ANESTHESIOLOGY®

Perioperative Nitric Oxide Conditioning Reduces Acute Kidney Injury in Cardiac Surgery Patients with Chronic Kidney Disease (the DEFENDER Trial): A Randomized Controlled Trial

Nikolay O. Kamenshchikov, M.D., Mark A. Tyo, M.D., Lorenzo Berra, M.D., Igor V. Kravchenko, M.D., Boris N. Kozlov, M.D., Ph.D., Anna M. Gusakova, Ph.D., M.D., Yuri K. Podoksenov, M.D., Ph.D.

ANESTHESIOLOGY 2025; 143:287–99

ABSTRACT

Background: Postoperative acute kidney injury (AKI) is a significant concern for cardiac surgery patients with chronic kidney disease (CKD). Effective pharmacologic interventions to mitigate these risks are urgently needed. This study aimed to evaluate the efficacy and safety of perioperative nitric oxide (NO) administration in preventing AKI and limiting CKD progression in patients undergoing cardiac surgery.

Methods: A total of 136 patients with CKD undergoing elective cardiac surgery with cardiopulmonary bypass were randomized into two equal groups: the NO group (n = 68), receiving 80 parts per million NO during the intraoperative period and for 6 h postsurgery, and the control group (n = 68), receiving a sham treatment. The primary outcome was AKI incidence within 7 days postsurgery.

Results: AKI incidence was significantly lower in the NO group (16 of 68 patients, 23.5%) compared to the control group (27 of 68 patients, 39.7%) with a relative risk of 0.59 (95% CI, 0.35 to 0.99; $P = 0.043$). Six months postsurgery, the glomerular filtration rate was higher in the NO group (50 ml · min^{-1} · 1.73 m^{-2} [45; 54]) compared to the control group (45 ml · min^{-1} · 1.73 m^{-2} [41; 51]; $P = 0.038$). Postoperative pneumonia was significantly less frequent in the NO group: 10 of 68 (14.7%) *versus* 20 of 68 (29.4%) with a relative risk of 0.5 (95% CI, 0.25 to 0.99; $P = 0.039$). NO administration was safe: methemoglobin and nitrogen dioxide levels remained within acceptable ranges, oxidative-nitrosyl stress did not increase, and there were no significant differences between the groups in blood transfusion requirements, platelet counts, or postoperative blood loss volumes

Conclusions: Perioperative NO administration in CKD patients undergoing cardiac surgery with cardiopulmonary bypass is safe, reduces the incidence of AKI, and slows the progression of renal dysfunction.

(ANESTHESIOLOGY 2025; 143:287–99)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Patients with chronic kidney disease are at increased risk of developing acute kidney injury after cardiac surgery, which can worsen long-term kidney function
- Despite the clinical significance of this problem, effective pharmacologic strategies to prevent acute kidney injury in this high-risk population remain limited

What This Article Tells Us That Is New

- This randomized clinical trial in cardiac surgical patients demonstrates that perioperative nitric oxide administration reduces acute kidney injury and improves renal function 6 months postoperatively in patients with chronic kidney disease
- Nitric oxide treatment was associated with a lower incidence of postoperative pneumonia without increased oxidative or nitrosyl stress, nitrogen dioxide levels, methemoglobin levels requiring discontinuation of therapy, or differences in bleeding or transfusion-related outcomes

This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 247. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. N.O.K. and M.A.T. contributed equally as co–senior authors to the work.

Submitted for publication November 22, 2024. Accepted for publication April 3, 2025. Published online first on April 9, 2025.

 ANESTHESIOLOGY 2025; 143:287–99. DOI: 10.1097/ALN.0000000000005494

Abbreviations: **AKI**, acute kidney injury; **CKD**, chronic kidney disease; **CPB**, cardiopulmonary bypass; **CSA-AKI**, cardiac surgery–associated acute kidney injury; **eGFR**, estimated glomerular filtration rate; **KDIGO**, Kidney Disease: Improving Global Outcomes; **MACE**, major adverse cardiac event; **MAKE**,major adverse kidney event; **MetHb**, methemoglobin; **NO**, nitric oxide; **NT-proBNP**, N-terminal pro B-type natriuretic peptide; **ppm**, parts per million; **ppb**, parts per billion; **RCT**, randomized controlled trial; **RR**, relative risk

<zdoi;10.1097/ALN.0000000000005494>

Preoperative renal dysfunction is one of the strongest predictors of cardiac surgery–associated acute kidney injury (CSA-AKI), as well as in-hospital morbidity and mortality. CSA-AKI remains a common complication after cardiac surgery, with an incidence of approximately 30% in the general cardiac surgery population and up to 66% in patients with chronic kidney disease (CKD).[1,2] Preoperative CKD is the most significant risk factor for CSA-AKI, and patients who develop postoperative acute kidney injury (AKI) face exceptionally poor outcomes.[3]

Nitric oxide (NO) has been shown to reduce the incidence of CSA-AKI in the general cardiac surgery population, but its protective effects in high-risk patients, particularly those with CKD, remain underexplored.[4,5] In CKD, endogenous NO homeostasis is impaired, leading to decreased endothelial and intrarenal NO production.[6] Additionally, cardiopulmonary bypass (CPB) exacerbates NO depletion due to hemolysis and scavenging by cell-free hemoglobin, further increasing the risk of AKI.[7]

We hypothesized that perioperative NO replacement therapy could counteract intrarenal NO deficiency and, through its systemic and pleiotropic effects, serve as a novel nephroprotective strategy in high-risk cardiac surgery patients.[8] This randomized clinical trial aimed to evaluate the efficacy and safety of perioperative NO conditioning at 80 parts per million (ppm), administered intraoperatively and for 6 h postoperatively, in reducing AKI and mitigating CKD progression after cardiac surgery involving CPB.

Materials and Methods

Study Design, Randomization, and Blinding

This single-center, single-blind, randomized, controlled trial adhered to the ethical principles outlined in the Declaration of Helsinki for human research. The study was approved by the local biomedical ethics committee (approval No. 237, December 20, 2022) and conducted at the Laboratory of Critical Care Medicine and the Department of Cardiovascular Surgery, Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, between March 2023 and July 2024. The trial was registered at ClinicalTrials.gov (NCT05757557; Principal Investigator: Nikolay O. Kamenshchikov, M.D.; initial posting: March 7, 2024). Written informed consent was obtained from all participants.

Patients eligible for enrollment in the study were diagnosed with CKD according to the Kidney Disease Outcomes Quality Initiative (defined as an estimated glomerular filtration rate (eGFR) less than 60 ml · min^{-1} · 1.73 m^{-2} for at least 3 months before surgery, regardless of etiology). The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equations.

Inclusion Criteria.

1. Elective cardiac surgery under CPB.
2. CKD (C3a to C4).

Exclusion Criteria.

1. Emergency surgery.
2. Administration of potentially nephrotoxic drugs within 24 h before surgery (*e.g.*, radiocontrast agents, aminoglycosides, amphotericin).
3. Critical preoperative status (*e.g.*, need for mechanical ventilation, inotrope and vasopressor administration, circulatory support).
4. Pregnancy.
5. Concurrent participation in another randomized controlled trial (RCT).
6. Active endocarditis and/or sepsis.
7. Pulmonary hypertension more severe than group 3 (pulmonary artery systolic pressure greater than 65 mmHg according to preoperative transthoracic echocardiography).
8. Age less than 18 yr.
9. History of kidney transplantation.

Patients were randomly assigned (1:1) to the NO group or the control group using a secure web-based randomization system developed by Sealed Envelope (https://sealedenvelope.com). Randomization was performed by research personnel not involved in treatment or data analysis. Patients, treating physicians, operating surgeons, anesthesiologists, perfusionists, researchers, and other specialists were blinded to group allocation until the study concluded.

In the NO group, inhalation therapy with NO at 80 ppm, produced *via* plasma chemical synthesis (Tianox nitric oxide inhalation therapy device, Russian Federal Nuclear Center, All-Russian Research Institute of Experimental Physics, Russia), was delivered *via* the anesthesia breathing circuit, the CPB machine gas–air mixture supply line, and the ventilator circuit postoperatively. NO conditioning began immediately after tracheal intubation, continued in the intraoperative

Nikolay O. Kamenshchikov, M.D.: Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

Mark A. Tyo, M.D.: Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

Lorenzo Berra, M.D.: Department of Anaesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts; Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts; and Respiratory Care Service, Patient Care Services, Massachusetts General Hospital, Boston, Massachusetts.

Igor V. Kravchenko, M.D.: Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

Boris N. Kozlov, M.D., Ph.D.: Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

Anna M. Gusakova, Ph.D., M.D.: Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

Yuri K. Podoksenov, M.D., Ph.D.: Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, Tomsk, Russia.

period (including the CPB), and extended for 6 h after surgery. If a patient was extubated within 6 h after surgery, NO therapy was discontinued. The delivery schema is depicted in figure 1. The control group did not receive NO inhalation; instead, they received an air mixture without NO as a placebo.

Both groups received a multimodal approach to reduce the risk of AKI, including goal-directed perfusion with oxygen delivery of greater than 280 ml · min^{-1} · m^{-2} during CPB and adherence of Kidney Disease: Improving Global Outcomes (KDIGO) bundle recommendations intraoperatively and for 48 h postoperatively. A detailed description of anesthesia, CPB, intensive care unit management, blinding, rationale for the dosing regimen and weaning from NO provided in the online supplementary digital content (https://links.lww.com/ALN/D967).

Outcomes

Primary Outcomes. Incidence of AKI within 7 days after surgery compared to the control group according to the 2012 KDIGO guidelines.

Secondary Outcomes.

1. The severity and duration of AKI within 7 days after surgery.
2. eGFR at 30 days, 90 days, and 6 months after surgery.
3. AKI biomarkers: urine neutrophil gelatinase-associated lipocalin, urinary kidney injury molecule-1, interleukin-18, serum cystatin C, and intestinal fatty acid–binding protein at baseline and 6 h postoperatively were assessed in 40 patients in each group.
4. Renal regional oximetry at baseline and 6 and 24 h after surgery were assessed in 40 patients in each group.
5. Exhaled NO levels at baseline and 2 and 24 h after surgery were measured in 30 patients in each group.
6. Incidence of postoperative complications and clinical outcomes.
7. Major adverse kidney events (MAKEs; death, renal replacement therapy, decrease in eGFR by 25%), and major adverse cardiac events (MACEs; myocardial infarction, stroke, death) at 30 days, 90 days, and 6 months after surgery.

Exploratory Endpoints.

1. Biomarkers of myocardial injury and strain (troponin I at baseline and 6 and 24 h after surgery, N-terminal pro B-type natriuretic peptide [NT-proBNP] at baseline and 6 h after surgery) were assessed in 40 patients in each group.
2. Cardiovascular profile of patients by De Backer[9] before surgery (after intubation) and 6 and 24 h after surgery were assessed in 40 patients in each group.

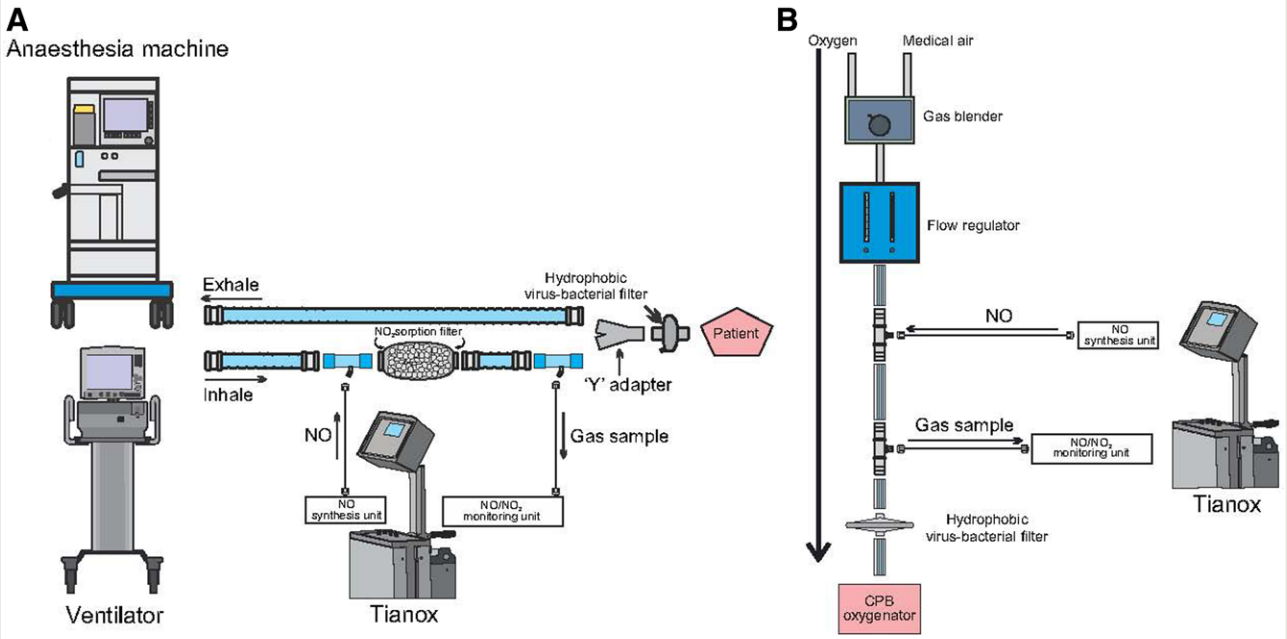

Fig. 1. (*A*) Scheme of 80 ppm NO delivery to the anesthesia machine and ventilator circuits. Two adapters with a Luer-lock connector are built into the inhale tube. NO is supplied through the proximal adapter, and the gas mixture is collected through the distal adapters for continuous monitoring of NO and NO_2 levels. The inhale and exhale tubes are connected with a Y-adapter (*B*) Scheme of NO delivery to the CPB oxygenator. Two ¼ inch Luer-lock adapters are attached to a gas supply line connected to the oxygenator. NO is supplied through the proximal one, and the gas mixture is collected through the distal one for continuous monitoring of NO and NO_2 levels. CPB, cardiopulmonary bypass.

Safety Endpoints.

1. Inspiratory NO_2 levels greater than 3 ppm.
2. Methemoglobin (MetHb) levels greater than 5%, requiring NO discontinuation.
3. Frequency of blood transfusion, volume of blood loss, and platelet counts on postoperative day 1.
4. Oxidative and nitrosyl stress markers (*e.g.*, surfactant associated protein D, nitrotyrosine) at baseline, immediately postoperatively, and at 6 and 24 h postoperatively.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 26. Quantitative variables were assessed for normality using the Shapiro–Wilk test (sample size less than 50) or the Kolmogorov–Smirnov test (sample size greater than 50). The categorical data are presented as numbers and percentages, and the quantitative data are expressed as means ± standard deviations or medians and interquartile ranges as appropriate.

The primary outcome, *i.e.*, the incidence of AKI within 7 days after surgery, was analyzed by chi-square test, and differences between the two groups are expressed as the relative risk (RR) and 95% CI.

As for secondary outcomes, exploratory and safety endpoints: categorical data (including the incidence of postoperative complications; incidence of MACEs, MAKEs, mortality, and CKD progression to a more severe stage 6 months after operation; and incidence of blood component transfusion in the intensive care unit) were analyzed by chi-square test or Fisher's exact test, and differences are expressed as the RR and 95% CI; in intergroup comparisons of continuous data, the Mann–Whitney U test (duration of AKI within 7 days after surgery, eGFR and AKI biomarkers levels at the stages of the study, renal regional oximetry value, MetHb, plasma surfactant–associated protein D, nitrotyrosine, troponin I and NT-proBNP levels, platelet counts on the first postoperative day, and volumes of postoperative blood loss) or Student's *t* test (body mass index, baseline hemoglobin and platelet level) was performed, and the *P* value was calculated; intragroup differences in continuous data (plasma surfactant–associated protein D, troponin I, NT-proBNP, exhaled NO, eGFR, and AKI biomarkers levels, renal regional oximetry values, and nitrotyrosine concentration) at the study stages were analyzed by Wilcoxon signed-rank test or Friedman test. Bonferroni correction was used for multiple comparisons. A two-tailed *P* value of less than 0.05 was considered to indicate statistically significant differences.

To test the primary hypothesis of the study on the efficacy of NO therapy for the effectiveness of preventing AKI in cardiac surgery in patients with CKD, the "intention-to-treat" set of all randomized patients who started NO therapy regardless of whether it was completed in accordance with the protocol to ensure an "intention-to- treat" was analyzed. Because patients were randomized in the operating room immediately before starting NO therapy, the intention-to-treat set did not differ from the full analysis set, *i.e.*, all randomized patients. A similar approach was used to test secondary hypotheses on the efficacy of NO therapy for the secondary endpoints. To assess qualitative variables at 30 days, 90 days, and 6 months after surgery in deceased patients, a pessimistic scenario was used, and to assess quantitative variables, data from the last observation were used.

Sample Size Calculation

The sample size estimation was based on previous studies indicating a 66% AKI incidence in high-risk cardiac surgery patients undergoing CPB.[2] The perioperative KDIGO bundle is expected to reduce this by 16%, yielding a 50% AKI incidence in the control group.[10]

A previous study conducted at our center demonstrated a 50% reduction in AKI incidence with NO therapy.[5] Based on these findings, we estimated an AKI incidence of 25% in the NO group.

Using Lehr's formula, 61 patients per group were required to achieve 80% power at $\alpha = 0.05$. Accounting for a 10% dropout rate, the final sample size was increased to 68 patients per group, totaling 136 participants.

Results

Demographic Data

A total of 136 patients were enrolled in the study according to the inclusion/exclusion criteria and randomized in a 1:1 ratio. All patients remained in their assigned groups, and no crossover occurred. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is presented in figure 2. Patient demography, the severity of baseline condition did not differ between the groups (table 1).

Intraoperative data, surgical procedures, general anesthesia procedures, KDIGO bundle, and goal-directed perfusion were comparable between groups (supplemental digital content, table E1). Routine laboratory values and therapy in the intensive care unit also showed no significant differences (supplemental digital content, table E2). The average NO treatment duration in the NO group was 678 min (mean ± SD, 678 ± 30; minimum, 600; maximum, 750).

Primary Outcome

Administration of NO significantly reduced the incidence of AKI within 7 days after surgery compared to the control group: 16 of 68 (23.5%) in the NO group *versus* 27 of 68 (39.7%) in the control group with a RR of 0.59 (95% CI, 0.35 to 0.99; $P = 0.043$).

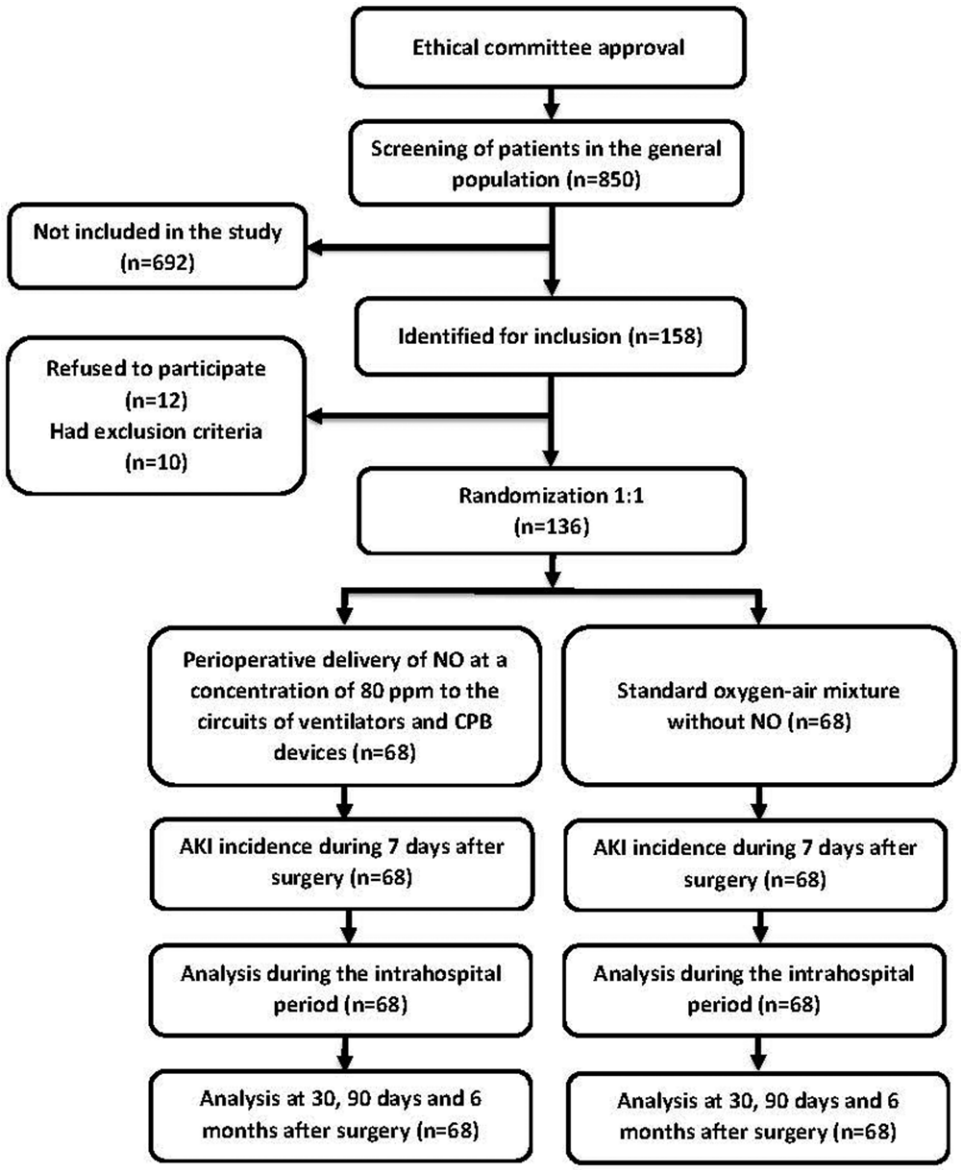

Fig. 2. The Consolidated Standards of Reporting Trials (CONSORT) flow chart of the study. AKI, acute kidney injury; CPB, cardiopulmonary bypass.

Secondary Outcomes

The stages and duration of CSA-AKI did not differ between groups (supplemental digital content, table E3). Data on eGFR dynamics are provided in supplemental digital content, table E4.

Kidney injury biomarkers showed no significant difference between groups (supplemental digital content, table E5). Organ injury markers are presented in figure 3.

Renal regional oximetry values at various study time points were comparable between the groups (fig. 4A; supplemental digital content, table E6). In the NO group, exhaled NO concentrations were higher compared to the control group at 2 h postoperatively (19 parts per billion [ppb] [14; 32] *vs.* 4 ppb [2; 10]; $P < 0.001$) and 24 h postoperatively (21 ppb [12; 28] *vs.* 15 ppb [12; 20]; $P = 0.035$). Within-group comparisons showed a significant reduction in exhaled NO levels in the control group after 2 h compared to baseline ($P < 0.001$), while levels in the NO group remained stable ($P = 0.966$; fig. 4B; supplemental digital content, table E7).

Postoperative pneumonia occurred significantly less frequently in the NO group: 10 of 68 (14.7%) *versus* 20 of 68 (29.4%) with a RR of 0.50 (95% CI, 0.25 to 0.99; $P = 0.039$). Other in-hospital outcomes showed no significant

Table 1. Clinical and Demographic Data

Variables	NO Group (n = 68)	Control (n = 68)	*P* Value
Age (mean [quartile 1; quartile 3]), yr	68 [63.5; 72]	69 [64.5; 74.5]	0.374
Women, n (%)	17 (25)	23 (33.8)	0.259
Body mass index (mean ± SD), kg/m^2	30.1 ± 4.47	28.8 ± 4.94	0.120
Coronary artery disease, n (%)	60 (88.2)	60 (88.2)	> 0.999
Myocardial infarction in history, n (%)	38 (55.9)	32 (47.1)	0.303
NYHA			0.764
1, n (%)	4 (5.9)	5 (7.4)	
2, n (%)	36 (52.9)	32 (47.1)	
3, n (%)	27 (39.7)	31 (45.6)	
4, n (%)	1 (1.5)	0 (0)	
EuroSCORE II (mean [quartile 1; quartile 3]), %*	2.17 [1.51; 2.86]	2.38 [1.55; 3.69]	0.234
Cleveland Clinic Score†			0.135
Low risk, n (%)	23 (33.8)	28 (41.2)	
Intermediate risk, n (%)	39 (57.4)	39 (57.4)	
High risk, n (%)	6 (8.8)	1 (1.5)	
Smoking, n (%)	31 (45.6)	25 (36.8)	0.296
Radiofrequency ablation in history, n (%)	0 (0)	1 (1.5)	> 0.999
Hypertensive disease, n (%)	67 (98.5)	66 (97.1)	> 0.999
LVH, n (%)	27 (39.7)	32 (47.1)	0.387
Baseline hemoglobin (mean ± SD), g/l	137 ± 15.4	132 ± 20.5	0.104
Peripheral artery disease, n (%)	63 (92.6)	63 (92.6)	> 0.999
Atrial fibrillation, n (%)	15 (22.1)	20 (29.4)	0.327
Diabetes mellitus, n (%)	19 (27.9)	19 (27.9)	> 0.999
COPD, n (%)	14 (20.6)	9 (13.2)	0.253
Asthma, n (%)	2 (2.9)	1 (1.5)	> 0.999
eGFR (mean [quartile 1; quartile 3]), ml · min^{-1} · 1.73 m^{-2}	53 [46; 56.5]	53 [47; 56.5]	0.408
Creatinine (mean [quartile 1; quartile 3]), μmol/l	119 [106.5; 134]	115 [102.5; 126]	0.208
Carotid artery stenosis, n (%)	64 (94.1)	62 (91.2)	0.744
Stroke, n (%)	8 (11.8)	11 (16.2)	0.622
TIA, n (%)	0 (0)	1 (1.5)	> 0.999
Hepatitis, n (%)	2 (2.9)	4 (5.9)	0.680
Platelets (mean ± SD), × 10^9/l	207 ± 54.2	208 ± 49.7	0.978
LVEF (mean [quartile 1; quartile 3]), %	58 [50; 63.5]	59.5 [46; 67]	0.580
CO (mean [quartile 1; quartile 3]), l/min	5.3 [3.35; 5.1]	4 [3.35; 4.95]	0.532
Pulmonary artery hypertension, n (%)	38 (55.9)	35 (51.5)	0.606
Surgical modalities			0.108
Isolated CABG, n (%)	48 (70.6)	42 (61.8)	
Single non-CABG, n (%)	11 (16.2)	6 (8.8)	
Two procedures, n (%)	6 (8.8)	12 (17.6)	
Three procedures and more, n (%)	3 (4.4)	8 (11.8)	
Number of grafts			0.256
1, n (%)	0 (0)	3 (5.4)	
2, n (%)	8 (14.8)	7 (12.5)	
3, n (%)	37 (68.5)	32 (57.1)	
4, n (%)	9 (16.7)	14 (25)	
CPB time (mean [quartile 1; quartile 3]), min	95 [85; 111]	96.5 [85; 115]	0.429
Aortic cross-clamping (mean [quartile 1; quartile 3]), min	56 [43.5; 71]	55 [46.5; 77.5]	0.471
Intra-aortic balloon pump	1 (1.5)	0 (0)	> 0.999
Positive hydrobalance per operation (mean [quartile 1; quartile 3]), ml	575 [50; 1,225]	650 [275; 1,075]	0.357
Intraoperative blood transfusion, n (%)	8 (11.8)	9 (13.2)	> 0.999
Blood transfusion volume (mean ± SD), ml	317.5 ± 11.34	318.1 ± 10.53	0.910

*EuroSCORE II is a European system for cardiac operative risk evaluation. †The Cleveland Clinic Score is a clinical score to assess dialysis risk after cardiac surgery. Scores of 0 to 2 indicate low risk, scores of 3 to 5 indicate intermediate risk, and scores of 6 or higher indicate high risk.

CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; CO, cardiac output according to transthoracic echocardiography; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, functional class of chronic heart failure according to New York Heart Association classifications; TIA, transient ischemic attack.

differences (table 2). Six months after surgery, eGFR was significantly higher in the NO group (50 ml · min^{-1} · 1.73 m^{-2} [45; 54] *vs.* 45 ml · min^{-1} · 1.73 m^{-2} [41; 51]; $P = 0.038$). CKD progression to a more severe stage occurred in 7 of 68 (10.3%) patients in the NO group *versus* 15 of 68 (22.1%) in the control group ($P = 0.062$).

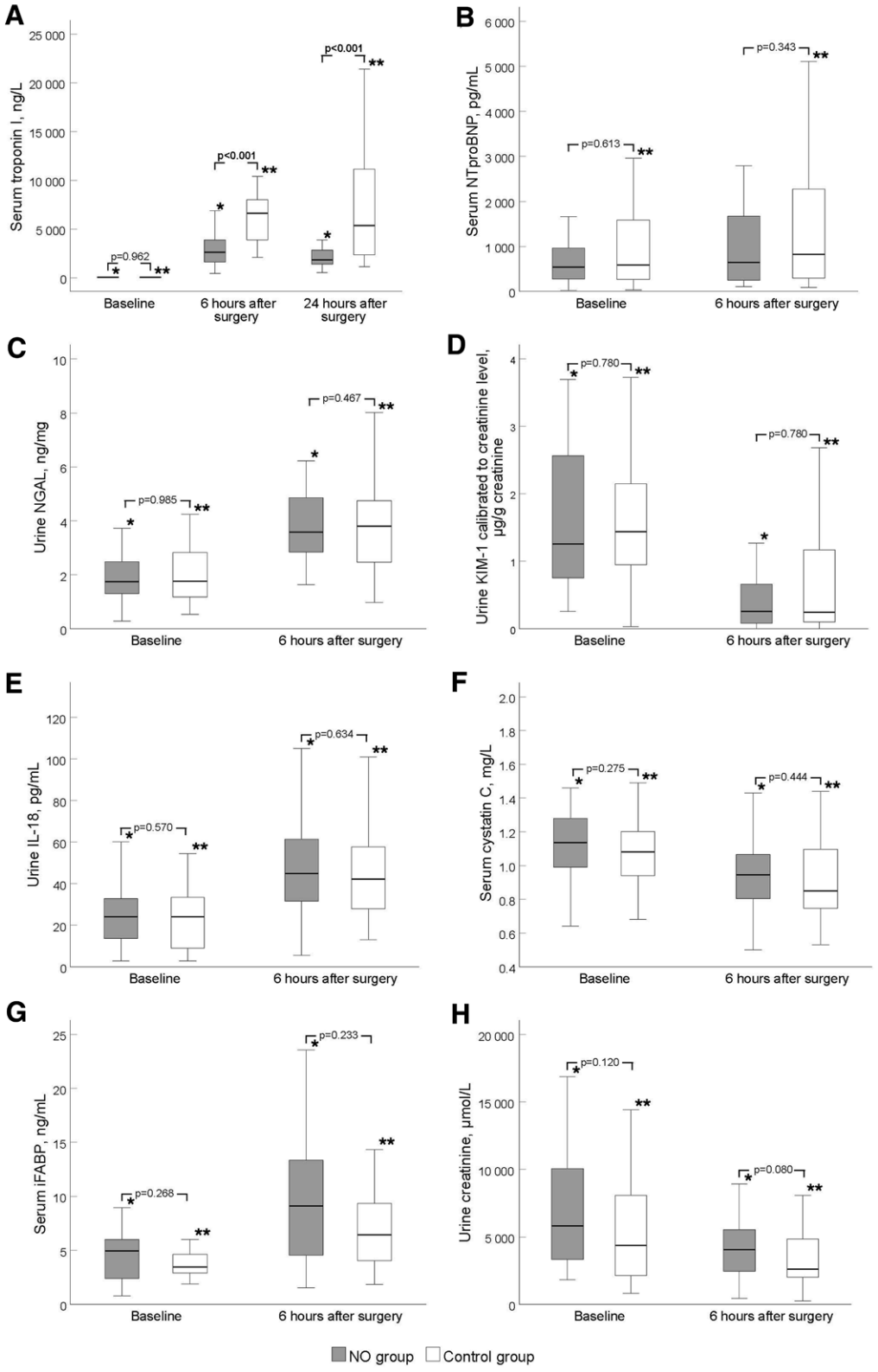

Fig. 3. Dynamics of intra- and intergroup differences in organ injury markers. *, significant dynamic differences in the NO group; **, significant dynamic differences in the control group. iFABP, intestinal fatty-acid binding protein; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; NTproBNP, N-terminal pro B-type natriuretic peptide.

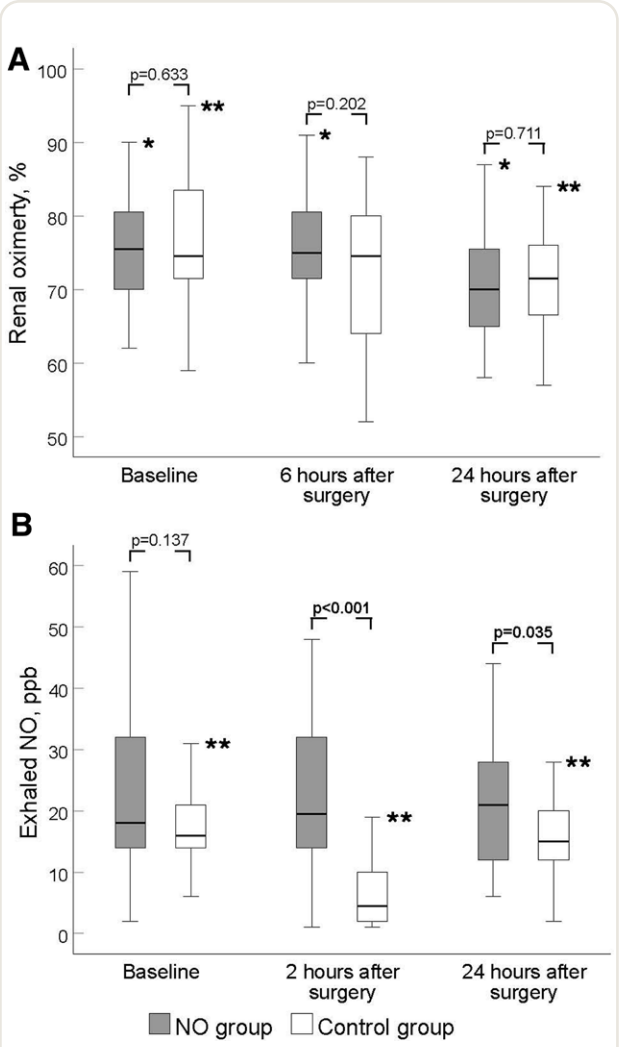

Fig. 4. Dynamics of intra- and intergroup differences in renal regional oximetry (*A*) and exhaled nitric oxide concentrations (*B*). *, significant intragroup difference in the NO group; **, significant intragroup difference in the control group.

Exploratory Endpoints

The NO group demonstrated significantly lower troponin I levels compared to the control group at 6 h (2,616 ng/ml [1,639; 3,901] *vs.* 6,605 ng/ml [3,881; 8,030]; $P < 0.001$) and 24 h after surgery (1,844 ng/ml [1,409; 2,847] *vs.* 5,346 ng/ml [2,384; 11,161]; $P < 0.001$). In the control group, NT-proBNP levels significantly increased at 6 h postoperatively compared to baseline (590 pg/ml [263; 1,582] *vs.* 825 pg/ml [294; 2,278]; $P = 0.038$). However, NT-proBNP levels in the NO group showed no significant changes over time (543 pg/ml [277; 967] *vs.* 642 pg/ml [249; 1,669]; $P = 0.061$; supplemental digital content, table E8). The groups did not differ in postoperative cardiovascular profile (supplemental digital content, table E9).

Safety Endpoints

NO therapy did not result in inspiratory NO_2 levels exceeding 2 ppm (range, 0.8 to 2.0). Plasma MetHb levels in the NO group significantly increased 6 h postoperatively compared to baseline and were higher than those in the control group (3.6% [2.8; 4.1] *vs.* 0.7% [0.4; 0.8]; $P = 0.001$). No patient exhibited MetHb levels exceeding 5% (range, 2.1 to 4.5).

Perioperative blood transfusions rates were 16 of 68 (23.5%) in the NO group *versus* 23 of 68 (33.8%) in the control group ($P = 0.184$). No cases of massive bleeding were recorded in either group. Platelet counts on the first postoperative day were similar (149×10^9/l [128; 179] *vs.* 142×10^9/l [114; 171]; $P = 0.237$), as were volumes of postoperative blood loss (305 ml [220; 400] *vs.* 300 ml [200; 485]; $P = 0.972$; supplemental digital content, table E10).

There was no difference between the groups in the surfactant-associated protein D levels immediately after surgery (5.87 ng/ml [4.75; 6.62] *vs.* 5.2 ng/ml [4.4; 6.5]; $P = 0.148$). Nitrotyrosine concentration did not differ between the groups at 6 h (4.83 nmol/mg [3.52; 5.6] *vs.* 4.73 nmol/mg [3.95; 5.85]; $P = 0.668$) and 24 h (4.37 nmol/mg [3.43; 6.94] *vs.* 5.11 nmol/mg [3.49; 6.86]; $P = 0.613$) after surgery (supplemental digital content, table E11).

All patients in the NO group were successfully weaned off therapy without complications, and no patient required reinitiation of NO therapy. There were no adverse events or organ dysfunctions associated with administration of NO.

Discussion

This prospective RCT demonstrates that perioperative NO administration in high-risk patients with CKD significantly reduces the incidence CSA-AKI by 41% (23.5% in the NO group *vs.* 39.7% in the control group). This reduction translated into a significantly higher eGFR at 6 months postsurgery and a reduced risk of CKD progression. However, no significant differences were observed between the groups regarding AKI duration or the need for renal replacement therapy.

To maximize NO delivery in blood, NO was administered at a concentration of at 80 ppm *via* CPB and ventilator circuits, integrating seamlessly into standard surgical workflow. While systemic NO bioavailability might depend on the delivery route, to ensure protocol consistency and avoid dosing variability, we opted for continuous 80 ppm NO administration rather than adjusting doses at different surgical stages.

Our intervention was safe: NO_2 levels remained within safe limits (0.8 to 2.0 ppm), and while MetHb levels were elevated in the NO group, they did not exceed clinically acceptable thresholds. A recent RCT by Ghadimi *et al.*[11] compared 20 ppm inhaled NO to inhaled epoprostenol in 230 + high-risk cardiac surgery patients undergoing surgery for end-stage heart failure. Primary and secondary

Table 2. Intrahospital Study Outcomes and Clinical Outcomes at 30 Days, 90 Days, and 6 Months after Cardiac Surgery

Variables	NO Group (n = 68)	Control (n = 68)	*P* Value	Risk Ratio (95% CI)
Intrahospital stay				
Intrahospital mortality, n (%)	2 (2.9)	3 (4.4)	> 0.999	0.667 (0.115 to 3.86)
25% decrease in eGFR, n (%)	18 (26.5)	23 (33.8)	0.350	0.783 (0.467 to 1.13)
Intrahospital renal replacement therapy, n (%)	2 (2.9)	0 (0)	0.496	5 (0.245 to 102)
MAKE, n (%)	18 (26.5)	24 (35.3)	0.265	0.75 (0.45 to 1.25)
Stroke, n (%)	1 (1.5)	3 (4.4)	> 0.999	0.333 (0.036 to 3.13)
Myocardial infarction, n (%)	1 (1.5)	5 (7.4)	0.208	0.2 (0.024 to 1.667)
MACE, n (%)	3 (4.4)	8 (11.8)	0.207	0.375 (0.104 to 1.35)
SOFA score, day 1	3 [2; 3]	3 [2; 4]	0.784	
Mechanical ventilation duration (mean [quartile 1; quartile 3]), min	500 [418; 655]	546 [430; 980]	0.317	
Pneumonia, n (%)	10 (14.7)	20 (29.4)	0.039	0.5 (0.253 to 0.988)
Neurologic complications*				
Type 1, n (%)	1 (1.5)	3 (4.4)	0.619	0.333 (0.036 to 3.13)
Type 2, n (%)	6 (8.8)	9 (13.2)	0.585	0.667 (0.251 to 1.77)
Respiratory failure, n (%)†	17 (25)	18 (26.5)	0.844	0.944 (0.533 to 1.67)
Wound infections, n (%)	3 (4.4)	5 (7.4)	0.718	0.6 (0.149 to 2.41)
Sepsis, n (%)	2 (2.9)	3 (4.4)	> 0.999	0.667 (0.115 to 3.87)
Tracheostomy	1 (1.5)	3 (4.4)	0.619	0.333 (0.036 to 3.125)
ICU readmission, n (%)	6 (8.8)	6 (8.8)	> 0.999	1 (0.339 to 2.95)
ICU stay (mean [quartile 1; quartile 3]), days	1 [1; 2.5]	1 [1; 2.5]	0.782	
Intrahospital stay (mean [quartile 1; quartile 3]), days	16 [14; 22]	16 [14; 22]	0.932	
eGFR at discharge (mean [quartile 1; quartile 3]), ml · min^{-1} · 1.73 m^{-2}	55 [47; 64.5]	54.5 [46; 63.5]	0.591	
30 days				
eGFR (mean [quartile 1; quartile 3]), ml · min^{-1} · 1.73 m^{-2}	50 [42; 54]	48.5 [42; 52]	0.220	
MACE, n (%)	4 (5.9)	9 (13.2)	0.243	0.444 (0.144 to 1.37)
MAKE, n (%)	18 (26.5)	24 (35.3)	0.265	0.75 (0.45 to 1.25)
90 days				
eGFR (mean [quartile 1; quartile 3]), ml · min^{-1} · 1.73 m^{-2}	50 [43; 53]	47 [41; 52.5]	0.277	
MACE, n (%)	5 (7.4)	10 (14.7)	0.273	0.5 (0.18 to 1.39)
MAKE, n (%)	18 (26.5)	25 (36.8)	0.197	0.72 (0.435–1.19)
6 months				
eGFR (mean [quartile 1; quartile 3]), ml · min^{-1} · 1.73 m^{-2}	50 [45; 54]	45 [41; 51]	0.038	
MACE, n (%)	7 (10.3)	12 (17.6)	0.323	0.583 (0.245 to 1.39)
MAKE, n (%)	19 (27.9)	26 (38.2)	0.202	0.731 (0.449 to 1.189)
Mortality, n (%)	3 (4.4)	4 (5.9)	> 0.999	0.75 (0.174 to 3.23)
CKD progression to a more severe stage, n (%)	7 (10.3)	15 (22.1)	0.062	0.467 (0.203 to 1.07)

*Type 1 neurologic complications include stroke, coma, transient ischemic attack, while type 2 neurologic complications include delirium and postoperative cognitive dysfunction.

†Respiratory failure indicates a decrease in P/F ratio of less than 300 with the need for high-flow oxygen therapy or noninvasive ventilation. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; MACE, major adverse cardiac events (myocardial infarction, stroke, cardiovascular death); MAKE, major adverse kidney events (death, renal replacement therapy, a 25% decrease in eGFR); SOFA, sequential organ failure assessment score.

outcomes, including AKI, renal replacement therapy rates, and safety endpoints, were comparable between groups, reinforcing the safety of NO therapy in this population. These findings highlight the feasibility of incorporating NO into broader clinical practice and underscore the need for multicenter trials to refine its role in perioperative organ protection.

NO therapy was employed as an adjunct to established nephroprotective strategies, including the KDIGO-bundle and goal-directed perfusion strategies, both proven effective in cardiac surgery.[12,13] Our findings align with previous RCTs demonstrating that NO reduces postoperative AKI in low- and moderate-risk patients,[4,5] likely by mitigating pulmonary and systemic vasoconstriction and reducing cell-free oxyhemoglobin toxicity.[14,15] Furthermore, there is molecular, serological, and histologic evidence supporting NO-mediated renal protection during CPB.[16,17]

Hemolysis during extracorporeal perfusion is a key contributor to perioperative kidney injury, as free hemoglobin depletes endogenous NO, compromising its bioavailability.[18] Peak NO deficiency and free hemoglobin concentrations occur during CPB.[19] CKD patients experience intrarenal NO deficiency due to reduced L-arginine production, inadequate regeneration, and increased NO synthase inhibitors.[6] This imbalance may lead to endothelial dysfunction, glomerular hypertension, and CKD progression.[20] In a recent multicenter study, Landoni *et al.*[21] demonstrated a reduction in the incidence of postoperative AKI among cardiac surgical patients through the intravenous infusion of a mixture of amino acid, including 11.7 g/l of L-arginine, a known precursor of NO. It is tempting to speculate that

the nephroprotective effects observed in that trial may be associated, among other factors, with an increased substrate volume for NO synthesis and the activation of cortical nitric oxide synthase, ultimately improving intrarenal hemodynamic.[22]

In this trial, NO replacement therapy successfully corrected perioperative NO deficiency, as evidenced by stable exhaled NO levels in the NO group, while the control group showed significant declines 2 h after surgery. These findings suggest that NO therapy *via* CPB and ventilator circuits effectively addresses NO deficiency, although no significant differences were observed in cardiovascular profiles or renal regional tissue oximetry between groups.

Renal function improved significantly with NO treatment, but injury biomarkers did not differ between groups. This discrepancy may stem from the high prognostic value of these biomarkers in patients with normal baseline function.[23,24] Their relevance in CKD remains uncertain, as they display diverse pathophysiological roles. In CKD, renal function and nephron reserve vary, complicating the interpretation of kidney injury biomarkers. The disconnect between functional markers (*e.g.*, creatinine) and structural injury markers has been described in CSA-AKI and other settings.[25] Similar to findings in the work of Coca *et al.*,[25] a rise in serum creatinine does not always indicate histological kidney damage. Hemodynamic shifts, altered tubular creatinine handling, or preexisting nephron loss may lead to functional AKI without overt injury, while structural biomarkers may remain unchanged due to baseline CKD alterations. These findings underscore the need for caution in interpreting AKI biomarkers in high-risk surgical patients. Future studies should refine biomarker-based AKI detection in CKD populations. Accurate diagnosis of subclinical AKI in CKD should involve comprehensive assessments beyond eGFR alone, including renal blood flow, tubular injury, and nephron functionality.[26]

Patients with preoperative renal impairment face increased risks of in-hospital mortality and postoperative complications, such as a 2.7-fold rise in pneumonia risk. Enhancing renal function may reduce such risks in CKD patients.[27] In our study, the NO group had a significantly lower incidence of pneumonia (14.7% *vs.* 29.4% in controls), likely due to improved renal function, reduced myocardial stress, and less pulmonary congestion. Nitric oxide has demonstrated antibacterial effects against major causative agents of hospital-acquired pneumonia.[28] In this study, the NO group had a significantly lower incidence of postoperative pneumonia, suggesting a potential protective role. While not a primary outcome, this finding is hypothesis-generating and aligns with previous evidence of NO's antimicrobial properties.

Di Fenza *et al.*[29] further support this concept by demonstrating that high-dose inhaled NO also reduced viral burden in critically ill COVID-19 patients. The mechanisms underlying NO's antibacterial effects include direct microbial toxicity, improved mucociliary clearance, and enhanced host immune response. These pulmonary and extrapulmonary pleiotropic effects may contribute to infection prevention in postoperative patients, warranting further investigation.

Troponin I levels were significantly lower in the NO group at 6 and 24 h postsurgery, consistent with reduced myocardial injury and stress, as shown in other studies.[30,31] This aligns with meta-analyses indicating that NO reduces postoperative troponin I levels, right ventricular failure, and AKI.[32] The reduction in AKI may be secondary to NO's cardioprotective effects, disrupting the heart–kidney injury continuum.[33] While no statistically significant differences were noted in MAKEs, for MACEs there was a trend toward fewer adverse outcomes in the NO group.

The safety profile of NO therapy is particularly relevant in CKD patients, who are prone to platelet dysfunction and increased bleeding risks.[34] This study confirms that NO administration *via* CPB and ventilator circuits is safe, with NO_2 and MetHb levels remaining within clinically acceptable ranges. In this study, NO administration *via* CPB and ventilator circuits was safe within the trial's duration, with NO_2 and MetHb levels remaining within clinically acceptable ranges. However, as exposure time was limited by the study protocol, further trials are needed to evaluate the safety of higher doses and longer durations of NO administration in broader clinical settings. Furthermore, no intergroup differences were observed in oxidative stress markers, postoperative blood loss, transfusion requirements, or platelet counts, underscoring the reliability of this method.[35]

This study has important clinical and economic implications, particularly for high-risk CKD patients undergoing cardiac surgery. From an economic perspective, CSA-AKI without renal replacement therapy adds approximately $26,000 per hospitalization, while CSA-AKI requiring renal replacement therapy incurs approximately $69,000, leading to over $1 billion in short-term costs and potentially tens of billions in long-term healthcare expenses.[36] Early identification of high-risk patients could help target perioperative NO therapy where it is most beneficial.

Regarding cost-effectiveness, traditional cylinder-based NO therapy costs ~$150/hour, whereas bedside NO synthesis reduces this to ~$50/hour, making short-term perioperative NO conditioning a potentially viable intervention.[37] The Tianox delivery system is available in Russia. No issues were encountered during the study, and no reports of NO synthesis device failures from other centers are known to us. Future research should refine patient selection, dosing strategies, and long-term outcomes to maximize NO's therapeutic benefits.

Given the complex phenotype of cardiac surgery patients, perioperative care should be tailored to individual needs. CKD patients, characterized by specific NO

deficiency pathways, are an ideal population for personalized NO dosing. Previous RCT failures may relate to the nonselective enrollment of heterogeneous populations and suboptimal NO dosing regimens.[38]

This study highlights the value of a nephroprotective approach, combining pharmacologic and nonpharmacologic strategies. High-risk cardiac surgery patients with CKD benefit from NO conditioning, which also helps prevent long-term CKD progression. NO delivery through CPB and ventilator circuits offers a safe, efficient, and scalable method for clinical use. Additionally, the use of plasma chemical synthesis technology for NO delivery demonstrates a cost-effective, logistically feasible solution, paving the way for large-scale multicenter trials.[39]

The study has several limitations. First, being single-center study and involving a small sample size may affect the generalizability. Local protocols for anesthesia, surgery, and postoperative care could have influenced outcomes, which should be considered when extrapolating these findings. We used simple randomization without stratification. Fortunately, the analysis of baseline data did not show differences between groups. Second, although we used eGFR for patient selection, kidney functional reserve was not assessed.[40] Biomarkers such as tissue inhibitor of metalloproteinase-2 and insulin-like growth factor–binding protein 7, which are less affected by comorbidities, were unavailable in our clinic.[41] Third, advancing personalized care for CKD patients requires genomic, transcriptomic, and metabolomic profiling to identify specific endotypes in cardiac surgery. Last, we did not assess NO's direct impact on pulmonary circulation pressure or right ventricular overload using prepulmonary manometry and thermodilution, which are crucial for understanding cardiac function. Right ventricular function was not continuously assessed in this study. It should be taken into account that the response to NO therapy in patients with right ventricular failure may differ from those without.

Conclusions

Perioperative NO administration in CKD patients undergoing elective cardiac surgery with CPB is safe and significantly reduces the incidence of AKI and progression of renal dysfunction. Furthermore, it is also associated with a lower incidence of hospital-acquired pneumonia, supporting its potential use as a protective strategy in this high-risk population.

Acknowledgments

The authors thank Elena Kim, Laboratory of Critical Care Medicine, Russian Academy of Sciences, Tomsk, Russia for contributions to the editing of the article. The authors also thank the staff of the Department of Anesthesiology and Intensive Care and the Department of Cardiovascular Surgery, Russian Academy of Sciences, Tomsk, Russia, for daily work and sensitivity to patients.

Research Support

Supported by grant No. 122123000017-3 from the Ministry of Science and Higher Education of the Russian Federation (Moscow, Russia) in the framework of the state assignment for basic research.

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: nikolajkamenof@mail.ru. Raw data available at: nikolajkamenof@mail.ru.

Correspondence

Address correspondence to Dr. Kamenshchikov: Cardiology Research Institute, Tomsk NRMC, 111a Kievskaya Street, Tomsk, 634012, Russian Federation. no@cardio-tomsk.ru or nikolajkamenof@mail.ru

Supplemental Digital Content

Supplemental digital content, https://links.lww.com/ALN/D967
Supplemental File 1. Blinding.
Supplemental File 2. Rationale for the nitric oxide dose selection.
Supplemental File 3. Weaning protocol for inhaled nitric oxide.
Supplemental File 4. Anesthetic management, CPB and staying in the ICU.
Supplemental File 5. Tables E1 to E11.

References

1. Zhang D, Teng J, Luo Z, Ding X, Jiang W: Risk factors and prognosis of acute kidney injury after cardiac surgery in patients with chronic kidney disease. Blood Purif 2023; 52:166–73. doi:10.1159/000526120
2. Cho JS, Shim JK, Lee S, et al.: Chronic progression of cardiac surgery associated acute kidney injury: Intermediary role of acute kidney disease. J Thorac Cardiovasc Surg 2021; 161:681–8.e3. doi:10.1016/j.jtcvs.2019.10.101
3. Molinari L, Sakhuja A, Kellum JA: Perioperative renoprotection: General mechanisms and treatment approaches. Anesth Analg 2020; 131:1679–92. doi:10.1213/ANE.0000000000005107
4. Lei C, Berra L, Rezoagli E, et al.: Nitric oxide decreases acute kidney injury and stage 3 chronic kidney disease after cardiac surgery. Am J Respir Crit Care Med 2018; 198:1279–87. doi:10.1164/rccm.201710-2150OC
5. Kamenshchikov NO, Anfinogenova YJ, Kozlov BN, et al.: Nitric oxide delivery during cardiopulmonary bypass reduces acute kidney injury: A randomized trial.

J Thorac Cardiovasc Surg 2022; 163:1393–403.e9. doi:10.1016/j.jtcvs.2020.03.182
6. Baylis C: Nitric oxide deficiency in chronic kidney disease. Am J Physiol Renal Physiol 2008; 294:F1–9. doi:10.1152/ajprenal.00424.2007
7. Vermeulen Windsant IC, de Wit NC, Sertorio JT, et al.: Hemolysis during cardiac surgery is associated with increased intravascular nitric oxide consumption and perioperative kidney and intestinal tissue damage. Front Physiol 2014; 5:340. doi:10.3389/fphys.2014.00340
8. Kamenshchikov NO, Duong N, Berra L: Nitric oxide in cardiac surgery: A review article. Biomedicines 2023; 11:1085. doi:10.3390/biomedicines11041085
9. De Backer D: Detailing the cardiovascular profile in shock patients. Crit Care 2017; 21:311. doi:10.1186/s13054-017-1908-6
10. Meersch M, Schmidt C, Hoffmeier A, et al.: Prevention of cardiac surgery–associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. Intensive Care Med 2017; 43:1551–61. doi:10.1007/s00134-016-4670-3
11. Ghadimi K, Cappiello JL, Wright MC, et al.; INSPIRE-FLO Investigators: Inhaled epoprostenol compared with nitric oxide for right ventricular support after major cardiac surgery. Circulation 2023; 148:1316–29. doi:10.1161/CIRCULATIONAHA.122.062464
12. Zarbock A, Küllmar M, Ostermann M, et al.: Prevention of Cardiac surgery–associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: The PrevAKI-multicenter randomized controlled trial. Anesth Analg 2021; 133:292–302. doi:10.1213/ANE.0000000000005458
13. Mukaida H, Matsushita S, Yamamoto T, et al.: Oxygen delivery-guided perfusion for the prevention of acute kidney injury: A randomized controlled trial. J Thorac Cardiovasc Surg 2023; 165:750–60.e5. doi:10.1016/j.jtcvs.2021.03.032
14. Signori D, Magliocca A, Hayashida K, et al.: Inhaled nitric oxide: Role in the pathophysiology of cardiocerebrovascular and respiratory diseases. Intensive Care Med Exp 2022; 10:28. doi:10.1186/s40635-022-00455-6
15. Spina S, Lei C, Pinciroli R, Berra L: Hemolysis and kidney injury in cardiac surgery: The protective role of nitric oxide therapy. Semin Nephrol 2019; 39:484–95. doi:10.1016/j.semnephrol.2019.06.008
16. Greenberg JW, Hogue S, Raees MA, et al.: Exogenous nitric oxide delivery protects against cardiopulmonary bypass-associated acute kidney injury: Histologic and serologic evidence from an ovine model. J Thorac Cardiovasc Surg 2023; 166:e164–73. doi:10.1016/j.jtcvs.2023.03.030
17. Kamenshchikov NO, Podoksenov YK, Kozlov BN, et al.: The nephroprotective effect of nitric oxide during extracorporeal circulation: An experimental study. Biomedicines 2024; 12:1298. doi:10.3390/biomedicines12061298
18. Vermeulen Windsant IC, Snoeijs MG, Hanssen SJ, et al.: Hemolysis is associated with acute kidney injury during major aortic surgery. Kidney Int 2010; 77:913–20. doi:10.1038/ki.2010.24
19. Billings FT 4th, Ball SK, Roberts LJ 2nd, Pretorius M: Postoperative acute kidney injury is associated with hemoglobinemia and an enhanced oxidative stress response. Free Radic Biol Med 2011; 50:1480–7. doi:10.1016/j.freeradbiomed.2011.02.011
20. Kishi S, Nagasu H, Kidokoro K, Kashihara N: Oxidative stress and the role of redox signalling in chronic kidney disease. Nat Rev Nephrol 2024; 20:101–19. doi:10.1038/s41581-023-00775-0
21. Landoni G, Monaco F, Ti LK, et al.; PROTECTION Study Group: A randomized trial of intravenous amino acids for kidney protection. N Engl J Med 2024; 391:687–98. doi:10.1056/NEJMoa2403769
22. Yao B, Xu J, Qi Z, Harris RC, Zhang MZ: Role of renal cortical cyclooxygenase-2 expression in hyperfiltration in rats with high-protein intake. Am J Physiol Renal Physiol 2006; 291:F368–74. doi:10.1152/ajprenal.00500.2005
23. Cheruku SR, Raphael J, Neyra JA, Fox AA: Acute kidney injury after cardiac surgery: Prediction, prevention, and management. Anesthesiology 2023; 139:880–98. doi:10.1097/ALN.0000000000004734
24. 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; 49:746–55. doi:10.1093/ejcts/ezv199
25. Coca SG, Garg AX, Swaminathan M, et al.; TRIBE-AKI Consortium: Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. Nephrol Dial Transplant 2013; 28:2787–99. doi:10.1093/ndt/gft405
26. Casanova AG, Sancho-Martínez SM, Vicente-Vicente L, et al.: Diagnosis of cardiac surgery–associated acute kidney injury: State of the art and perspectives. J Clin Med 2022; 11:4576. doi:10.3390/jcm11154576
27. Wang D, Lu Y, Sun M, et al.: Pneumonia after cardiovascular surgery: Incidence, risk factors and interventions. Front Cardiovasc Med 2022; 9:911878. doi:10.3389/fcvm.2022.911878
28. Kalashnikova TP, Arsenyeva IA, Kamenshchikov NO, et al.: Antibacterial effect of nitric oxide on the causative agents of hospital-acquired pneumonia (experimental study). General Reanimatol 2024; 20:32–41. doi:10.15360/1813-9779-2024-3-2424
29. Di Fenza R, Shetty NS, Gianni S, et al.; Nitric Oxide Investigators: High-dose inhaled nitric oxide in acute hypoxemic respiratory failure due to COVID-19: A multicenter phase II trial. Am J Respir Crit Care Med 2023; 208:1293–304. doi:10.1164/rccm.202304-0637OC

30. Gianetti J, Del Sarto P, Bevilacqua S, et al.: Supplemental nitric oxide and its effect on myocardial injury and function in patients undergoing cardiac surgery with extracorporeal circulation. J Thorac Cardiovasc Surg 2004; 127:44–50. doi:10.1016/j.jtcvs.2002.08.001
31. Kolcz J, Karnas E, Madeja Z, Zuba-Surma EK: The cardioprotective and anti-inflammatory effect of inhaled nitric oxide during Fontan surgery in patients with single ventricle congenital heart defects: A prospective randomized study. J Intensive Care 2022; 10:48. doi:10.1186/s40560-022-00639-y
32. 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
33. Coutrot M, Dépret F, Legrand M: Is nitric oxide nephro- or cardioprotective? Am J Respir Crit Care Med 2019; 199:1441–2. doi:10.1164/rccm.201812-2344LE
34. Baaten CCFMJ, Sternkopf M, Henning T, Marx N, Jankowski J, Noels H: Platelet function in CKD: A systematic review and meta-analysis. J Am Soc Nephrol 2021; 32:1583–98. doi:10.1681/ASN.2020101440
35. Gwozdzinski K, Pieniazek A, Gwozdzinski L: Reactive oxygen species and their involvement in red blood cell damage in chronic kidney disease. Oxid Med Cell Longev 2021; 2021:6639199. doi:10.1155/2021/6639199
36. Schurle A, Koyner JL: CSA-AKI: Incidence, epidemiology, clinical outcomes, and economic impact. J Clin Med 2021; 10:5746. doi:10.3390/jcm10245746
37. Yang Y, Qi PK, Yang ZL, Huang N: Nitric oxide based strategies for applications of biomedical devices. Biosurf Biotribol 2015; 1:177–201. doi:10.1016/j.bsbt.2015.08.003
38. Schlapbach LJ, Gibbons KS, Horton SB, et al.; NITRIC Study Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG), and the ANZICS Paediatric Study Group (PSG): Effect of nitric oxide via cardiopulmonary bypass on ventilator-free days in young children undergoing congenital heart disease surgery: The NITRIC randomized clinical trial. JAMA 2022; 328:38–47. doi:10.1001/jama.2022.9376
39. Muenster S, Zarragoikoetxea I, Moscatelli A, et al.: Inhaled NO at a crossroads in cardiac surgery: Current need to improve mechanistic understanding, clinical trial design and scientific evidence. Front Cardiovasc Med 2024; 11:1374635. doi:10.3389/fcvm.2024.1374635
40. Armenta A, Madero M, Rodriguez-Iturbe B: Functional reserve of the kidney. Clin J Am Soc Nephrol 2022; 17:458–66. doi:10.2215/CJN.11070821
41. Göcze I, Jauch D, Götz M, et al.: Biomarker-guided intervention to prevent acute kidney injury after major surgery: The prospective randomized BigpAK study. Ann Surg 2018; 267:1013–20. doi:10.1097/SLA.0000000000002485