https://doi.org/10.15360/1813-9779-2025-2-2523

Nitric Oxide as a Nephroprotective Agent in Cardiac Surgery

Alexander M. Boyko*, Nikolai O. Kamenshchikov, Yuri K. Podoksenov, Maria L. Dyakova, Yulia S. Svirko, Anna M. Gusakova, Elena B. Kim, Dmitry S. Panfilov, Boris N. Kozlov

Research Institute for Cardiology, Tomsk National Research Medical Center, Russian Academy of Sciences, 111-A Kievskaya Str., 634012 Tomsk, Russia

For citation: *Alexander M. Boyko, Nikolai O. Kamenshchikov, Yuri K. Podoksenov, Maria L. Dyakova, Yulia S. Svirko, Anna M. Gusakova, Elena B. Kim, Dmitry S. Panfilov, Boris N. Kozlov.* Nitric Oxide as a Nephroprotective Agent in Cardiac Surgery. *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 34–41. https://doi.org/10.15360/1813-9779-2025-2-2523 [In Russ. and Engl.]

***Correspondence to:** Alexander M. Boyko, boiko.cardio@yandex.ru

Summary

Aim. To evaluate the efficacy of perioperative nitric oxide (NO) administration in reducing the incidence of acute kidney injury (AKI) during hemiarch surgery for nonsyndromic ascending aortic aneurysms under cardiopulmonary bypass and hypothermic circulatory arrest (HCA).

Materials and Methods. A single-blind, prospective, randomized, controlled study included 80 patients older than 18 years who underwent hemiarch aortic surgery with HCA for nonsyndromic ascending aortic aneurysms between 2020 and 2023. Patients were randomized (1:1) into two groups: the NO group (who received perioperative NO at 80 ppm) and the control group (who received standard perioperative management without NO administration). The primary endpoint was the incidence of AKI according to KDIGO criteria. Secondary endpoints included biomarker levels of subclinical renal injury and clinical outcomes.

Results. Postoperatively, the incidence of AKI was 25% in the NO group compared to 50% in the control group (OR=0.26; 95% CI: 0.10–0.69; P=0.036). Patients in the NO group had significantly lower levels of urinary neutrophil gelatinase-associated lipocalin (uNGAL, P=0.03) and cystatin C (P<0.001) 4 hours after surgery. In addition, the length of stay in the intensive care unit (ICU) was significantly shorter in the NO group (P=0.03) compared to the control group.

Conclusion. Perioperative NO therapy at 80 ppm during hemiarch aortic surgery with HCA reduces the incidence of acute kidney injury, lowers the levels of kidney injury biomarkers (uNGAL and cystatin C), and shortens the ICU stay.

Keywords: nitric oxide; acute kidney injury; nephroprotection; aortic aneurysm; circulatory arrest

Conflict of interest. The authors declare no conflict of interest. Some results have been published in the Proceedings of the Congress of the Federation of Anesthesiologists and Reanimatologists and Russian Forum of Anesthesiologists and Reanimatologists (RFAR-2024), St. Petersburg. 2024: 25. https://cdn.congressfar.ru/140/material.pdf (In Russ.).

Funding. The study was conducted as part of the basic research project «Organ Protection with Nitric Oxide in Cardiovascular Surgery: Technological Support (Synthesis and Delivery Devices), Mechanisms of Protective Effects, and Impact on Clinical Outcomes» (No. 122123000017-3).

Information about the authors:
Alexander M. Boyko: http://orcid.org/0000-0002-2408-8874
Nikolai O. Kamenshchikov: http://orcid.org/0000-0003-4289-4439
Yuri K. Podoksenov: http://orcid.org/0000-0002-8939-2340
Maria L. Dyakova: http://orcid.org/0000-0001-9353-7234
Yulia S. Svirko: http://orcid.org/0000-0002-2258-3564
Anna M. Gusakova: http://orcid.org/0000-0002-3147-3025
Elena B. Kim: http://orcid.org/0009-0001-5610-3506
Dmitry S. Panfilov: http://orcid.org/0000-0003-2201-350X
Boris N. Kozlov: http://orcid.org/0000-0002-0217-7737

Introduction

The rising prevalence of ascending aortic disease over the past decade has inevitably led to an increase in the number of surgical procedures. According to the literature, there are 9–16 cases of thoracic aortic aneurysm per 100,000 population per year [1–3], with the ascending aorta accounting for 60% of these aneurysms [4, 5]. The preferred treatment for thoracic aortic aneurysms is surgical repair with cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) [6]. However, this approach has been associated with serious complications such as persistent neurological deficits, myocardial infarction, respiratory failure, and acute kidney injury (AKI) [7]. AKI associated with ascending aortic reconstructive surgery is a common complication with an incidence of up to 77.6% [8–12], and it has a negative impact on both short-term surgical outcomes and long-term prognosis [13]. The development of nephroprotective strategies as part of the preoperative management of thoracic aortic aneurysm surgery remains a pressing issue.

Nitric oxide (NO) is a pleiotropic molecule that plays an important role in protecting the kidney from ischemia-reperfusion injury. The use of NO to slow the progression of AKI appears to be a promising strategy [14]. However, current data on the potential use of NO for renoprotection in patients undergoing ascending aortic surgery with HCA are limited [15].

The aim of this study was to test the hypothesis that the administration of exogenous nitric oxide during hemiarch aortic surgery under hypothermic circulatory arrest can protect the kidneys.

Materials and Methods

To investigate the nephroprotective properties of nitric oxide (NO), we conducted a single-center, prospective, randomized, controlled trial (approved by the Ethics Committee of the Research Institute of Cardiology, Tomsk National Research Medical Center, Protocol No. 260, February 2, 2024).

The study was conducted in the laboratory of intensive care medicine. A total of 80 patients who underwent surgery in the Department of Cardiovascular Surgery of the Research Institute of Cardiology, a branch of Tomsk National Research Medical Center of the Russian Academy of Sciences (Research Institute of Cardiology, Tomsk NRMC) in 2020–2023 were included in the study.

The inclusion criteria were

- age ⩾18 years
- presence of nonsyndromic ascending aortic aneurysms
- elective aortic hemiarch repair under circulatory arrest and moderate hypothermia (30–32°C)
- signed informed consent to participate in the study.

Patients were excluded from the study if they met any of the following criteria:

- Chronic kidney disease (glomerular filtration rate [GFR] < 60 mL/min/1.73 m²)
- Need for emergency surgery
- Critical preoperative condition (preoperative need for mechanical ventilation, inotropic or vasopressor support, or mechanical circulatory support)
- Need for repeat cardiac surgery or extended surgical procedures (aortic root reconstruction, thoracic aortic replacement using the «frozen elephant trunk» technique)
- Absolute contraindications to NO therapy (congenital or acquired methemoglobinemia)
- Relative contraindications to NO therapy (coagulation disorder, intracranial hemorrhage, severe left ventricular failure classified as NYHA III–IV)
- Acute massive perioperative hemorrhage.

All patients were randomly assigned in a 1:1 ratio to two groups: the main group (NO group, in which perioperative administration of NO at a concentration of 80 ppm was administered, *N*=40) and the comparison group (standard perioperative care group, in which NO was not administered, *N*=40). Randomization was performed using sealed opaque envelopes. The envelopes were prepared before patient enrollment began, and their number corresponded to the calculated sample size. Each envelope contained a single code word: «NO» or «Control». On the morning of surgery, one envelope was randomly selected and opened by the anesthesiologist, and the contents of the envelope were not disclosed. The selection of patients for the study is shown in Fig. 1.

The administration of nephrotoxic drugs (contrast media, amphotericin, and/or aminoglycosides) within 48 hours before surgery was excluded.

Anesthetic support was performed according to the standardized protocol adopted at the clinic. Premedication, administered to all patients on arrival in the operating room, included opioid analgesics, antihistamines, and benzodiazepines. Induction of anesthesia was performed with propofol (1.5–3.0 mg/kg) and fentanyl (3.0–5.0 mcg/kg). Neuromuscular blockade was achieved with vecuronium bromide at a dose of 0.1 mg/kg. Anesthesia was maintained with sevoflurane (1.9–3.1 vol%), and propofol (3.0–5.0 mg/kg/h) and fentanyl (3–5 mcg/kg/h) were used during mechanical perfusion.

Mechanical ventilation (MV) was performed with the Primus ventilator (Dräger, Germany) in controlled mandatory ventilation (CMV) mode with

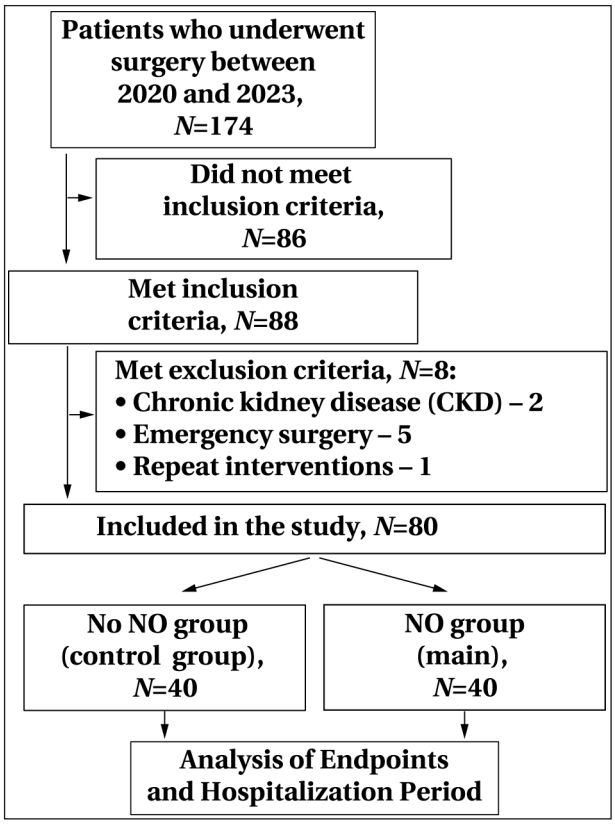

Fig. 1. Flowchart of patient selection for the study.

volume control, with a tidal volume of 6–7 mL/kg, a respiratory rate of 12–14 breaths per minute, a FiO_2 of 0.35 (increased as needed), and a positive end-expiratory pressure (PEEP) of 5 cm H_2O.

To monitor vital parameters, standard controls were performed: continuous ECG analysis, invasive monitoring of arterial and central venous pressure, pulse oximetry, nasopharyngeal and rectal temperature measurements using the Infinity Delta XL monitor (Dräger, Germany). Invasive arterial pressure measurements and blood samples for laboratory gas composition analysis were obtained by catheterization of both radial (or brachial) arteries (using a 20G arterial cannula, B Braun, Germany). For central venous pressure (CVP) monitoring, inotropic and infusion-transfusion therapy, the superior vena cava was catheterized via the right internal jugular vein with a 12F central venous catheter (Certofix; B Braun, Germany). The depth of sedation during general anesthesia was controlled by BIS monitoring, maintaining the index between 60 and 40. Cerebral oximetry (rSO_2, %) was monitored using near-infrared spectroscopy on an Invos 5100 device (Somanetics Corp.).

Cardiopulmonary bypass (CPB) was performed in non-pulsatile mode using a Stockert machine (Stockert Ins., Germany) with Skipper disposable membrane oxygenators (Eurosets, Italy). Perfusion index was maintained at 2.5 L/min/m². Hypocoagulation was achieved just before the start of CPB with a dose of heparin (3 mg/kg), controlled by the activated clotting time (target value >450 seconds). CPB was started in the following order: «brachiocephalic trunk — right atrium», after which the patient was «cooled» and an aortic clamp was applied. Selective pharmacological crystalloid cardioplegia was performed with the «Custodiol» solution (GmbH, Germany). The cardioplegia solution was infused for 6–8 minutes (according to the manufacturer's recommendations). The target body temperature in the rectal probe was maintained at 30–32°C. Once this temperature was reached, aortic occlusion distal to the left subclavian artery was performed, followed by induction of hypothermic circulatory arrest (HCA) with unilateral brain perfusion (perfusion flow rate 10 mL/kg/min). A hemiarch thoracic aortic replacement was performed. After completion of the distal anastomosis, CPB was discontinued and warming was started with artificial and parallel circulation. When body temperature reached 37°C, patients were weaned from CPB.

To inactivate the effects of heparin, a 1:1 solution of protamine sulfate was administered. To inhibit fibrinolysis, tranexamic acid was administered in a bolus dose of 10 mg/kg, followed by an infusion of 1–2 mg/kg/h until the end of surgery.

In the study, a sample of the plasma-chemical synthesis system for nitric oxide «TIANOKS» (RFNC-VNIIEF, Sarov, Russia) was used. This system was used for inhalation delivery of NO in the concentration of 80 ppm, and the concentration of NO in the gas-air mixture supply line was monitored. After tracheal intubation and transition to mechanical ventilation, NO was delivered through a connector with a Luer adapter embedded in the breathing circuit. The gas-air mixture was then passed through an absorber containing calcium hydroxide to remove nitrogen dioxide (NO_2). A gas sampling line to monitor the NO/NO_2 concentration in the inhaled mixture was placed as close to the patient as possible in the inspiratory limb of the circuit. In addition to inhaled NO delivery, NO was also delivered to the extracorporeal circuit at a concentration of 80 ppm after CPB was initiated and the calculated perfusion flow rate was achieved. Two ¼-inch Luer adapter connectors were inserted into the main gas-air supply line: NO was delivered through the proximal connector, and gas was sampled to monitor the fractional concentration of NO/NO_2 through the distal connector. The connector of the NO delivery line with a bacterial filter was placed as close as possible to the oxygenator of the CPB machine. During the period of hypothermic circulatory arrest, NO delivery was stopped (Fig. 2).

After the CPB machine was turned off, NO delivery continued at the same dose through the modified breathing circuit for 6 hours after surgery.

The primary endpoint of the study was the incidence of acute kidney injury (KDIGO criteria). Secondary endpoints were: duration of mechanical ventilation, cases of acute cerebrovascular event (ACVE) during the inpatient treatment phase, length of stay in the ICU, length of hospital stay, and urinary biochemical markers of acute kidney injury (uNGAL, cystatin C).

Intraoperative parameters such as duration of CPB, surgical procedure, and time of cardiac and circulatory arrest were monitored and recorded.

Acute kidney injury (AKI) was diagnosed according to the KDIGO criteria [16]: an increase in serum creatinine (SCr) ⩾0.3 mg/dL (⩾26.5 μmol/L) within 48 hours, or an increase in SCr ⩾1.5 times the baseline value (if known or assumed to have occurred within the previous 7 days), or a urine output rate <0.5 mL/kg/h over 6 hours. SCr levels were monitored for 7 days after surgery.

Levels of uNGAL and cystatin C (markers of AKI) were determined in urine samples. Urine was collected after bladder catheterization and 4 hours after the end of surgery. The urine was then centrifuged at 1500±3 rpm for 10 minutes and frozen at –20°C. The concentrations of uNGAL and cystatin C were measured using an enzyme-linked immunosorbent assay (ELISA) method (Hycult Biotech, Uden, The Netherlands) on a Sunrise analyzer (Tecan, Mannedorf, Switzerland).

Statistical data analysis was performed using Statistica 10.0 software (StatSoft, Inc, USA). The Shapiro–Wilk test was used to assess the normality

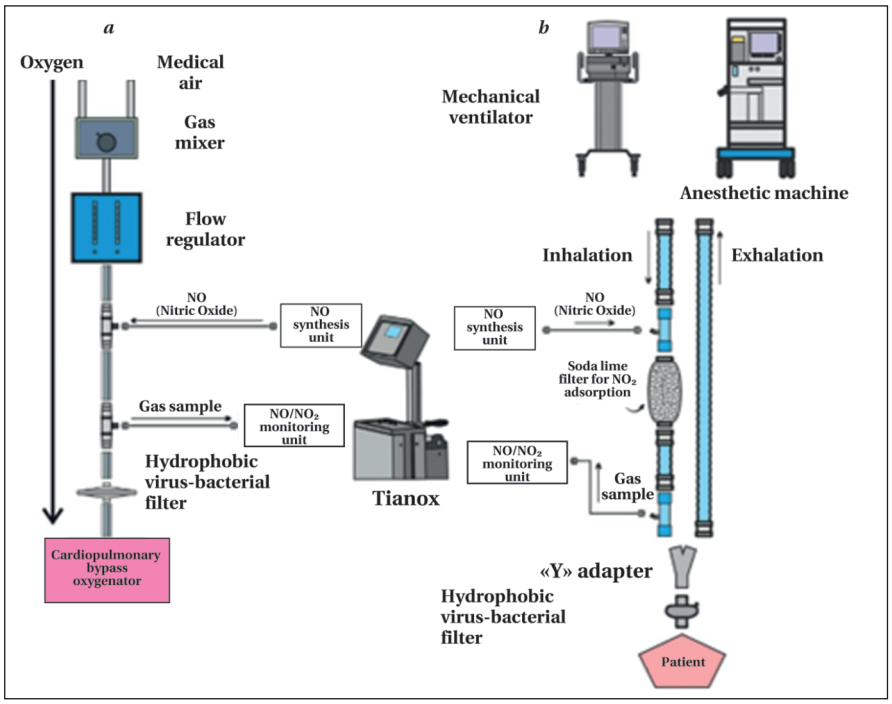

Fig. 2. Scheme of nitric oxide delivery.
Note. *a* — NO delivery to the cardiopulmonary bypass machine oxygenator; *b* — NO delivery to the mechanical ventilation system.

of the distribution of the variables. For non-normal distributions, quantitative data were expressed as median and 25th and 75th percentiles (*Me* [25; 75]), and categorical data were expressed as *N* (%). Quantitative parameters were analyzed using the Mann–Whitney *U* test for two independent samples. Fisher's exact test or χ^2 test was used to compare nominal variables in independent groups. Differences were considered statistically significant at $P<0.05$, with a two-tailed *P* value. Sample size calculation was based on a preliminary pilot study of 16 patients (8 patients in each group). The incidence of AKI was 20% in the NO group and 50% in the control group without NO administration. The required sample size for each group with alpha = 0.05, power = 0.8, and the observed proportions was 39 patients.

Results and Discussion

The groups were comparable with respect to the main clinical characteristics. Patient characteristics are shown in Table 1.

An analysis of intraoperative data and early postoperative period was performed in the study groups. The groups were comparable in terms of duration of cardiopulmonary bypass, surgery, and cardiac and circulatory arrest (Table 2).

The incidence of AKI was 25% in the NO group and 50% in the group without NO administration (RR=0.5; AR=0.25; 95% CI: 0.10–0.69; *P*=0.036) [17].

Table 1. Clinical and demographic characteristics of patients, *Me* [25; 75] or *N* (%).

Parameter	Values in groups		*P value*
	without NO (*N*=40)	NO (*N*=40)	
Age, years	67 [58; 72]	61 [52; 67]	0.06
Men	28 (70)	24 (60)	0.35
BMI, kg/m²	28.4 [26.0; 32.1]	29.0 [24.7; 31.1]	0.54
LVEF, %	64 [61; 68]	63 [58; 68]	0.56
CHD	22 (55)	16 (40)	0.18
Previous MI	4 (10)	2 (5)	0.67
Hypertension	36 (90)	30 (75)	0.14
Diabetes mellitus	3 (7.5)	7 (17.5)	0.18
Creatinine, μmol/L	87.0 [77.5; 95.5]	86.0 [74.0; 98.0]	0.76
GFR, mL/min/1.73 m²	81.0 [63.5; 92.5]	77.0 [64.0; 89.5]	0.91
Ascending aorta diameter, mm	50.0 [48.0; 54.5]	50.0 [48.5; 52.0]	1

Note. BMI — body mass index; LVEF — left ventricular ejection fraction; CHD — coronary heart disease; MI — myocardial infarction; GFR — glomerular filtration rate.

Table 2. Perioperative period characteristics, *Me* [25; 75] or *N* (%).

Parameter	Values in groups		*P value*
	without NO (*N*=40)	NO (*N*=40)	
Duration of circulatory arrest, min	18 [17; 20]	18 [16; 21]	0.74
Duration of cardiac arrest, min	101 [81; 135]	99.5 [82; 135]	0.59
CPB, min	140 [115; 166]	125 [105; 162]	0.20
Duration of surgery, min	360 [310; 370]	320 [285; 380]	0.15
ACVE	0	1 (2.5)	0.32
Myocardial infarction	1 (2.5)	0	0.32
Duration of lung ventilation, hours	12 [7; 18]	11 [7; 15]	0.85
Length of stay in the ICU, days	2 [1; 5]	1 [1; 2]	0.03
Length of hospital stay, days	20 [15; 28]	19 [14; 22]	0.23

Note. CPB — cardiopulmonary bypass; ACVE — acute cerebrovascular event.

Table 3. Urinary biomarker concentrations of AKI markers, *Me* [25; 75].

Parameter, ng/mL	Values in groups		*P value*
	without NO (*N*=40)	NO (*N*=40)	
	uNGAL		
Baseline	1.02 [0.61; 1.34]	1.03 [0.76; 1.08]	0.76
4 hours post-op	3.52 [2.72; 6.42]	1.85 [1.66; 3.82]	0.03
	Cystatin C		
Baseline	1.66 [1.17; 3.90]	1.54 [0.58; 3.77]	0.84
4 hours post-op	100.79 [80.06; 117.23]	45.02 [34.04; 73.41]	<0.001

Note. uNGAL — neutrophil gelatinase-associated lipocalin.

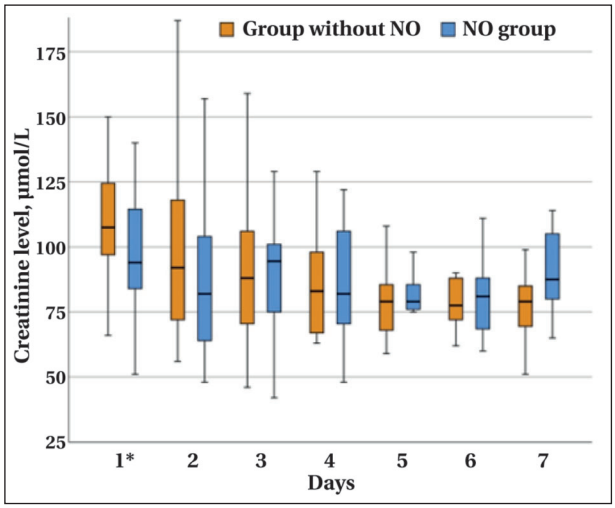

Fig. 3. Changes in serum creatinine level, *Me* [25; 75].
Note. * *P*=0.02.

The changes in creatinine concentration are shown in Fig. 3.

In the NO group, lower levels of uNGAL and cystatin C were observed 4 hours after surgery compared to the group without NO administration (*P*=0.03 and *P*<0.001, respectively) (Table 3).

No significant differences were found between the groups in the incidence of stroke, myocardial infarction, duration of mechanical ventilation, or length of hospital stay (Table 2). However, the NO group showed a reduction in ICU length of stay (*P*=0.03) (Table 2).

Throughout the study, NO_2 levels did not exceed the clinically acceptable threshold of 3 ppm.

A statistically significant reduction in the incidence of AKI according to KDIGO criteria was observed with perioperative NO administration. Previous clinical studies have shown that patients undergoing cardiac surgery experience impaired endogenous NO homeostasis and a hemolysis-associated NO-deficient state [18, 19]. Restoring NO levels and increasing its bioavailability is a promising nephroprotective strategy, as supported by several experimental studies [20–24]. According to a meta-analysis by J. Wang et al. [19], NO administration reduces the postoperative risk of AKI in cardiac surgery patients by 20%. Our results are consistent with the existing literature [25, 26].

Four hours after surgery, urinary uNGAL levels were lower in the NO group compared to patients who did not receive NO (*P*=0.03), indicating less pronounced renal injury. uNGAL is considered one of the most extensively studied biomarkers of AKI associated with cardiac surgery and is often referred to as a «troponin-like» biomarker in the laboratory diagnosis of AKI.

De Geus et al. [27] developed the CSA-NGAL score, a renal tubular injury scale based on NGAL levels in urine or plasma. In a study by E. A. Mostafa et al. [28], a positive correlation was observed between the severity of renal injury according to the CSA-NGAL score (cardiac surgery-associated neutrophil gelatinase-associated lipocalin scale) and AKI severity according to KDIGO criteria.

A meta-analysis by M. Haase et al. [29] confirmed NGAL as a sensitive and specific biomarker for AKI, a finding further supported by the meta-analysis by F. Zhou et al. [30]. In addition, a study by O. Dymova et al. [31] in patients undergoing thoracic aortic surgery with cardiopulmonary bypass highlighted the high prognostic value of NGAL in assessing AKI risk just hours after surgery.

Research suggests that urinary NGAL changes not only serve as an effective early diagnostic marker of AKI, even before the loss of excretory renal function, but also help to assess treatment efficacy and disease severity [31]. Thus, the data suggest that urinary NGAL measurement can be used for early diagnosis of AKI in the immediate postoperative period.

In our study, urinary cystatin C levels were also lower in the NO group four hours after surgery (p < 0.001), further confirming less pronounced renal injury with perioperative NO administration. Cystatin C is considered a promising biomarker for AKI, as its levels reflect changes in GFR and can be effectively used to predict AKI, especially in combination with NGAL [32–34].

According to a meta-analysis, cystatin C had the highest AUC value for predicting AKI and showed greater specificity compared to other biomarkers studied [35].

Perioperative NO administration has a nephroprotective effect in hemiarch aortic surgery performed under hypothermic circulatory arrest, as evidenced by the observed reduction in urinary uNGAL and cystatin C levels, indicating a lower in-

cidence of clinically manifest AKI and milder subclinical AKI.

These findings are of practical importance; however, further studies with larger patient cohorts are recommended to determine the optimal NO concentration and duration of administration to reduce the incidence of AKI in hemiarch aortic surgery under hypothermic circulatory arrest.

Study Limitations. This was a single-center study with a relatively small cohort of patients and no assessment of long-term outcomes. Local protocols for anesthesia management, CPB, CA, and surgical techniques and postoperative care may have influenced the results. In addition, the study protocol was not registered.

Conclusion

Perioperative administration of NO at a concentration of 80 ppm during hemiarch aortic replacement under hypothermic circulatory arrest has a nephroprotective effect. This is supported by a reduced incidence of acute kidney injury, changes in urinary biomarkers of subclinical kidney injury (uNGAL and cystatin C), and a shorter stay in the intensive care unit.

References

1. *Clouse W. D., Hallett J. W. Jr, Schaff H. V., Gayari M. M., Ilstrup D. M., Melton L. J.* 3rd. Improved prognosis of thoracic aortic aneurysms: a population-based study. *JAMA.* 1998; 280 (22): 1926–1929. DOI: 10.1001/jama.280.22.1926. PMID: 9851478.
2. *Olsson C., Thelin S., Ståhle E., Ekbom A., Granath F.* Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation.* 2006; 114 (24): 2611–2618. DOI: 10.1161/CIRCULATIONAHA.106.630400. PMID: 17145990.
3. *Downey R. T., Aron R. A.* Thoracic and thoracoabdominal aneurysms: etiology, epidemiology, and natural history. *Anesthesiol Clin.* 2022; 40 (4): 671–683. DOI: 10.1016/j.anclin.2022.08.011. PMID: 36328622.
4. *Ortega-Loubon C., Tamayo E., Jorge-Monjas P.* Cardiac surgery-associated acute kidney injury: current updates and perspectives. *J Clin Med.* 2022; 11 (11): 3054. DOI: 10.3390/jcm11113054. PMID: 35683442.
5. *Isselbacher E. M.* Thoracic and abdominal aortic aneurysms. *Circulation.* 2005; 111 (6): 816–828. DOI: 10.1161/01.CIR.0000154569.08857.7A. PMID: 15710776.
6. *Zhou Z., Cecchi A. C., Prakash S. K., Milewicz D. M.* Risk factors for thoracic aortic dissection. *Genes (Basel).* 2022; 13 (10): 1814. DOI: 10.3390/genes13101814. PMID: 36292699.
7. *Козлов Б. Н., Панфилов Д. С., Базарбекова Б. А., Сондуев Э. Л., Бойко А. М.* Непосредственные результаты хирургического лечения аневризмы восходящей аорты в сочетании со стенотическим поражением аортального клапана. *Сибирский журнал клинической и экспериментальной медицины.* 2023; 38 (3): 135–142. *Kozlov B. N., Panfilov D. S., Bazarbekova B. A., Sonduev E. L., Boyko A. M.* The immediate results of surgical treatment of an ascending aortic aneurysm in conjuction with a stenotic lesion of the aortic valve. *Siberian Journal of Clinical and Experimental Medicine = Sibirskiy Zhurnal Eksperimentalnoy i Klinicheskoy Meditsiny.* 2023; 38 (3): 135–142. (in Rus.). DOI: 10.29001/2073-8552-2022-424.
8. *Gambardella I., Gaudino M., Lau C., Munjal M., Di Franco A., Ohmes L. B., Hameedi F., et al.* Contemporary results of hemiarch replacement. *Eur J Cardiothorac Surg.* 2017; 52 (2): 333–338. DOI: 10.1093/ejcts/ezx071. PMID: 28387791.
9. *Amano K., Takami Y., Ishikawa H., Ishida M., Tochii M., Akita K., Sakurai Y., et al.* Lower body ischaemic time is a risk factor for acute kidney injury after surgery for type A acute aortic dissection. *Interact Cardiovasc Thorac Surg.* 2020; 30 (1): 107–112. DOI: 10.1093/icvts/ivz220. PMID: 31501854.
10. *Wu H. B., Ma W. G., Zhao H. L., Zheng J., Li J. R., Liu O., Sun L. Z.* Risk factors for continuous renal replacement therapy after surgical repair of type A aortic dissection. *J Thorac Dis.* 2017; 9 (4): 1126–1132. DOI: 10.21037/jtd.2017.03.128. PMID: 28523169.
11. *Wang J., Yu W., Zhai G., Liu N., Sun L., Zhu J.* Independent risk factors for postoperative AKI and the impact of the AKI on 30-day postoperative outcomes in patients with type A acute aortic dissection: an updated meta-analysis and meta-regression. *J Thorac Dis.* 2018; 10 (5): 2590–2598. DOI: 10.21037/jtd.2018.05.47. PMID: 29997920.
12. *Ghincea C. V., Reece T. B., Eldeiry M., Roda G. F., Bronsert M. R., Jarrett M. J., Pal J. D., et al.* Predictors of acute kidney injury following aortic arch surgery. *J Surg Res.* 2019; 242: 40–46. DOI: 10.1016/j.jss.2019.03.055. PMID: 31063910.
13. *Arnaoutakis G. J., Vallabhajosyula P., Bavaria J. E., Sultan I., Siki M., Naidu S., Milewski R. K., et al.* The impact of deep versus moderate hypothermia on postoperative kidney function after elective aortic hemiarch repair. *Ann Thorac Surg.* 2016; 102 (4): 1313–1321. DOI: 10.1016/j.athoracsur.2016.04.007. PMID: 27318775.
14. *Kamenshchikov N. O., Duong N., Berra L.* Nitric oxide in cardiac surgery: a review article. *Biomedicines.* 2023; 11 (4): 1085. DOI: 10.3390/biomedicines11041085. PMID: 37189703.
15. *Kamenshchikov N. O., Anfinogenova Y. J., Kozlov B. N., Svirko Y. S., Pekarskiy S. E., Evtushenko V. V., Lugovsky V. A., et al.* Nitric oxide delivery during cardiopulmonary bypass reduces acute kidney injury: a randomized trial. *J Thorac Cardiovasc Surg.* 2022; 163 (4): 1393–1403.e9. DOI: 10.1016/j.jtcvs.2020.03.182. PMID: 32718702.
16. *Kellum J. A., Lameire N. KDIGO AKI Guideline Work Group.* Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care.* 2013; 17 (1): 204. DOI: 10.1186/cc11454. PMID: 23394211.
17. Сборник тезисов *Съезд Федерации анестезиологов и реаниматологов, Форум анестезиологов и реаниматологов России (ФАРР-2024)*, СПб: 2024: 25. *Collection of abstracts Congress of the Federation of anesthesiologists and reanimatologists, Forum of anesthesiologists and reanimatologists of Russia (FARR-2024)*, SPb: 2024: 25. https://cdn.congressfar.ru/140/material.pdf. (in Russ.).
18. *Arellano D. L.* Acute kidney injury following cardiothoracic surgery. *Crit Care Nurs Clin North Am.* 2019; 31 (3): 407–417. DOI: 10.1016/j.cnc.2019.05.008. PMID: 31351558.
19. *Wang J., Cong X., Miao M., Yang Y., Zhang J.* Inhaled nitric oxide and acute kidney injury risk: a meta-analysis of randomized controlled trials. *Ren Fail.* 2021; 43 (1): 281–290. DOI: 10.1080/0886022X.2021.1873805. PMID: 33494652.
20. *Minneci P. C., Deans K. J., Zhi H., Yuen P. S., Star R. A., Banks S. M., Schechter A. N., et al.* Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. *J Clin Invest.* 2005; 115 (12): 3409–17. DOI: 10.1172/JCI25040. PMID: 16294219.
21. *Troncy E., Francoeur M., Salazkin I., Yang F., Charbonneau M., Leclerc G., Vinay P., Blaise G.* Extra-pul-

monary effects of inhaled nitric oxide in swine with and without phenylephrine. *Br J Anaesth*. 1997; 79 (5): 631–640.
DOI: 10.1093/bja/79.5.631. PMID: 9422904.

22. *Ross J. T., Robles A. J., Mazer M. B., Studer A. C., Remy K. E., Callcut R. A.* Cell-free hemoglobin in the pathophysiology of trauma: a scoping review. *Crit Care Explor*. 2024; 6 (2): e1052.
DOI: 10.1097/CCE.0000000000001052.
PMID: 38352942.
23. *Kamenshchikov N. O., Diakova M. L., Podoksenov Y. K., Churilina E. A., Rebrova T. Y., Akhmedov S. D., Maslov L. N., et al.* Potential mechanisms for organoprotective effects of exogenous nitric oxide in an experimental study. *Biomedicines*. 2024; 12 (4): 719.
DOI: 10.3390/biomedicines12040719.
PMID: 38672075.
24. *Те М. А., Каменщиков Н. О., Подоксенов Ю. К., Мухомедзянов А. В., Маслов Л. Н., Козлов Б. Н.* Влияние донации оксида азота на выраженность митохондриальной дисфункции почечной ткани при моделировании искусственного кровообращения: экспериментальное исследование. *Вестник интенсивной терапии им. А. И. Салтанова*. 2023; 4: 176–184. *Te M. A., Kamenshchikov N. O., Podoksenov Yu. K., Mukhomedzyanov A. V., Maslov L. N., Kozlov B. N.* The effect of nitric oxide donation on the severity of mitochondrial dysfunction to the renal tissue in cardiopulmonary bypass simulation: an experimental study. *Ann Crit Care = Vestnik Intensivnoy Terapii im AI Saltanova*. 2023; 4: 176–184. (in Russ.).
DOI: 10.21320/1818-474X-2023-4-176-184.
25. *Hu J., Spina S., Zadek F., Kamenshchikov N. O., Bittner E. A., Pedemonte J., Berra L.* Effect of nitric oxide on postoperative acute kidney injury in patients who underwent cardiopulmonary bypass: a systematic review and meta-analysis with trial sequential analysis. *Ann Intensive Care*. 2019; 9 (1): 129.
DOI: 10.1186/s13613-019-0605-9. PMID: 31754841.
26. *Yan Y., Kamenshchikov N., Zheng Z., Lei C.* Inhaled nitric oxide and postoperative outcomes in cardiac surgery with cardiopulmonary bypass: a systematic review and meta-analysis. *Nitric Oxide*. 2024; 146: 64–74.
DOI: 10.1016/j.niox.2024.03.004. PMID: 38556145.
27. *de Geus H. R., Ronco C., Haase M., Jacob L., Lewington A., Vincent J. L.* The cardiac surgery-associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage. *J Thorac Cardiovasc Surg*. 2016; 151 (6): 1476–1481.
DOI: 10.1016/j.jtcvs.2016.01.037. PMID: 26952930.
28. *Mostafa E. A., Shahin K. M., El Midany A. A. H., Hassaballa A. S., El-Sokkary I. N., Gamal M. A., Elsaid M. E., et al.* Validation of cardiac surgery-associated neutrophil gelatinase-associated lipocalin score for prediction of cardiac surgery-associated acute kidney injury. *Heart Lung Circ*. 2022; 31 (2): 272–277.
DOI: 10.1016/j.hlc.2021.05.084. PMID: 34219024.
29. *Haase M., Bellomo R., Devarajan P., Schlattmann P., Haase-Fielitz A.; NGAL Meta-analysis Investigator Group.* Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis*. 2009; 54 (6): 1012–1024.
DOI: 10.1053/j.ajkd.2009.07.020. PMID: 19850388.
30. *Zhou F., Luo Q., Wang L., Han L.* Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. *Eur J Cardiothorac Surg*. 2016; 49 (3): 746–755.
DOI: 10.1093/ejcts/ezv199. PMID: 26094017.
31. *Дымова О. В., Еременко А. А., Минболатова Н. М.* Нейтрофильный желатиназа-ассоциированный липокалин (UNGAL) в ранней диагностике и прогнозировании острого почечного повреждения, СПОН и исходов лечения у кардиохирургических пациентов. *Анестезиология и реаниматология*. 2017; 62 (5): 347–351. *Dymova O. V., Eremenko A. A., Minbolatova N. M.* The value of neutrophilic gelatinase-associated lipocalin (UNGAL) in the early diagnosis and prognosis of acute renal injury, MOSF and outcomes in cardiosurgical patients. *Russ J Anesthesiol Reanimatol = Anesteziologiya i Reanimatologiya*. 2017; 62 (5): 347–351. (in Russ.).
DOI: 10.18821/0201-7563-2017-62-5-347-351.
32. *Wen Y., Parikh C. R.* Current concepts and advances in biomarkers of acute kidney injury. *Crit Rev Clin Lab Sci*. 2021; 58 (5): 354–368.
DOI: 10.1080/10408363.2021.1879000.
PMID: 33556265.
33. *Schrezenmeier E. V., Barasch J., Budde K., Westhoff T., Schmidt-Ott K. M.* Biomarkers in acute kidney injury — pathophysiological basis and clinical performance. *Acta Physiol (Oxf)*. 2017; 219 (3): 554–572.
DOI: 10.1111/apha.12764. PMID: 27474473.
34. *Pode Shakked N., de Oliveira M. H. S., Cheruiyot I., Benoit J. L., Plebani M., Lippi G., Benoit S. W., et al.* Early prediction of COVID-19-associated acute kidney injury: are serum NGAL and serum Cystatin C levels better than serum creatinine? *Clin Biochem*. 2022; 102: 1–8.
DOI: 10.1016/j.clinbiochem.2022.01.006.
PMID: 35093314.
35. *Lan H., Liu X., Yang D., Zhang D., Wang L., Hu L.* Comparing diagnostic accuracy of biomarkers for acute kidney injury after major surgery: a PRISMA systematic review and network meta-analysis. *Medicine (Baltimore)*. 2023; 102 (40): e35284.
DOI: 10.1097/MD.0000000000035284.
PMID: 37800811.

Received 19.10.2024
Accepted 14.02.2025
Accepted in press 20.03.2025