undetectable in either plasma or urine in patients with normal kidney function and its levels are predictive of AKI and AKI outcomes.⁶ In addition to identifying new biomarkers of AKI, there is also a pressing need to find novel preventive interventions. Among the most promising and intriguing nonpharmacological strategies is remote ischemic preconditioning (RIPC). This simple procedure, consisting of brief, nonlethal episodes of ischemia and reperfusion applied in a single tissue or organ, has been found to protect remote tissues or organs from subsequent injury. RIPC was first applied to the hearts of dogs by brief occlusion of the circumflex branch(es) followed by sustained occlusion of the left anterior descending coronary artery, resulting in reduction in infarct size from the left anterior descending coronary artery bed.⁷ Nowadays, RIPC is performed in a clinically feasible way using a series of systolic blood pressure cuff inflations and deflations, typically on the upper limb. RIPC has since been found to demonstrated protective potential for the heart, kidneys, liver, brain, retina, skeletal muscles, and intestine. Although the complex mechanisms underpinning RIPC are becoming better understood, the precise nature of its pathways of action remain unclear.⁸

The present prospective, randomized, sham-controlled clinical study evaluates whether RIPC reduces the incidence of CI-AKI based on SCr concentration and on serum NGAL level which has been proposed as a potential biomarker of kidney injury. In addition, the investigation examines the safety of RIPC and its clinical outcomes after elective coronary angiography (CA) followed by PCI.

Materials and Methods

Study design

This study was performed as a prospective, single-center, double-blind, randomized, sham-controlled trial. The protocol was prospectively approved and registered by the ethics committee of the Medical University of Lodz (approval No.: RNN/219/13/KE) and was conducted in accordance with the Helsinki Declaration and national law. The study was retrospectively registered in the service of the National Institutes of Health. All participants provided written, informed consent before enrollment to the study. The study design, together with data collection and analysis, was prepared solely by the authors.

Patients

The participants were recruited from the Intensive Cardiac Therapy Clinic, Medical University of Lodz, during the period March 2015 to June 2018, and were scheduled for elective CA with follow-up PCI. All eligible patients were older than age 18 years, and presented with stable angina pectoris. The exclusion criteria comprised any history of severe injuries and surgeries within 2 months before intervention, any history of cancer, acute inflammation during hospitalization, the presence of chronic autoimmune diseases, stage 4 or 5 chronic kidney disease (estimated glomerular

filtration rate [eGFR] <30 mL/min/1.73 m²) or peripheral vascular disease affecting the upper limbs, in addition, any patient currently undergoing hemodialysis was excluded. The patients were recruited during a preadmission consultation that included clinical evaluation and standardized lab tests.

Experimental protocol

After admission to the department, patients were randomly assigned in a 1:1 ratio to either a control group or an RIPC group by means of a computerized randomization table. The assigned procedure was performed by a blinded investigator not involved in either the CA or randomization process. In the RIPC group, a cuff was placed on the upper left arm and 4 cycles comprising a 5-minute inflation to 200 mm Hg followed by a 5-minute deflation were performed (contralaterally to subsequent further radial catheters placement). In the control group a deflated cuff was placed on the left arm for 40 minutes. The RIPC protocol began within 1 hour before CA, and was completed before the start of the procedure. The time between the end of the last inflation of the blood pressure cuff and the placement of the right radial PCI catheter was <25 minutes.

Pharmacology and CA procedures

In accordance with European Society of Cardiology guidelines, all patients received standard care for patients with stable coronary artery disease.⁹ In addition, according to Kidney Disease Improving Global Outcomes guidelines, all participants received routine care for patients with impaired renal function:¹⁰ hydration according to the clinical state by continuous intravenous saline infusion (0.9%)—12 hours before to 12 hours after CA—this was followed with PCI (1 mL/kg body weight/h), 2 doses of IV 600 mg N-acetylcysteine (ie, 2 hours before and 12 hours after PCI), discontinuation of nephrotoxic drugs (such as metformin, nonsteroidal anti-inflammatory drugs, or calcineurin inhibitors), and the lowest possible dose of contrast medium application. Agents that could interfere with RIPC, such as sulphonylurea, were transiently withdrawn 24 hours before the procedure. In all patients, CA with follow-up PCI was performed by right radial access according to standard clinical practice and using Iomeron 400 ([Bracco Imaging SpA, Milan, Italy] iomeperolum, mean [SD] osmolality 726 [34] mOsm/kg water at 37°C), a nonionic low-osmolar contrast medium. PCI was performed according to the current European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on Myocardial Revascularization.¹¹

Blood sampling and analysis

Three sets of venous blood samples were drawn for measurement of SCr and NGAL concentrations: once before CA, upon admission to the hospital, and then again at 3 and 48 hours after the procedure. NGAL concentration was measured using ELISA test (Human Lipocalin-2/NGAL ELISA; BioVendor, Brno, Czech Republic). Scr levels were measured with an enzymatic assay (Crea Creatinine OSR6578; Beckman Coulter, Brea, California). eGFR was calculated by the Modification of Diet in Renal Disease equation: $186 \times (\text{serum creatinine [mg/L]})^{-1.154} \times (\text{age [years]})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if of African descent})$. The risk of developing CI-AKI was evaluated using Mehran's risk score.¹²

End points

The primary end point of the study was the incidence of CI-AKI, which was defined as an absolute rise ≥ 0.5 mg/dL (44 $\mu\text{mol/L}$) in

SCr level and/or a relative increase of 25% compared with baseline, within 48 to 72 hours after contrast exposure.⁴ Secondary end points included a need for renal replacement therapy, cardiogenic shock, or death.

Statistical analysis

Statistical analysis was performed using STATISTICA 12.5 software (StatSoft Inc, Tulsa, Oklahoma). For all tests, $P=0.05$ was assumed as the level of statistical significance. Categorical variables were summarized as frequencies with percentage. The Shapiro-Wilk test was used to assess the normal distribution of variables, those without a normal distribution were tested using non-parametric statistics and expressed as medians quartile 25, quartile 75 with interquartile range (IQR). Correlations were assessed using Spearman rank correlation coefficient. Differences between continuous variables were compared using Mann-Whitney U test, whereas differences between categorical variables were compared using χ^2 test with Yates's correction for continuity. The Wilcoxon signed-rank test was used to compare repeated measurements. To assess the suitability of NGAL values for estimating the probability of CI-AKI, receiver operator characteristic curve analysis was performed. Based on risk reduction findings from a previous study examining the use of RIPC to reduce the incidence of AKI, it was calculated at least 50 patients were needed in each arm of the study (study power of 0.80 and $\alpha = 0.05$).¹³

Results

Study population characteristics and operative data

A total of 277 patients were assessed for eligibility; however, 176 were excluded before randomization based on the exclusion criteria or withdrawal of the consent. In total, 101 patients with median age 65 years; that is, 66 men (65.3%) and 35 women (34.7%), were enrolled and randomized to receive either RIPC ($n=50$) or sham RIPC ($n=51$), and were included in the primary analysis (Fig. 1). The participants were experiencing arterial hypertension (81.2%), dyslipidemia (73.3%), or diabetes mellitus (33.7%), and the vast majority had a history of heart attack (82.2%). In addition, 41.6% of patients reported being active smokers. The pre-PCI characteristics and medical history of the patients are presented in Tables 1 and 2. On admission the RIPC and control groups were found to demonstrate similar SCr concentrations (median = 87 $\mu\text{mol/L}$; IQR, 81–96 $\mu\text{mol/L}$ vs median = 88 $\mu\text{mol/L}$; IQR, 82–101 $\mu\text{mol/L}$; $P=0.54$), serum NGAL concentrations (median, 71.3 ng/mL; IQR, 55.8–86.8 ng/mL vs median = 80.6 ng/mL; IQR, 55.8–101.2 ng/mL; $P=0.27$) and eGFR levels (median = 81.6 mL/min/1.73 m²; IQR, 62.5–86.1 mL/min/1.73 m² vs median = 76.8 mL/min/1.73 m²; IQR, 59.7–85.0 mL/min/1.73 m²; $P=0.41$); however, the groups differed with regard to serum potassium concentration (median, 4.48 mmol/L; IQR, 4.16–4.64 mmol/L vs median = 4.29 mmol/L; IQR, 4.03–4.48 mmol/L; $P=0.037$), but these values were between normal limits in both groups. Although the patients in both the RIPC and control groups received similar volumes of contrast medium (median = 100 mL; IQR, 80–140 mL vs median = 110 mL; IQR, 90–140 mL; $P=0.15$), those in the RIPC group were exposed to higher doses of radiation during PCI (243 mGy; IQR, 134–339 mGy vs 338 mGy; IQR, 203–493 mGy; $P=0.0043$). The Mehran's score (probability of developing CI-AKI) was low or moderate in 48 patients from the RIPC group as well as 48 patients from the control group with a median score of 5. Cardiovascular medication use was similar in both groups (Table 2). The time between the end of the last inflation of the blood pressure cuff and contrast medium application was 25 minutes (± 5 minutes).

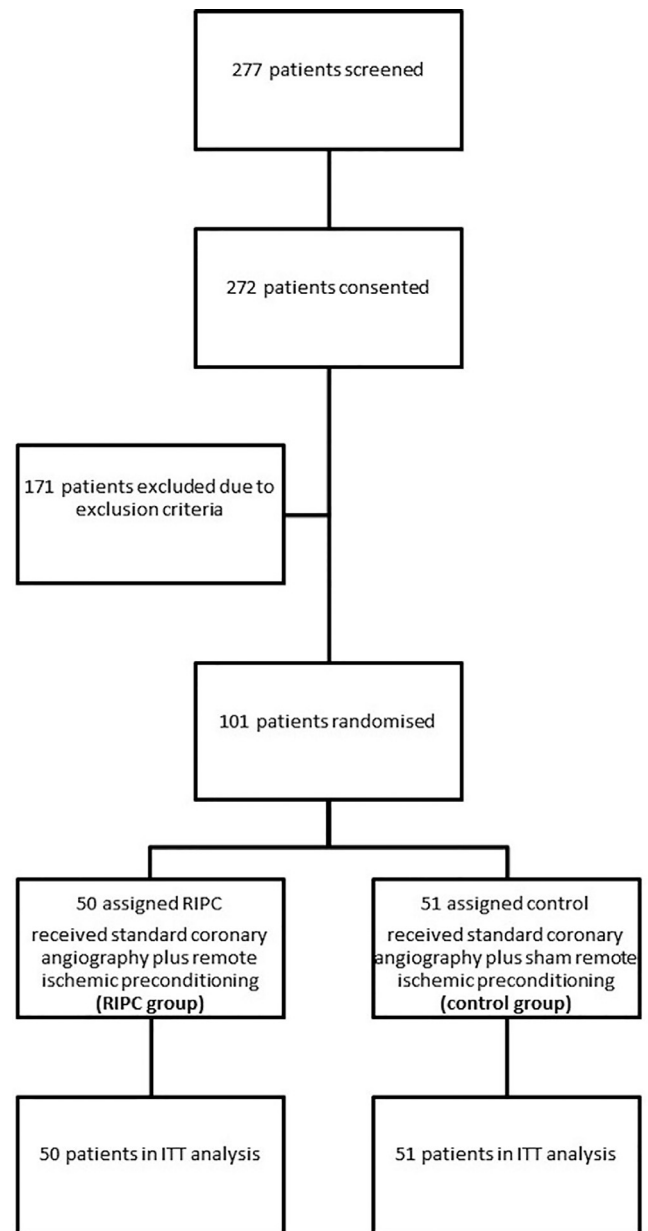


Fig. 1. Flowchart of patients in the study. ITT=intention-to-treat analysis; RIPC=remote ischemic preconditioning.

Primary outcomes

No significant differences in the postprocedure SCr levels were observed between the RIPC and control groups; however, significant differences were found for the postprocedure eGFR levels (median = 85 mL/min/1.73 m²; IQR, 68.3–93.1 mL/min/1.73 m² vs median = 78.5 mL/min/1.73 m²; IQR, 63.4–86.9 mL/min/1.73 m²; $P=0.041$). Despite this, the primary study end point (ie, CI-AKI) occurred in 5 patients (4.95%)—2 from the RIPC group (4%) and three from the control group (5.9%). However, this difference was not significant ($P=0.98$). In addition, the RIPC and control groups demonstrated similar serum NGAL concentrations measured 3 hours after PCI (median = 71.3 ng/mL; IQR, 62.0–96.1 ng/mL vs median = 80.6 ng/mL; IQR, 70.2–102.3 ng/mL; $P=0.206$) (see Table 1 and Fig. 2). All patients who developed CI-AKI in both the RIPC and control groups also presented an increase in serum NGAL. Receiver operator characteristic curve analysis of serum NGAL with

Table 1
Characteristics of the study population.

Characteristic	RIPC (n = 50)			Control (n = 51)			P value
	Median	Q25	Q75	Median	Q25	Q75	
Age, y	66	59	70	65	60	74	0.44
Body mass index	27.72	25.15	29.76	26.23	24.69	31.02	0.52
Contrast medium intake, mL	100	80	140	110	90	140	0.15
Radiation exposition, mGy	243	134	339	338	203	493	0.0043
WBC, 10 ³ /μL	7.05	6.00	8.38	7.00	5.60	8.10	0.60
RBC, mln/ μL	4.45	4.16	4.71	4.51	3.96	4.73	0.67
HGB, g/dL	13.55	12.4	14.7	13.5	12.5	14.8	0.98
MCV, fL	91	88	93	94	91	97	0.0003
HCT, %	40.7	37.8	43.5	41.1	37.9	44.6	0.31
PLT, 10 ³ /μL	241	194	273	216	174	277	0.12
Serum urea concentration, mmol/L	6.41	5.15	7.77	6.80	4.94	9.22	0.73
SCr on admission, μmol/L	87	81	96	88	82	101	0.54
SCr 48-72 h after PCI, μmol/L	79.5	70.0	91.0	85.0	77.0	94.0	0.086
CRP on admission, mg/L	2.0	0.8	3.8	2.6	1.1	5.1	0.37
Serum potassium concentration on admission, mmol/L	4.48	4.16	4.64	4.29	4.03	4.48	0.037
Serum NGAL concentration on admission, ng/mL	71.3	55.8	86.8	80.6	55.8	101.2	0.27
Serum NGAL concentration 3 h after PCI, ng/mL	71.3	62.0	96.1	80.6	70.2	102.3	0.206
eGFR on admission, mL/min/1.73 m ²	81.6	62.5	86.1	76.8	59.7	85.0	0.41
eGFR 48-72 h after PCI, mL/min/1.73 m ²	85.0	68.3	93.1	78.5	63.4	86.9	0.041
Mehran's CI-AKI risk score	4	2	8	5	2	8	0.603

CI-AKI=contrast medium-induced acute kidney injury; CRP=C-reactive protein; eGFR=estimated glomerular filtration rate; HCT=hematocrit; HGB=hemoglobin; Q25=quartile 25; Q75=quartile 75; RBC=red blood cells; RIPC=remote ischemic preconditioning; MCV=mean corpuscular volume; NGAL=neutrophil gelatinase-associated lipocalin; PLT=platelets; SCr=serum creatinine concentration; WBC=white blood cells.

Table 2
Characteristics of the medical history of the study population.

Characteristic	RIPC (n=50) n (%)	Control (n=51)	P value
History of heart attack	44 (88)	39 (77)	0.13
Atrial fibrillation	3 (6)	11 (22)	0.05
History of cardiac surgery	0 (0)	4 (8)	0.43
History of stroke/ transient ischemic attack	5 (10)	5 (10)	0.97
Current smoking	24 (48)	18 (35)	0.19
Hypertension	37 (74)	45 (88)	0.07
Chronic heart failure	18 (36)	12 (24)	0.17
Dyslipidemia	42 (84)	32 (63)	0.16
Diabetes mellitus	17 (34)	17 (33)	0.94
COPD	3 (6)	9 (18)	0.13
Chronic kidney disease	5 (10)	6 (12)	0.78
Use of diuretics	21 (42)	22 (43)	0.91
Use of ARB	0 (0)	3 (6)	0.24
Use of ACEI	49 (98)	46 (90)	0.21
Use of statins	49 (98)	51 (100)	0.99

ACEI=angiotensin-converting-enzyme inhibitors; ARB=angiotensin receptor blocker; COPD=chronic obstructive pulmonary disease; RIPC=remote ischemic preconditioning.

regard to the occurrence of CI-AKI yielded an area under the curve value of 0.97 (95% CI, 0.938–1.00; $P < 0.00$) and an optimal cut-off point value for serum NGAL of 118.9 ng/mL (sensitivity = 100%, specificity = 91%, and Youden's index = 0.92) (Fig. 3). In addition, serum NGAL on admission, as a factor of renal damage, was found to correlate with eGFR on admission as a parameter of impaired renal function (Fig. 4A); also NGAL measured 3 hours after PCI correlated with eGFR measured 48 hours after PCI (Fig. 4B).

Secondary Outcomes

No patient in either group needed renal replacement therapy. One patient in each group developed cardiogenic shock. No deaths were observed during hospitalization in either group. One patient from the RIPC group reported small petechiae on the skin of the preconditioned arm, distal to the upper-arm cuff placement.

Discussion

CI-AKI is known to be a serious complication of contrast medium exposure and PCI. It has been shown to be an indepen-

dent predictor of 1-year mortality in patients with coronary artery disease.¹² Despite this, only a few prophylactic strategies for CI-AKI are known. With this in mind, RIPC appears to represent a simple and inexpensive way of protecting tissues against ischemic damage, including kidney protection.

The effect of RIPC on kidney function differs between studies. Its effectiveness was first demonstrated by Er et al¹³ in the Renal Protection Trial, which indicated that RIPC induced by intermittent upper-arm ischemia before an elective CA, dramatically reduces the incidence of contrast-induced nephropathy in patients with chronic kidney disease and high risk of developing CI-AKI. In their trial, CI-AKI was observed in 40% of the control group and 12% in RIPC group was attributed to the inclusion of a high-risk population in the study. A similar study by Valappil et al¹⁴ examined whether RIPC could offer protection against CI-AKI in high-risk patients undergoing elective PCI with >100 mL contrast medium administration. Although the patients who received RIPC demonstrated a lower incidence of CI-AKI compared with the control group, this difference was not significant (22% vs 36%; $P = .123$). However, RIPC significantly reduced serum creati-

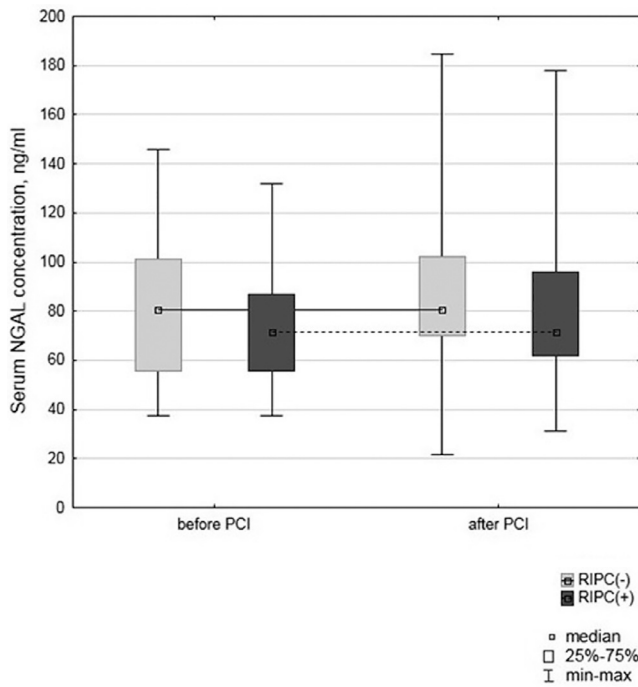


Fig. 2. Serum neutrophil gelatinase-associated lipocalin (NGAL) concentration changes (difference between value at baseline and 3 hours after percutaneous coronary intervention [PCI]) in remote ischemic preconditioning (RIPC)(+) and RIPC(-) patients.

nine level at 24 hours, 48 hours, 2 weeks, and 6 weeks after PCI (respectively: $P=0.013$, $P=0.015$, $P=0.003$, and $P=0.003$) and significantly improved the postprocedure eGFR values (respectively: $P=0.026$, $P=0.044$, $P=0.015$, and $P=0.011$). These findings correspond with those of recent studies that recruited only patients with type 2 diabetes and pre-existing chronic kidney disease (eGFR <60 mL/min/1.73 m²) undergoing elective PCI.¹⁵ In the present study, RIPC before PCI was not effective in completely preventing CI-AKI, which occurred in 13.7% of patients in both the control and RIPC groups. Furthermore, no significant differences in postprocedural creatinine and NGAL levels were observed between groups. Similar results were obtained by Menting et al¹⁶ in patients under-

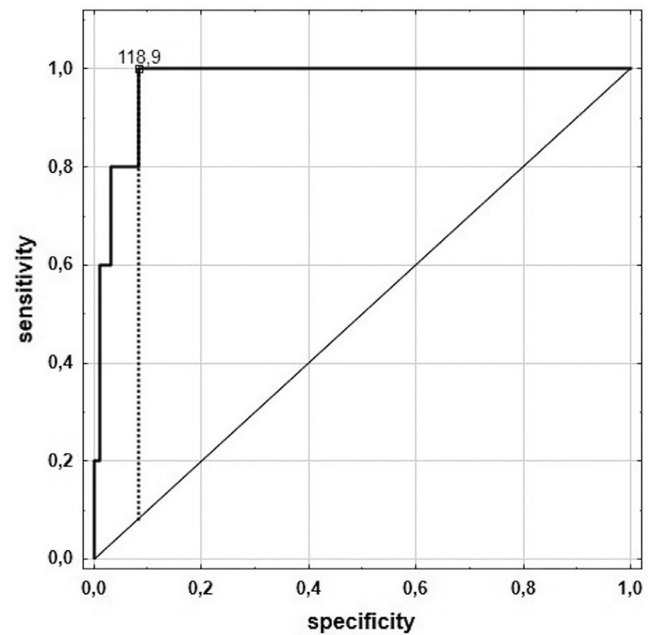


Fig. 3. Receiver operating characteristic curve and the optimal cutoff point of serum neutrophil gelatinase-associated lipocalin concentration 3 hours after percutaneous coronary intervention (118.9 ng/mL) with respect to the occurrence of contrast-induced acute kidney injury (area under curve = 0.97; sensitivity = 100%, specificity = 91%, and Youden's index = 0.92).

going an interventional or diagnostic radiological procedures with use of >100 mL intravascular contrast medium. In this case, RIPC induced by intermittent upper-arm ischemia before the contrast were administered did not reduce occurrence of CI-AKI, measured by changed in SCr level from baseline to 48 to 72 hours after contrast administration. However, it was found that the subgroup of patients at high or very high risk of developing CI-AKI might benefit from RIPC as an adjunctive preventive measure.

Contrasting results were obtained in a recently published multicenter clinical trial based on 223 patients with moderate renal insufficiency who were scheduled for angiography: either elective revascularization procedure or acute coronary syndrome without ST-segment elevation in a clinically stable condition.¹⁷ A signifi-

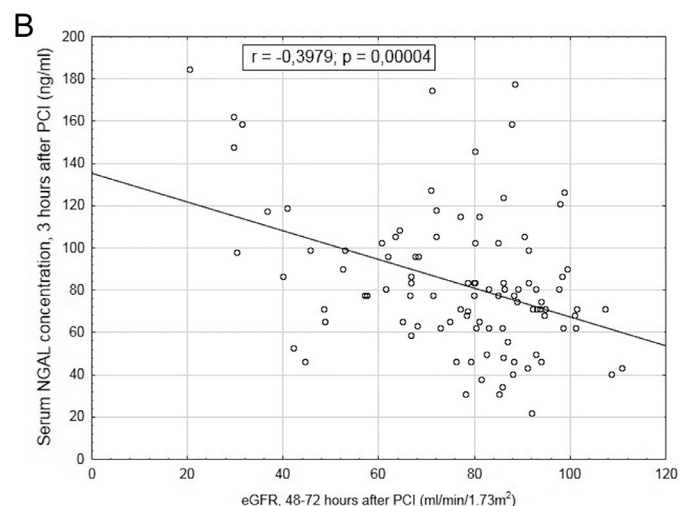
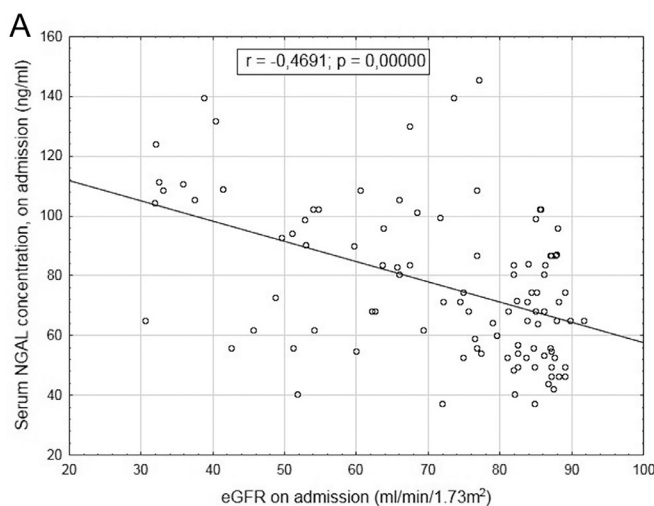


Fig. 4. Serum neutrophil gelatinase-associated lipocalin (NGAL) concentration on admission, as a factor of renal damage, correlates with estimated glomerular filtration rate (eGFR) on admission, as a parameter of impaired renal function (A) and NGAL level 3 hours after percutaneous coronary intervention (PCI) also correlates with eGFR 48 to 72 hours after PCI (B).

cant reduction in the incidence of CI-AKI was observed in the RIPC group compared with controls (24.1% vs 12.1%; $P=0.025$). Although these findings look promising, the recruited cohort appears highly heterogeneous with regard to the clinical indication for PCI, including patients with non-ST-elevation myocardial infarction, silent ischemia, stable angina, and unstable angina. In addition, little information is given about the hydration and preparation protocols before PCI. A similar randomized study was performed on a group of 51 patients with coronary heart disease and eGFR below 80 ml/min/1.73m², undergoing CA (with following stent implantation in 25 patients). RIPC was found to demonstrate a nephroprotective effect and considerably prevented CI-AKI in patients with a low to moderate risk of developing CI-AKI: the incidence was 3.8% of cases, compared with 28% of cases in the control group.¹⁸ These findings correspond with those from a recent study of 161 patients with acute coronary syndrome undergoing PCI, which indicated that RIPC can effectively reduce the incidence of CI-AKI and protect renal function. The patients from the RIPC group demonstrated a significantly lower postprocedural incidence of CI-AKI than controls (10% vs 26.3%; $P < 0.05$) as well as SCr, cystatin C, and blood NGAL levels after PCI.¹⁹

In the present study, RIPC performed before elective CA with follow-up PCI showed no effect in preventing CI-AKI. Although 2 cases of CI-AKI were observed in the RIPC group compared with 3 cases in the control group, this difference was not statistically significant (4% vs 5.9%; $P=0.98$). Furthermore, the incidence of CI-AKI observed in the present study is lower than in other comparable publications. This may be due to the fact that the enrolled patients were at low to moderate risk for occurrence of CI-AKI, and that the study was designed according to a strict preparation protocol, including pre- and postintravenous hydration. Furthermore, most patients were taking angiotensin-converting-enzyme inhibitors and statins, which are believed to prevent renal function impairment. However, among the patients who developed CI-AKI, a positive correlation was observed between elevated serum NGAL concentration 3 hours after PCI and increased SCr concentration 48 to 72 hours after PCI.

CI-AKI is believed to have composite pathophysiology. The underlying mechanisms are believed to be vasoconstriction, cellular hypoxia, and direct toxicity of contrast media to renal tubular cells, which together lead to acute tubular necrosis.^{20,21} Although various criteria are used to define CI-AKI, all current definitions rely on SCr levels as a gold standard. Despite being the most widely used marker of renal function, its normal level is influenced by age, gender, muscle mass, comorbidities, hydration status, nutritional status, and medications. Furthermore, creatinine can only be used to assess glomerular filtration and functional changes: it does not recognize kidney damage occurring without functional change. Additionally, a number of acute and chronic kidney conditions associated with worse outcomes, including mortality, need for renal replacement therapy, and greater length of stay, can exist with no increase in SCr level.^{22,23} Moreover, SCr-based definition of AKI is highly limited because it provides no information on its etiology, prognosis, molecular pathways, or responses to treatment. Furthermore, it must be remembered that kidney injury can also occur without a rise in SCr concentration and that elevations in SCr concentration may not always represent kidney injury. These disjunctions arguably constitute the greatest limitations to the use of current, SCr-based AKI and CI-AKI definitions and reinforce the need to discover novel biomarkers, tests, or algorithms to improve AKI detection.²⁴ Although NGAL, a marker of tubular injury, may be used to diagnose CI-AKI much more quickly and without the need for changes in creatinine, its level can also be influenced by other factors, such as inflammation, and as such, NGAL may not always be predictive of AKI. Demitras et al²⁵ suggest that NGAL is not a stable predictive biomarker for AKI in patients after cardiac bypass

surgery: NGAL levels were only significantly different at 6 hours after surgery ($P=0.045$) and these levels were not correlated with serum creatinine levels. However, other studies have found NGAL to be of great value in predicting AKI following cardiac surgery in children or critically ill patients.^{26–28}

Although NGAL was for several years considered the troponin of the kidney, the complex mechanisms underlying CI-AKI, and the fact that NGAL is produced by a number of tissues, question whether NGAL is indeed a perfect marker for detecting AKI.

Limitations of the study

Our study has some limitations. Firstly, it is a single-center trial with a relatively small sample size. In addition we were unable to observe a sufficient number of events, such as CI-AKI, mortality, and the need for dialysis as end points. Knowing that SCr level peaks between 48 and 72 hours after contrast medium exposure, it would have been optimal to measure SCr at both 48 and 72 hours, but in practice, most of our patients were discharged within 48 hours after PCI. Further studies are needed to redefine the clinical utility of RIPC in current practice and to obtain evidence of its potential benefits. Furthermore, remains the matter for debate and further studies the choice of the most optimal and sensitive biomarker of renal function impairment.

Conclusions

CI-AKI is a complication of elective PCI that is rarely observed in patients properly prepared for the procedure and at low or moderate risk of developing CI-AKI. Moreover, the use of RIPC before elective CA with follow-up PCI, was not found to prevent CI-AKI in this group of patients when used as an adjunct to standard preventive protocols. This suggests that the incidence of CI-AKI can be decreased by more careful preparation rather than by the use RIPC. Furthermore, serum NGAL level as a factor of renal damage may be predictive for the occurrence of CI-AKI in patients undergoing elective PCI.

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Conflicts of Interest: The authors have indicated that they have no conflicts of interest regarding the content of this article.

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