Clinical Hemorheology and Microcirculation xx (20xx) x–xx
DOI 10.3233/CH-16184
IOS Press

Nephroprotective effects of remote ischemic preconditioning in coronary angiography

Naufal Zagidullin*, Alina Dunayeva, Alexander Gilmanov, Shamil Zagidullin and Valentin Pavlov

Abstract.
BACKGROUND: Contrast-induced nephropathy (CIN) is a formidable side effect of iodinated contrast medium use in subjects undergoing coronary angiogram (CAG). Remote ischemic preconditioning (RIPC) may reduce the risk of CIN.
AIM: The aim of the study was to investigate the nephroprotective effects of RIPC in coronary heart disease (CHD) in patients, undergoing CAG, with mild to moderate lowered estimated glomerular filtration rate (eGFR).
MATERIALS: In the randomized, blinded, sham RIPC (sRIPC) controlled study 51 patients with CHD and GFR less than 80 mL/min/m^2, undergoing CAG, were investigated. The patients were randomized for RIPC ($n = 26$, 60.5 ± 2.0 years) or sRIPC ($n = 25$, 62.96 ± 1.7). RIPC was performed before the CAG by means of 3–5-minute cycle cuff pumped on the upper arm + 50 mm Hg above the systolic blood pressure (BP), while in sRIPC it corresponded to diastolic BP. The primary endpoint was the development of CIN and secondary – change of biomarkers (creatinine, urea, neutrophil gelatinase-associated lipocalin (NGAL), cystatin-C).
RESULTS: In RIPC group, CIN occurred in 28% of cases, while in sRIPC –3.8%. All investigated markers increased in sRIPC and declined in RIPC; the difference was significant in markers between the groups before and after CAG.
CONCLUSIONS: RIPC proved nephroprotective effect in prevention of contrast-induced nephropathy in CHD subjects with mild to moderate lowered eGFR.

Keywords: CIN, RIPC, cystatin, NGAL

Contrast induced nephropathy (CIN) is a lowering of glomerular filtration rate (GFR) after the administration of iodinated contrast-agent. In the most of cases, after intravascular injection of contrast agent, the kidney tissue is impaired as CIN develops, though in the majority of cases, no obvious clinical manifestations are observed [8, 29]. Up to 8% of patients with CIN require hemodialysis, and 35% of them die [21, 23]. In a prospective trail in 294 patients the rate of mid-term (1 year) adverse effects was 2 times higher in patients with CIN than without CIN [35]. Serum creatinine usually rises during the first 24–48 hours after the injection of contrast agent, reaches a peak on 3–4 days and returns to baseline within 3 weeks. CIN is defined as a relative ($\geq$25%) and/or an absolute ($\geq$44 mmol/l) increase in serum creatinine in comparison with the baseline [33]. Functionally CIN is considered as an acute kidney injury (AKI) that results in certain complications including death [31], so early diagnostics and its prevention are of great clinical relevance. Kidney-specific markers can potentially predict development or worsening of chronic kidney disease (CKD) and hemodialysis start in the long term period, and among them there are cystatin C, or Neutrophil gelatinase-associated lipocalin (NGAL). Multivariate logistic regression analysis revealed eight independent factors which were associated with CIN development and highlighted the limited baseline renal function as the strongest predictor [23, 24].

Various methods of CIN prevention are studied, showing effective methods like intravenous hydration with saline solutions and questionable results of using vasoactive drugs or acetylcysteine [3, 38, 44]. Nephroprotective effect of classic ischemic preconditioning (IPC) and especially remote ischemic

*Corresponding author: Naufal Zagidullin, E-mail: znaufal@mail.ru.

preconditioning (RIPC) has been widely studied recently. RIPC is performed, for example, by means of intermittent inflation and deflation of the arm with the help of a blood pressure cuff [1, 34]. In animals, both IPC and RIPC effectively reduced renal damage after ischemia reperfusion injury, with higher efficacy in the late window of protection [40]. Recent data and metaanalysis supports nephroprotective effect of RIPC in vascular but not surgical interventions mostly in high-risk patients [10, 22, 28, 39, 41, 43]. However, RIPC efficacy in patients with low-moderate GFR decline patients seems to be controversial.

The aim of the study was to investigate nephroprotective effects of remote ischemic preconditioning to prevent contrast-induced nephropathy in patients, undergoing coronary angiography with a lower-moderate glomerular filtration rate decline.

1. Materials

In this prospective, randomized, blinded, and active (sham) controlled trial, subjects with CHD, who underwent routine CAG were enrolled. Patients had impaired renal function with low-moderate decline of kidney excretory function with estimated glomerular filtration rate (eGFR) $\leq$80 mL/min/1,73 m^2. In 90% of patients, GFR was within 45–70 ml/min/1,73 m^2, which corresponds to the C2-C3a stages of chronic kidney failure. All patients signed informed consent. 6–12 hours before before contrast use, all patients received body weight adapted intravenous 0.9% NaCI solution. "Omnipaque" contrast was used in all the cases. The day before CAG all patients underwent a biochemical blood test to determine baseline levels of creatinine, urine and cystatin-C and NGAL. Follow-up testing was performed on day 2.

Inclusion criteria for the study:

- written informed consent,
- eGFR <80 ml/min/1,73m^2,
- non-hemodialysis patients,
- planned CAG.

Exclusion criteria:

- acute coronary syndrome,
- acute kidney injury/decompensation of chronic kidney disease.

The primary endpoints was the development of CIN, which was defined as an absolute (44 mmol/L) or relative increase in creatinine (by 25%), and secondary – the increase/decrease in the kidney-sensitive biomarkers concentration including the comparison of the values change between the groups. Secondary endpoints included death, myocardial infarction, acute coronary syndrome and need for hemodialysis during index hospitalization.

Ischemic preconditioning was accomplished within one hour before CAG by means of a 5-minutes cycle cuff inflation on the upper arm with blood pressure cuff and with a 5-minutes rest between the cycles (Fig. 1). By using random number generator (at www.randomizer.org) patients were randomized in 2 groups with probability 0.5 for RIPC and sham RIPC (sRIPC). In RIPC arm the cuff pressure was inflated up to systolic blood press (SBP) plus 50 mm Hg, while in sRIPC – the cuff was inflated to diastolic (DBP) for blinding purposes.

51 patients (61.52 $\pm$ 1.3 years) with CHD were enrolled in the study. Study group characteristics and baseline data are presented in Tables 1 and 2. In 22 (43%) impairments of kidney function was newly diagnosed, in 29 (57%) subjects had a known chronic renal failure. Reasons for CKD and kidney failure were as far as detectable, glomerulonephritis, pyelonephritis, diabetic nephropathy, one

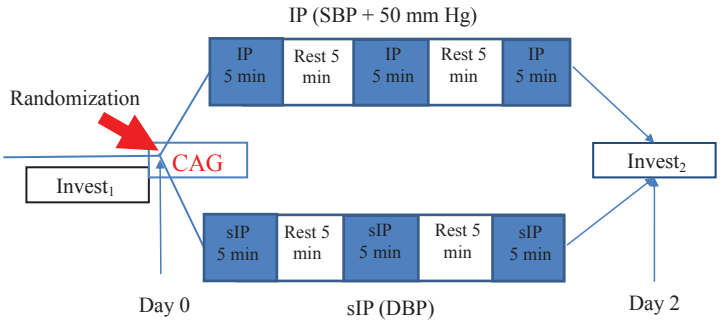

Fig. 1. Study design (RIPC – Ischemic preconditioning. sRIPC – sham RIPC. "Invest" – creatinine. urea. lipocalin-2 and cystatin-C estimation).

Table 1
Characteristics of the study group

Parameter	Value
Cardiovascular diseases	
Arterial hypertension, n, (%)	11(21.6)
Atrial fibrillation, n, (%)	6 (11.8)
Stroke in anamnesis, n, (%)	10 (19.6)
Renal diseases	
Diabetic nephropathy, n, (%)	9 (17.6)
Glomerulonephritis, n, (%)	2 (3.9)
Pyelonephritis, n, (%)	9 (17.6)

kidney disease, polycystic kidney disease, aortic and renal artery aneurysm, uratosis, and systemic rheumatoid arthritis. By CAG, right coronary artery (RCA) stenosis was found more often than left anterior descending artery (LAD) and left circumflex artery (LCX); in more than half of all cases two or more arteries were occluded. 25 (49%) patients underwent stent implantation.

Ethical clearance for the study was approved by Ethics Committee of Bashkir state Medical University (Ufa, Russian Federation) in conformity with ethical guidelines of the 1975 Declaration of Helsinki and all the participants gave written inform consent. Statistical analysis was performed with the help of the paired Student *T*-Test. $P < 0.05$ was considered as significant.

2. Results

Patients were randomized into RIPC ($n = 26$) and sRIPC ($n = 25$) groups. Basic characteristics of the groups are compared in Table 2 – no significant difference was found between the groups in presented parameters. In RIPC group baseline creatinine level was higher than in sRIPC (124.8 ± 11.04 vs. 106.9 ± 10.0 mmol/l, $p = 0.064$), respectively eGFR was higher in sRIPC group (62.24 ± 5.3 vs. 71.88 ± 6.1 ml/min/1.73 m^2, $p = 0.061$). There was also a trend for older age in sham patients compared to the RIPC group (60.5 ± 1.95 vs. 62.96 ± 1.72, $p = 0.078$). RCA and LCA were occluded more often in RIPC group, while RCA stenosis was more frequent in sRIPC group. Injected contrast volume in RIPC group was slightly higher than in sRIPC (155.8 ± 16.9 ml vs. 148.3 ± 16.7, respectively, $p = 0.071$). The groups were also comparable according to smoking, diabetes mellitus and history of myocardial infarction and cardiovascular medication (Table 3).

Table 2
Comparison of RIPC/sRIPC groups

	All ($n=51$)	RIPC ($n=26$)	sRIPC ($n=25$)
Age, years	61.52 ± 1.3	60.5 ± 1.95	62.96 ± 1.72
Gender, m/f	43/8	21/5	22/3
Height, cm	170.8 ± 1.13	169.6 ± 1.8	171.96 ± 1.3
Weight, kg	87.2 ± 2.46	84.6 ± 3.0	89.7 ± 3.7
BMI, kg/m^2	29.8 ± 0.73	29.4 ± 0.89	30.2 ± 1.13
Coronary stenosis, (%)			
LAD	27 (52.9)	16 (61.5)	11 (44.0)
RCX	24 (47.1)	13 (50.0)	11 (44.0)
RCA	33 (64.7)	14 (53.8)	19 (76.0)
Previous myocardial infarction, (%)	17 (33.0)	10 (38.5)	7 (28.0)
Smoking, (%)	25 (49)	12 (46.2)	13 (52.0)
Diabetes mellitus II, (%)	16 (31.4)	8 (30.8)	8 (32.0)
Previous coronary intervention, (%)	25 (49.0)	12 (46.2)	13 (52.0)
Contrast volume, ml	153.2 ± 10.9	155.8 ± 16.9	148.3 ± 16.7
Hospital stay, days	5.9 ± 0.92	5.84 ± 1.3	5.94 ± 0.6

Table 3
Baseline cardiovascular medication taken by the patients

Cardiovascular medication	RIPC ($n=26$)	sRIPC ($n=25$)
Beta-blocker, n (%)	24 (92.3)	24 (96,0)
Angiotensin-converting enzyme inhibitor, n (%)	20 (76.9)	18 (72.0)
Angiotensin-receptor blocker, n (%)	2 (7.7)	4 (16.0)
Calcium channel blocker, n (%)	8 (30.8)	2 (8.0)
Thiazide diuretics, n (%)	12 (46.1)	8 (32.0)
Loop diuretics, n (%)	2 (7.6)	1 (4.0)
Mineralcorticoids receptor antagonists, n (%)	4 (3.8)	3 (12.0)

Mehran score was used to calculate the risk of CIN in which the number of rate of CIN increases exponentially with increasing risk score ($p<0.0001$) [24]. According to the Mehran score, risk was estimated as moderate or low in the majority of patients (Table 4). In sRIPC group more patients were at low risk spectrum than in RIPC group (16 vs. 11, respectively), while in the RIPC group more patients had moderate risk (4 vs. 10).

During hospitalization (5–7 days after CAG) no deaths, coronary restenosis or need for hemodialysis occurred. Two days after CAG the blood (serum) test for creatinine, urea, NGAL and cystatin-C was accomplished (Table 5). In RIPC group only in one case (3.8%) creatinine increased from 69 to 120 mmol/l and the CIN, according to criteria [33], was diagnosed. In sRIPC group, CIN was diagnosed in 7 subjects (28%), in 4 subjects by increased creatinine more than 44 mmol/l, and in 6 subjects by more than 25% from baseline. In one case, serum creatinine increased from 29 mmol/l to 285 mmol/l. The level of creatinine in RIPC group tended to decrease from 124.8 ± 11.45 to 121.3 ± 9.67 mmol/l ($p=0.089$), but in sRIPC group, on the contrary, the decline was evident (from 106.9 ± 10.02 to 129.37 ± 11.5, $p=0.047$). The difference between the changes of markers concentration before and after CAG in two arms was also significant ($p=0.038$). Creatinine, urea in RIPC group tended to decrease (from 9.65 ± 1.22 to 8.29 ± 0.97 mmol/l, $p=0.087$), but in sRIPC group –

Table 4
Mehran risk score in patients, undergoing CAG

Score	RIPC ($n=26$)	sRIPC ($n=25$)
≤5 points, n	11	16
6–10 points, n	10	4
11–15 points, n	4	3
≥16 points, n	1	2

Table 5
Changes in creatinine and urea level after coronary angiography

	Creatinine, mmol/l		Urea, mmol/l	
	RIPC	sRIPC	RIPC	sRIPC
Baseline	124.8 ± 11.45	106.91 ± 10.02	9.65 ± 1.22	7.43 ± 0.63
Follow-up	121.3 ± 9.67	129.37 ± 11.5† ($p=0.047$)	8.29 ± 0.97	8.47 ± 0.76 ($p=0.067$)
			8.29 ± 0.97	
Difference, Δ	3.5 ± 5.83	-22.46 ± 0.86* ($p=0.038$)	1.31 ± 0.47	-1.04 ± 0.49** ($p=0.007$)

P.s.: †$p<0.05$ when compared before and after coronary angiography; *$p<0.05$; **$p<0.01$ - difference between RIPC and sRIPC groups.

to upraise (from 7.43 ± 0.63 to 8.47 ± 0.76 mmol/l, $p=0.093$). The comparison of parameter changes showed prominent difference between the groups (1.04 ± 0.49 mmol/l, $p=0.007$).

As previously demonstrated, NGAL and cystatin-C are more sensitive biomarkers than creatinine and urea [6, 27]. After CAG in RIPC group the raise of cystatin-C in 19 cases from 25 (76%) and of NGAL in 12 cases (48%) was observed (Table 6). In one case (4%) cystatin-C level did not change and in 5 cases (20%) – increased. In 3 patients (11.5%) cystatin-C value exceeded 25% as compared to baseline, and NGAL – in 7 (27%). By now, some studies interpret increase of cystatin-C by 10% from the baseline as CIN. In such instance, CIN occurred in 3 cases (11.5%) in RIPC group, while in sRIPC – in 9 (36%). In sRIPC group cystatin-C decreased in 14 cases (53.8%), and NGAL – in 16 cases from 26 (61.5%). The level of cystatin-C in RIPC group significantly decreased from 4.17 ± 0.54 to 3.20 ± 0.32 mg/ml ($p=0.041$), and in sRIPC it showed the tendency to increase from 3.2 ± 0.32 to 3.83 ± 0.51 ($p=0.073$). Moreover, the comparison of changes in the markers between the groups showed the difference ($p=0.018$). The dynamics of NGAL changed accordingly, though no significant difference of the biomarker in RIPC and sRIPC groups separately before and after CAG was found ($p=0.078$ and 0.057, respectively); the significance of differences was obtained ($p=0.0024$) when the changes were compared against each other.

3. Discussion

Iodinated radiographic contrast media are widely used for the vascular diagnostics and intervention. Contrast-induced nephropathy is a serious complication that increases the risk of death, myocardial infarction and stroke both in short- and long-term period; it can also contribute to the development of chronic renal failure and transition to hemodialysis in the long-term period [12, 23]. In particular, the Cardiac Angiography in Renally Impaired Patients study [35], conducted on a large cohort of patients

Table 6
Changes in cystatin-C and NGAL values in RIPC and sRIPC groups before and after CAG

	Cystatin-C, mg/ml		NGAL, pmol/dl	
	RIPC	sRIPC	RIPC	sRIPC
Baseline	4.17 ± 0.54	3.2 ± 0.32	15.25 ± 4.07	8.30 ± 2.7
Follow-up	$3.2 \pm 0.32^{\dagger}$	3.83 ± 0.51	12.87 ± 3.01	$13.24 \pm 3.5^{\dagger}$
	($p = 0.041$)	($p = 0.073$)	($p = 0.078$)	($p = 0.057$)
Difference, Δ	0.97 ± 0.49	$-0.62 \pm 0.39^{*}$	2.38 ± 2.02	$-4.9 \pm 0.38^{**}$
	0.97 ± 0.49	($p = 0.018$)		($p = 0.0024$)

Note: $^{\dagger}p < 0.05$ when compared before and after CAG; $^{*}P < 0.05$ $^{***}p < 0.001$ significance of difference between the RIPC/sRIPC groups.

with low GFR, showed that the incidence of cardiovascular endpoints doubles in the patients who developed CIN. In the registry of more than 9.000 patients post-PCI renal failure due to CIN was associated with 4.31-fold hazard of mortality and a 1.77-fold – after adjustment to known predictors of mortality ($p < 0.0001$) [11]. CIN was reported in 4–20% of patients after use contract media in angiography [23, 26, 35] and one of the most important risk factor for CIN is a baseline GFR < 60 m/min/1.73m^2.

In spite of the intensive investigation of CIN *in vitro* and *in vivo*, the reason for CIN is still uncertain. The injection of iodine contrast leads to damage of both erythrocytes and endothelial cells – they become echinocystic in 3 min after the application [36]. It affects also the function of erythrocytes – a decline of velocity of erythrocytes in nailfold capillaries was observed [5]. Taking in account the fact that about 25% of blood from the heart enters the kidney, erythrocytes dysfunction leads to prominent kidney cortex and medulla hypoxia, effecting probably mostly sensitive TAL (thick ascending tubular limb) cells [5]. Kidney oxygenation decline leads to depletion of energy stores, collapse of electrolyte gradient, disruption of actin skeleton, activation of phospholipases and even changes of gene expression [4, 5]. One of the leading mechanisms of CIN seems to be the formation of free radicals and reactive oxygen species (ROS) that lead to direct cytotoxicity and renal tubular and glomerular apoptosis which in term, intensify renal parenchymal hypoxia by endothelial dysfunction and dysregulation of tubular transport [16, 30].

There are two main pathways to prevent CIN: optimal hydration with sodium bicarbonate proved to be superior to hydration with normal saline and application of less amount of contrast medium. Large-scale randomized clinical trials failed to prove the preventive power of N-acetylcysteine and other chemical substances against CIN. Ischemic preconditioning has proved to be an effective method of preventing cardiovascular events in acute coronary syndrome, cardiovascular surgery, organ transplantation, etc. In CHD patients undergoing CAG, AKI may develop, which makes it a potential target for RIPC [13]. RIPC is thought to activate several pathways, including systemic anti-inflammatory, neuronal, and humoral signaling pathways; it reduces the release of injury biomarkers and maintains organ function [13, 14, 39, 42]. The vascular protection effects may be mediated through the release of damage-associated molecular patterns, high-mobility group protein B1 that interact with pattern recognition receptors on renal tubular epithelial cells [20]. That is why it was hypothesized that these actions may counteract above-mentioned pathways in contrast-induced nephropathy.

In randomized, controlled, blinded, imitation-controlled study the nephroprotective effect of RIPC in CHD patients with low-moderate CIN risk was investigated. As a result, 26 patients were randomized for RIPC and 25 for sRIPC. It is considered, that CIN develops in 9% of cases when iodinated contrast agent is injected [18], and in 20–30% among those with a baseline creatinine >2 mg/dl [2]. In our study, CIN developed in 28% of cases in sRIPC group, and in RIPC – only in 3.8%. The results

approximately correspond to the data by Er et al. [9] who indicated 28% CIN reduction after RIPC, given the fact that in the above-referred study the GFR baseline threshold for inclusion in the study was higher –≤60 mL/min/1,73 m^2 in contrast to the present one (≤80 mL/min/1,73m^2). Menting et al. [25] not noted the effect of RIPC on CIN occurrence in patients with moderate CIN risk, but in the high risk ones (≥11 points according to the Mehran score). Our data corresponds also with study of Igarashi et al. [17], who used more RIPC cycles (4 versus 3 in our study) and estimated another kidney-sensitive marker – liver-type fatty acid-binding protein (L-FABR) in patients with moderate CKD. As a result, CIN incidence decreased from 26.9% to 7.7% in compare to sham and L-FABR declined ($p = 0{,}003$), due to, as proposed by the authors, oxidative stress modification.

As it is known, NGAL and cystatin-C have higher sensitivity and specificity of the predictive power in identification of AKI compared to creatinine and urea [7, 19]. For instance, creatinine increases in case of 50% of kidney tissue damage [15]. NGAL has proved as an early, sensitive, specific and predictive biomarker of AKI after contrast agent administration [32]. When the concentration of cystatin-C increases by 10%, it also shows itself to be a CIN marker which is 100% sensitive and 30% specificity [27, 32]. If in RIPC group there was a downward trend for all the four biomarkers after CAG, in the sRIPC group – they tended to increase, for creatinine and urea was significant. The comparison of changes between the sRIPC/RIPC groups before/after CAG was also significant.

Thus in the study RIPC showed nephroprotective effect and considerably prevented CIN in patients with CHD and low-moderate GFR decline.

This study has certain limitations. In particular, the sampling size is rather small; patients widely varied in kidney failure and GFR degree. However, the comparison of the obtained data with the findings of other studies allows us to suggest that the achieved results are reliable.

Acknowledgments

Scientific research has been supported by the grant of the President of the Russian Federation for young PhD MD-16.7395 and Russian Humanitarian Scientific Foundation N 15-36-01255/15. No conflict of interests is declared.

References

[1] A. Aimo, C. Borrelli, A. Giannoni, et al., Cardioprotection by remote ischemic conditioning: Mechanisms and clinical evidences, *World J Cardiol* **7**(10) (2015), 621–632.
[2] A.S. Berns, Nephrotoxicity of contrast media, *Kidney Int* **36** (1989), 730–740.
[3] S.S. Brar, A.Y. Shen, M.B. Jorgensen, et al., Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: A randomized trial, *JAMA* **300**(9) (2008), 1038–1046.
[4] M. Brezis and F.H. Epstein, Cellular mechanisms of acute ischemic injury in the kidney, *Annu Rev Med* **44** (1993), 27–37.
[5] M. Brezis and S. Rosen, Hypoxia of the renal medulla - its implications for disease, *N Engl J Med* **332** (1995), 647–655.
[6] C.L. Dent, Q. Ma, S. Dastrala, M Bennett, et al., Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: A prospective uncontrolled cohort study, *Crit Care* **11** (2007), R127.
[7] V.R. Dharnidharka, C. Kwon and G. Stevens, Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis, *Am J Kidney Dis* **40** (2002), 221–226.
[8] A.R. Dunaeva, A.S. Sherbakova, T.N. Haphyzov and S.Z. Zagidullin, Contrast-induced nephropathy in coronarography, *Prakticheskaya Medizina* **3** (2014), 39–44.
[9] F. Er, A.M. Nia, H. Dopp, et al., Randomized Pilot RenPro Trial (Renal Protection Trial). Ischemic Preconditioning for Prevention of Contrast Medium-Induced Nephropathy, *Circulation* **126** (2012), 296–303.

[10] A. Gholoobi, S.M. Sajjadi and M.S. Mohammadzadeh, The impact of remote Ischemic pre-conditioning on contrast-induced nephropathy in patients undergoing coronary angiography and angioplasty: A double-blind randomized clinical trial, *Electronic Physician* **7**(8) (2015), 1557–1565.
[11] R. Gupta, H.S. Gurm, D.L. Bhatt, et al., Renal failure after percutaneous coronary intervention is associated with high mortality, *Cathter Cardiovasc Interv* **64** (2005), 442–448.
[12] K.J. Harjai, A. Raizada, C. Shenoy, et al., A comparison of contemporary definitions of contrast nephropathy in patients undergoing percutaneous coronary intervention and a proposal for a novel nephropathy grading system, *Am J Cardiol* **101** (2008), 812–819.
[13] D.J. Hausenloy and D.M. Yello, Remote ischemic preconditioning: Underlying mechanisms and clinical application, *Cardiovascular Research* **79** (2008), 377–386.
[14] G. Heusch, H.E. Bøtker, K. Karin Przyklenk, et al., Remote Ischemic conditioning, *J Am Coll Cardiol* **65**(2) (2015), 177–195.
[15] R. Hirsch, C. Dent, H. Pfriem, J Allen, et al., NGAL is an early predictive biomarker of contrast-induced nephropathy in children, *Pediatr Nephrol* **22** (2007), 2089–2095.
[16] I. Hizoh and C. Haller, Radiocontrast-induced renal tubular cell apoptosis: Hypertonic versus oxidative stress, *Invest Radiol* **37** (2002), 428–434.
[17] G. Igarashi, K. Iino, H. Watanabe and H. Ito, Remote Ischemic pre-conditioning alleviates contrast-induced acute kidney injury in patients with moderate chronic kidney disease, *Circ J* **77** (2013), 3037–3044.
[18] R.P. Karlsberg, S.Y. Dohad and R. Sheng, Contrast-induced acute kidney injury (CI-AKI) following intra-arterial administration of iodinated contrast media, *J Nephrol* **23**(6) (2010), 658–666.
[19] E. Khan, V. Batuman and J.J. Lertora, Emergence of biomarkers in nephropharmacology, *Biomark Med* **4** (2010), 805–814.
[20] S. Koch, D. Della-Morte, K.R. Dave, et al., Biomarkers for ischemic preconditioning: Finding the responders, *Journal of Cerebral Blood Flow & Metabolism* **34** (2014), 933–941.
[21] E.M. Levy, C.M. Viscoli and R.I. Horwitz, The effect of acute renal failure on mortality. A cohort analysis, *JAMA* **275**(19) (1996), 1489–1494.
[22] L. Li, G. Li, C. Yu and Y. Li, The role of remote ischemic preconditioning on postoperative kidney injury in patients undergoing cardiac and vascular interventions: A meta-analysis, *J of Cardiothor Surg* **8** (2013), 43.
[23] P.A. McCullough, Radiocontrast-induced acute kidney injury, *Nephron Physiol* **109** (2008), 61–72.
[24] R. Mehran, E.D. Aymong, E. Nikolsky, et al., A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: Development and initial validation, *J Am CollCardiol* **44**(7) (2004), 1393–1399.
[25] T.P. Menting, T.B. Sterenborg, Y. de Waal, et al., Remote ischemic preconditioning to reduce contrast-induced Nephropathy: A randomized controlled trial, *Eur J Vasc Endovasc Surg* **50**(4) (2015), 527–532.
[26] C. Mrowietz, B. Hiebl, R.P. Franke, et al., Reversibility of echinocyte formation after contact of erythrocytes with various radiographic contrast media, *Clin Hemorheol Microcirc* **39**(1-4) (2008), 281–286.
[27] D.J. Newman, H. Thakkar, R.G. Edwards, et al., Serum cystatin C measured by automated immunoassay: A more sensitive marker of changes in GFR than serum creatinine, *Kidney Int* **47** (1995), 312–318.
[28] H. Pei, Y. Wu, Y. Wei, Y. Yang, S. Teng, et al., Remote Ischemic Preconditioning Reduces Perioperative Cardiac and Renal Events in Patients Undergoing Elective Coronary Intervention: A Meta-Analysis of 11 Randomized Trials, *PLoS One* **9**(12) (2014), e115500.
[29] J.M.J. Pickard, H.E. Boetker, G. Crimi, et al., Remote ischemic conditioning: From experimental observation to clinical application: Report from the 8th Biennial Hatter Cardiovascular Institute Workshop, *Basic Res Cardiol* **110** (2015), 453.
[30] A. Pisani, E. Riccio, M. Andreucci, et al., Role of reactive oxygen species in pathogenesis of radiocontrast-induced nephropathy, *Biomed Res Int* **2013** (2013), 868321.
[31] D. Radovanovic, P. Urban, R. Simon, et al., Outcome of patients with acute coronary syndrome in hospitals of different sizes. A report from the AMIS Plus Registry, *Swiss Med Wkly* **140**(21-22) (2010), 314–322.
[32] E. Randers and E.J. Erlandsen, Serum cystatin C as an endogenous marker of the renal function - a review, *Clin Chem Lab Med* **37** (1999), 389–395.
[33] C.M. Sandler, Contrast-agent-induced acute renal dysfunction – is iodixanol the answer? *N Engl J Med* **348**(6) (2003), 551–553.
[34] E.S. Sherbakova, A.R. Dunaeva, N.S. Zagidullin, Ischemic preconditioning in internal medicine, *Medizinskiy Vestnik Bashkortostana* **9**(1) (2014), 118–123.
[35] R.J. Solomon, R. Mehran, M.K. Natarajan, et al., Contrast-induced nephropathy an long-term adverse events: Cause and effect, *Clin J Am Soc Nephrol* **4** (2006), 1162–1169.
[36] S. Spitzer, W. Munster, R. Sternitzky, et al., Influence of Iodixanol-270 and Iopentol-150 on the microcirculation in man: Influence of viscosity on capillary perfusion, *Clin Hemorheol Microcirc* **20** (1999), 49–55.

[37] S. Tehrani, C. Laing, D.M. Yellon and D.J. Hausenloy, Contrast induced acute kidney injury following PCI, *Eur J Clin Invest* **43** (2013), 483–490.
[38] H. Thiele, L. Hildebrand, C. Schirdewahn, et al., Impact of high-dose N-acetylcysteine versus placebo on contrastinduced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial, *J Am Coll Cardiol* **55**(20) (2010), 2201–2209.
[39] K. Veighey and R. MacAllister, Pediatr Nephrol Clinical applications of remote ischaemic preconditioning in native and transplant acute kidney injury, **30** (2015), 1749–1759.
[40] K.E. Wever, T.P. Menting, R. Maroeska, et al., Ischemic preconditioning in the animal kidney, a systematic review and meta-analysis, *PLoS One* **7**(2) (2012), e32296.
[41] T. Yamanaka, Y. Kawai and T. Miyoshi, Remote ischemic preconditioning reduces contrast-induced acute kidney injury in patients with ST-elevation myocardial infarction: A randomized controlled trial, *Int J Cardiol* **178** (2015), 136–141.
[42] N. Zagidullin, E. Scherbakova, Y. Safina, R. Zulkarneev and S. Zagidullin, The impact of remote Ischemic preconditioning on arterial stiffness and heart rate variability in patients with angina pectoris, *J Clin Med* **5** (2016), 60.
[43] A. Zarbock, H. Van Aken and C. Schmidt, Remote ischemic preconditioning and outcome: Shall we all have an intermittent tourniquet? *Curr Opin Anaesthesiol* **28**(2) (2015), 165–171.
[44] T. Zhang, L.H. Shen, L.H. Hu and B. He, Statins for the prevention of contrast induced nephropathy: A systematic review and meta-analysis, *Am J Nephrol* **33**(4) (2011), 344–351.