Efficacy and safety of inhaled nitric oxide administered during cardiopulmonary bypass for pediatric cardiac surgery: a systematic review and meta-analysis

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Background and aims: Cardiopulmonary bypass (CPB) utilized for cardiac surgeries has been associated with significant mortality and adverse outcomes. The benefits of incorporating nitric oxide (NO) into the CPB circuit have been reported in terms of reduced inflammation, enhanced dynamic circulation, oxygenation, and end-organ function. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of inhaled NO introduced to the CPB circuit among pediatric patients undergoing various cardiac surgeries.

Methods: A systematic literature search was conducted on 26 July 2022, using the electronic databases of PubMed, Cochrane, Scopus, and Web of Science to include randomized controlled trials, with no restriction regarding the date of study conduction. The quality of studies was assessed using the Cochrane tool. RevMan 5.3 software was used to analyze data in the inverse variance method, with pooling data as mean difference (MD), risk ratio, and 95% CI.

Results: Six trials were included comprising 1666 children who had undergone the interventions of interest. All studies amenable to assessment were of good quality. NO was significantly superior to the control treatments regarding ventilation time (MD = -8.34; 95% CI [-14.50 to -2.17], $P = 0.008$), postoperative interleukin-6 (IL-6) levels (MD = -0.50; 95% CI [-0.54 to -0.46], $P < 0.001$), 24-h IL-6 levels (MD = -0.30; 95% CI [-0.32 to -0.20], $P < 0.001$), and 24-h tumor necrosis factor-alpha (TNF-α) levels (MD = -1.72; 95% CI [-3.44 to -1.00], $P = 0.05$). The side effects of NO and the control treatments were comparable ($P = 0.9$).

Conclusion: NO administered as part of the CPB circuit during cardiac surgeries is efficacious in terms of reducing ventilation time, postoperative IL-6, and TNF-α levels compared to control, with a comparable safety profile.

Keywords: cardiac surgery, cardiopulmonary bypass, efficacy, meta-analysis, nitric oxide, safety

Introduction

Congenital heart diseases (CHDs) are among the most devastating pathological entities affecting newborns, constituting the most common cause of death in infants with birth defects, with an incidence of 1 in 100 live birth children[1,2]. In addition, cardiopulmonary bypass (CPB) incorporated for surgical correction of

HIGHLIGHTS

- Cardiopulmonary bypass (CPB) incorporated for surgical correction of congenital heart disease (CHD) has been associated with significant mortality and adverse outcomes.
- In children with CHD, using inhaled nitric oxide (NO) may enhance dynamic circulation and oxygenation in critical patients.
- NO administered as part of the CPB circuit during cardiac surgeries reduced ventilation time, postoperative interleukin-6, and tumor necrosis factor-alpha levels compared to control, with a comparable safety profile.

CHD has been associated with significant mortality and adverse outcomes, despite the mortality reduction that has been reported in the past years[3–7].

A significant inflammatory process is caused by cardiac injury and contact of blood with broad artificial organ surfaces throughout the operation. Reperfusion injury and the release of injury-associated molecular patterns throughout the bypass further exacerbate this reaction[8]. Low cardiac output syndrome (LCOS) is caused by endotoxin release, leukocyte, and complement activation, broad proinflammatory cytokine activation, and endothelium leak after surgery[9]. Inotropes are required to preserve end-organ perfusion, arterial-venous oxygen extraction

increases, lactatemia, and oliguria are all clinical indicators of postoperative LCOS. Multiorgan failure brought on by LCOS may necessitate extracorporeal life support[10,11]. LCOS affects around 30% of children in the initial hours after heart surgery[12]. CBP entails several factors which culminate in the development of systemic inflammatory response syndrome (SIRS). SIRS can eventually manifest as multiple organ system dysfunctions with varying severities, including cardiac, pulmonary, renal, neurologic, and hematologic disorders[13,14].

Nitric oxide (NO) is used in the treatment of pulmonary hypertension in neonates, and some studies show that NO may have an anti-inflammatory effect. NO was associated with decreased plasma consumption in the presence of hemolysis. In children with CHD, using inhaled NO may enhance dynamic circulation and oxygenation in critical patients[15,16]. According to clinical and preclinical data, NO administered as adjuvant therapy in CPB surgery in children has shown a positive effect on myocardial ischemia and reperfusion. Some studies suggest that the use of NO in conjunction with CPB will reduce complications of the surgery, postoperative troponin levels, the incidence of LCOS, and shorten the duration of invasive mechanical ventilation[2].

This systematic review and meta-analysis aimed to evaluate the efficacy and safety profile of inhaled NO introduced to the CPB circuit among pediatric patients undergoing several cardiac surgeries.

Materials and methods

We followed the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions to conduct this systematic review and meta-analysis[17]. Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed[18], Supplemental Digital Content 1, http://links.lww.com/MS9/A96. This study was also reported in accordance with assessing the methodological quality of systematic reviews (AMSTAR) guidelines[19], Supplemental Digital Content 2, http://links.lww.com/MS9/A97.

Literature search

The systematic literature search was conducted on 26 July 2022, using the electronic databases of PubMed, Cochrane, Scopus, and Web of Science. The search was not restricted to a specific timeline. However, it was restricted to randomized controlled trials (RCTs) in terms of study design. The search terms used were (Child* OR infant* OR Neonate*) AND ('Heart Lung bypass*' OR 'Heart-Lung bypass*' OR 'Cardiopulmonary bypass*' OR 'Cardiac surgery*' OR 'Heart surgery*' OR 'Thoracic surgery*') AND ('Nitric oxide' OR 'Nitrogen Monoxide' OR 'Mononitrogen Monoxide' OR 'Nitrate Vasodilator').

Eligibility criteria and studies selection

All RCTs reporting sufficient information regarding the safety and efficacy of NO administration into the CPB circulation among children undergoing cardiac surgeries were included in this review. The exclusion criteria were postoperative NO administration and studies without sufficient data of interest.

The titles and abstracts of all articles retrieved from this search were screened by two independent reviewers for potential inclusion in the review. Then, the full text of all potentially included studies was reviewed for inclusion according to the defined eligibility criteria. Thereafter, screening was revised by a third reviewer and discrepancies were discussed to reach a consensus.

Quality assessment

The Cochrane Collaboration tool described in the Cochrane Handbook for Systematic Reviews of Intervention was used to evaluate the quality of all included studies[17]. To rate the caliber of the research, we considered the following six domains: incomplete data (attrition bias), selective reporting (reporting bias), random sequence generation and allocation concealment (selection bias), blinding of participants (performance bias), blinding of assessors (detection bias), incomplete data (attrition bias), and other possible sources of bias. Two independent reviewers assessed the quality of the included RCTs. A third reviewer revised the quality assessment and any disparity among the reviewers was resolved by discussion to reach a consensus. The funnel plot symmetry was evaluated to assess the risk of publication bias.

Data extraction

Four authors independently extracted the following data from the included studies: a summary of the study design and population, baseline characteristics of the participants, and the study outcomes. The outcomes assessed were: duration of ventilation (hours), length of hospital stay (days), length of ICU stay (hours), need for extracorporeal membrane oxygenation (ECMO) within 48 h, chest tube output within 48 h (ml), postoperative change in platelets count ($\times 10^9$/l), cardiac troponin level (ng/ml) just postoperatively, after 12 h, and after 24 h; interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α) levels (pg/ml) just postoperatively, after 12 h, and after 24 h, in addition to any adverse events. Unit conversions were done when required. A fifth author revised data extraction and conflicts were eventually resolved through group discussion.

Data synthesis

Cochrane Collaboration's RevMan software, version 5.3, was used for all statistical analyses. The 95% CI and mean difference (MD) were used to examine continuous data, whereas the 95% CI and risk ratio (RR) were used to examine binary data. Visual assessment of the forest plot was used to detect heterogeneity between the experiments. In addition, we used the statistical tests chi-squared (χ^2) and I-squared (I^2). High heterogeneity was indicated by an I^2 value of at least 50%[20,21]. A random-effect model was applied where there was significant heterogeneity. Alternatively, the fixed-effects model was used.

Results

Literature search and characteristics of the included studies

Our search included 209 studies from PubMed, 40 from Cochrane, 50 from Web of Science, and 294 from Scopus, making a total of 593 studies. After removing the duplicated results, 547 studies were included for screening. Title and abstract screening excluded 515, and full-text screening further excluded 26 studies, making a total of 6 included RCTs for qualitative and quantitative analysis (Fig. 1). The studies included a total of 1666 children who were undergoing cardiac surgery. Among these
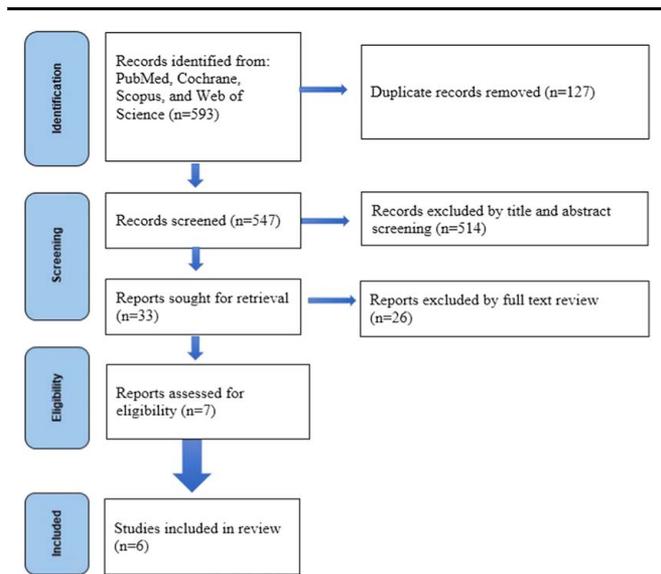
Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

children, 830 had undergone CPB with NO introduced to the oxygenator, while 836 had undergone conventional CPB. A summary of the features of included studies is shown in Table 1, and the characteristics of the enrolled children are shown in Table 2.

Risk of bias assessment

Overall, the included studies were of good quality. For random sequence generation and allocation concealment, a low risk of bias was detected in Checchia *et al*[26]. James *et al*[25]. And Niebler *et al*[22]. And it was unclear for the rest. Moreover, all studies had a low risk of performance, detection, attrition, and reporting biases, except for Zheng *et al*[24]. That had an unclear risk of attrition bias. The studies had no other potential source of bias, but Zheng *et al*.[24] had no available protocol, and James *et al*[25]. Protocol was registered retrospectively. The risk of bias graph and summary are presented in Figures 2 and 3, respectively. The risk of publication bias was low according to the funnel plot assessment (Fig. S1, Supplemental Digital Content 3, http://links.lww.com/MS9/A98, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).

Study outcomes

Ventilation time (hours)

Three studies reported this outcome[22,25,26] with a total of 254 patients enrolled (127 in each group). The ventilation time for the intervention group was significantly less than that for the control with an effect size of – 8.34 [– 14.50 to – 2.17]; and a *P* value of 0.008. The results were also homogenous ($P = 0.89\%$, $I^2 = 0$) (Fig. 4).

Length of hospital stay (days)

The analysis of this outcome was based on five trials[2,22,23,25,26] with 1642 patients enrolled (824 for NO and 818 for the control). The length of hospital stay in days was less in the intervention group (MD = – 0.42; 95% CI [– 1.18 to 0.34]), the results were yet insignificant with a *P* value of 0.27. The analysis revealed homogenous results ($P = 0.61$, $I^2 = 0$) (Fig. S2, Supplemental Digital Content 4, http://links.lww.com/MS9/A99, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).

Length of ICU stay (hours)

A total of four studies[2,23,25,26] reported this outcome, with 1602 patients enrolled (800 for NO and 802 for the control). The ICU stay duration in hours was less in the NO group (MD = – 5.46; 95% CI [– 15.52 to 4.60]) with a *P* value of 0.29 making the overall results statistically insignificant. The results were heterogeneous ($P = 0.04$, $I^2 = 65\%$) (Fig. S3, Supplemental Digital Content 5, http://links.lww.com/MS9/A100, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).

Need for ECMO within 48 h

Two studies[22,25] reported this outcome with 238 patients enrolled (119 in each group). The need for ECMO was assessed within 48 h, and the risk ratio was insignificantly favoring the NO group (RR = 0.23; 95% CI [0.05–1.0], $P = 0.05$). The analysis revealed homogenous results ($P = 0.17$, $I^2 = 46\%$) (Fig. S4, Supplemental Digital Content 6, http://links.lww.com/MS9/A101, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).

Chest tube output within 48 h (ml)

A total of 40 patients (20 in each group) from two studies[23,26] reported this outcome. Chest tube output within 48 h was lower in the intervention group, yet the finding was statistically insignificant (MD = – 9.05; 95% CI [– 36.70 to 18.60], $P = 0.52$). The results were homogenous ($P = 0.38$, $I^2 = 0\%$) (Fig. S5, Supplemental Digital Content 7, http://links.lww.com/MS9/A102, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).

Postoperative change in platelets count ($\times 10^9/l$)

Two studies[22,24] reported this outcome with 64 patients (30 for NO and 34 for the control). Postoperative reduction in platelets count did not differ significantly between the two groups (MD = 1.13; 95% CI [– 28.95 to 31.21], $P = 0.94$), and the results were homogenous ($P = 0.70$, $I^2 = 0\%$) (Fig. S6, Supplemental Digital Content 8, http://links.lww.com/MS9/A103, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).

Cardiac troponin level (ng/ml)

(i) Postoperatively

Three studies[2,23,26] reported cardiac troponin levels postoperatively, with 799 children enrolled (394 for NO and 405 for the control). The difference in the postoperative results was insignificant (MD = – 0.25; 95% CI [– 0.75 to 0.22], $P = 0.29$), and the results were homogenous ($P = 0.89$, $I^2 = 0\%$).

(ii) After 12 h

Two studies[23,26] reported cardiac troponin levels after 12 h, with 40 patients enrolled (20 in each group). The findings of cardiac troponin after 12 h were insignificant (MD = – 1.79;

Table 1

Summary of the included trials' key features.

Reference	Country	Sample size	Inclusion criteria	Exclusion criteria	Intervention protocol	Follow-up duration	Conclusion
Schlapbach et al., 2022[2]	Australia, New Zealand, and the Netherlands	1364 patients (683 for NO and 688 for control)	Children under 2 years undergoing elective open congenital heart disease surgery with CPB for correction of CHD	Children with persistently elevated pulmonary vascular resistance, chronic ventilator dependency, severe preoperative shock states and sepsis, acute respiratory distress syndrome, and methemoglobinemia. As well, those after cardiac arrest receiving ECMO or deemed unlikely to survive the next hours without surgery	NO was added to the CPB oxygenator until a concentration of 20 ppm was reached, which was then confirmed through continuous sampling. NO began when CPB was implemented, and continued until the bypass was weaned (the same process was repeated in the event that a patient performed many bypass runs they carry out)	48 h after the operation or until ICU discharge	This study supports not utilizing NO for CPB because it is ineffective
Niebler et al., 2021[22]	USA	40 patients (18 for NO and 22 for control)	Children under 1 year of age undergoing cardiac surgery requiring cardiopulmonary bypass	Patients with prior surgery requiring CPB within the same hospitalization, preoperative need for ECMO or mechanical circulatory support, known hypersensitivity to NO, and known hemostatic or thrombotic disorders that altered the transfusion/anticoagulation protocol	Patients in the NO group received NO at a dose of 20 ppm in the sweep gas upon beginning sweep gas flow	30 days	Similar clinical results between the treatment and placebo groups were supported, but statistically insignificant improvements were seen in the amount of platelet transfusion, length of hospital stay, and overall hospital cost, with an analogous negative impact
Elzein et al., 2020[23]	USA	24 patients (12 in each group)	Neonates delivered at full-term (> 37 weeks' gestation) and weighting > 2.5 kg with hypoplastic left heart syndrome or variant who are undergoing Norwood procedure	Preoperative sepsis, renal dysfunction (creatinine level > 1 mg/dl), intracranial hemorrhage, chromosomal abnormalities and/or genetic syndromes, and prior intervention (catheter or surgical)	NO delivery was started at 40 ppm as measured by the sampling line and maintained at 40 ppm during the procedure unless serum methhemoglobin level increased above 3%. Once the patient was weaned of CPB, NO delivery via the CPB was discontinued and switched to endotracheal tube administration	48 h after the operation	This study supports not utilizing NO for CPB because it is ineffective
Zheng et al., 2018[24]	China	60 patients (12 for NO, 12 for control, and 24 for other interventions)	Children aging from 6 to 36 months, ASA class I–III having CHD with pulmonary artery pressures <30 mmHg, requiring CPB surgery under general anesthesia	Patients born prematurely, patients with body temperatures <36.5 or > 37.5°C (ear temperature), abnormal liver or renal function, major chromosomal abnormalities, pulmonary inflammation, hemodynamic dysfunction, and patients refusing to participate	Patients in the NO group were given 20 ppm NO by inhalation from the bubble oxygenator throughout CPB	24 h after the operation	The administration of a NO can successfully prevent endothelial cell activation and safeguard pulmonary function brought on by CPB. Additionally, it clearly suppressed CPB-related platelet activation, unfavorable systemic reactions, and fibrinolytic system activation
James et al., 2016[25]	Australia	198 patients (101 for NO and 97 for control)	Children undergoing cardiac surgery with CPB for correction of CHD	Administration of inhaled NO immediately prior to surgery or emergency surgery	Patients in the NO group received 20 ppm NO blended into the CPB gas administration line upon initiation of CPB and continued throughout	48 h after the operation	Postoperative low cardiac output syndrome was less common after pediatric cardiac surgery when NO was administered to the CPB oxygenator. This effect was age-dependent, with

| Checchia et al., 2013[26] | USA | 16 children (8 in each group) | Children undergoing complete repair of tetralogy of Fallot | Those who showed signs of persistently elevated pulmonary vascular resistance preoperatively. Cardiac arrest 1 week before surgery, previous surgical procedure that required the use of CPB, recent treatment with steroids or condition that might require treatment with steroids, and the use of another investigational drug. | Patients in the NO group received 80 ppm NO initially until the return sample began to increase. Then, NO was delivered at 20 ppm. NO delivery was started with CPB and continued throughout | 48 h after the operation | younger children experiencing the highest impact. The postoperative outcomes of the children who received NO during CPB were better, as evidenced by shorter stays in the pediatric ICU, shorter periods of time requiring mechanical breathing, and improved measures of myocardial function and damage |

ASA, American Society of Anesthesiologists; CHD, congenital heart disease; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; NO, nitric oxide.

Table 2

Baseline characteristics of the enrolled participants

Reference	Number of children		Males, N (%)		Age (days)		Weight (kg)		Total CPB time (min)		Total cross-clamp time (min)	
	NO	Control	NO	Control	NO	Control	NO	Control	NO	Control	NO	Control
Schlapbach et al., 2022[2]	679	685	413 (60.8)	368 (53.7)	100.1 ± 128.1	108.5 ± 149.8	4.9 ± 2.3	5.1 ± 2.7	–	–	–	–
Niebler et al., 2021[22]	18	22	9 (50.0)	13 (59.1)	100.6 ± 77.7	112.4 ± 92.5	4.6 ± 1.5	4.8 ± 1.5	125.9 ± 45.5	123.8 ± 51.0	77.4 ± 40.6	74.1 ± 45.4
Elzein et al., 2020[23]	12	12	8 (66.7)	7 (58.3)	5.7 ± 1.9	5.9 ± 1.8	3.3 ± 0.5	3.2 ± 0.8	143.0 ± 17.1	150.7 ± 20.4	50.8 ± 8.7	53.6 ± 6.6
Zheng et al., 2018[24]	12	12	8 (66.7)	8 (66.7)	528 ± 174	519 ± 162	11.1 ± 3.5	10.7 ± 2.6	49.7 ± 7.2	50.7 ± 7.3	29.2 ± 6.2	28.3 ± 6.7
James et al., 2016[25]	101	97	61 (60.0)	55 (57.0)	501 ± 948	429 ± 834	8.6 ± 9.3	7.5 ± 8.1	133.3 ± 74.1	119.3 ± 91.1	66.5 ± 57.9	65.2 ± 56.4
Checchia et al., 2013[26]	8	8	7 (87.5)	4 (50.0)	191 ± 112	216 ± 114	–	–	118.0 ± 31.0	128.0 ± 36.0	60.0 ± 10.0	67.0 ± 9.0

Data are presented as number (proportion) or mean ± SD.

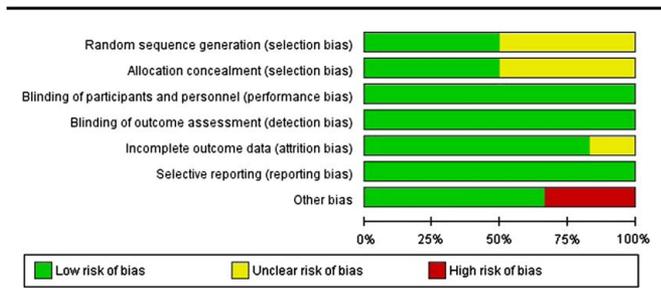CPB, cardiopulmonary bypass; NO, nitric oxide.

Elnaiem et al. Annals of Medicine & Surgery (2023)

Annals of Medicine & Surgery

Figure 2. Risk of bias graph.

95% CI [− 5.80 to 2.23], $P = 0.38$) and heterogeneous ($P = 0.01$, $I^2 = 84\%$).

(iii) After 24 h

Three studies[2,23,26] reported cardiac troponin levels after 24 h, with 731 patients enrolled (367 for NO and 364 for the control). The results were insignificant (MD = − 1.57; 95% CI [− 5.04 to 1.90], $P = 0.37$) and heterogeneous ($P = 0.007$, $I^2 = 0\%$) (Fig. S7, Supplemental Digital Content 9, http://links.lww.com/MS9/A104, Supplemental Digital Content 10, http://links.lww.com/MS9/A105, Supplemental Digital Content 11, http://links.lww.com/MS9/A106, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).
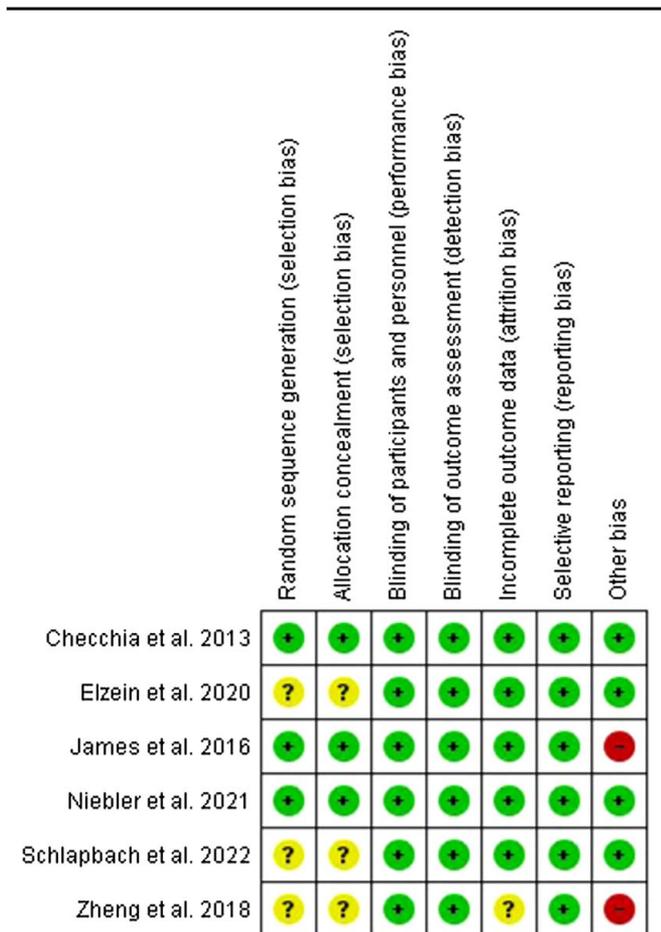

Figure 3. Risk of bias summary.

IL-6 level (pg/ml)

(i) Postoperatively

Three studies[23,24,26] assessed IL-6 level postoperatively, with 64 patients enrolled (32 in each group). The meta-analysis results were statistically favoring the NO group (MD = − 0.50; 95% CI [− 0.54 to − 0.46], $P < 0.001$), and the analysis revealed homogenous findings ($P = 0.51$, $I^2 = 0\%$).

(ii) After 12 h

Two studies[16,21] assessed IL-6 after 12 h, with 40 patients included (20 in each group). The analysis findings revealed insignificant but homogenous differences between the groups (MD = − 45.75; 95% CI [− 106.70 to 15.20], $P = 0.14$), ($P = 0.43$, $I^2 = 0\%$).

(iii) After 24 h

Three studies[23,24,26] assessed IL-6 after 24 h with 64 patients included (32 in each group). The 24 h findings were significant (MD = − 0.30; 95% CI [− 0.32 to − 0.20], $P < 0.001$) and homogenous ($P = 0.43$, $I^2 = 0\%$) (Fig. 5).

IL-8 level (pg/ml)

Two studies[23,26] reported IL-8 levels postoperatively, after 12 h, and after 24 h; with 40 patients included (20 in each group).

(i) Postoperatively

Analysis revealed lower IL-8 levels in the NO group, yet these findings were insignificant (MD = − 30.87; 95% CI [− 97.29 to 35.54], $P = 0.36$), and homogenous ($P = 0.44$, $I^2 = 0\%$).

(ii) After 12 h

Insignificant outcomes favoring the NO group (MD = 1.73; 95% CI [− 61.76 to 65.22], $P = 0.96$), and homogenous results ($P = 0.17$, $I^2 = 48\%$) were found.

(iii) After 24 h

The analysis was insignificant as well (MD = 50.93; 95% CI [− 32.62 to 134.49], $P = 0.23$), and the analysis revealed homogenous outcomes ($P = 0.52$, $I^2 = 0\%$) (Fig. S8, Supplemental Digital Content 12, http://links.lww.com/MS9/A107, Supplemental Digital Content 13, http://links.lww.com/MS9/A108, Supplemental Digital Content 14, http://links.lww.com/MS9/A109, Supplemental Digital Content 15, http://links.lww.com/MS9/A110).

TNF-α level (pg/ml)

Two studies[23,26] reported TNF-α levels postoperatively, after 12 h, and after 24 h, with 40 patients included (20 in each group).

(i) Postoperatively

Analysis revealed lower levels in the control group, yet the findings were insignificant (MD = 0.05; 95% CI [− 0.08 to 0.19], $P = 0.44$) and homogenous ($P = 0.22$, $I^2 = 34\%$).

(ii) After 12 h

Insignificant outcomes yet favoring the NO group (MD = − 0.27; 95% CI [− 1.00 to 0.45], $P = 0.46$), and homogenous results ($P = 0.55$, $I^2 = 0\%$) were found.

(iii) After 24 h

The analysis was significantly favoring the NO group (MD = − 1.72; 95% CI [− 3.44 to − 1.00], $P = 0.05$), and revealed homogenous outcomes ($P = 0.75$, $I^2 = 0\%$) (Fig. 6).

Any adverse events

Three studies[2,22,25] reported adverse reactions as outcomes with 1602 children enrolled (798 for NO and 804 for the control). Adverse outcomes were found to be more in the control group;
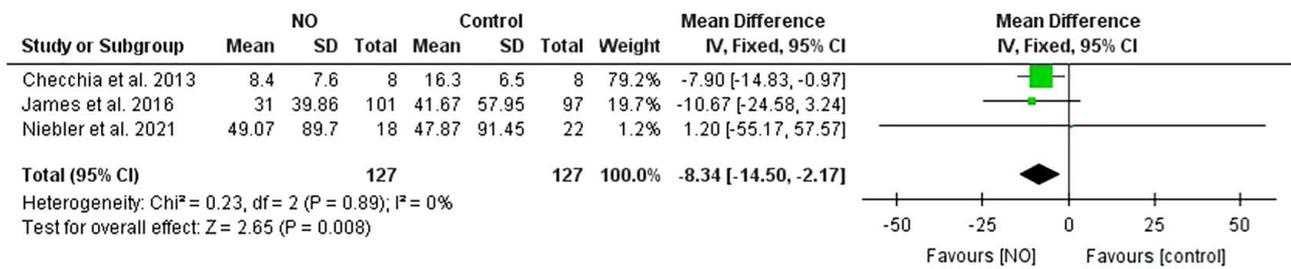
Figure 4. Forest plot of the analysis ventilation time (hours). NO, nitric oxide.

however, these findings were statistically insignificant (RR = 0.98; 95% CI [0.74–1.30], $P = 0.90$), and the analysis revealed homogenous results ($P = 0.28$, $I^2 = 20\%$) (Fig. 7). Death was reported in two papers; one cardiac arrest in the case group (paper 1) and four patients from the control group died before discharge from ICU (paper 5).

Discussion

CPB is required during the majority of surgical procedures on the heart. However, CPB induces a systemic inflammatory response in addition to the ischemia/reperfusion injury. Together, these effects result in multiorgan damage, including the heart and lungs. The choice to study intraoperative rather than postoperative NO prescription is based on the fact that intraoperative NO has been reported to have a protective effect against the inflammatory response induced by CPB. In contrast, postoperative NO prescription may not be as effective in mitigating the inflammatory response, as the damage has already been done[27]. By including studies on the intraoperative administration of NO, this review is focused on

studying the effects of NO therapy during the most critical period of the surgery.

This systematic review was conducted with a meta-analysis to evaluate the clinical effectiveness and safety profile of introducing inhaled NO to the CPB circuit for pediatric patients undergoing various cardiac surgeries. This review was based on six RCTs enrolling 1666 children; among these children, 830 had undergone CPB with NO introduced to the oxygenator, while 836 had undergone conventional CPB. Our comparative meta-analysis revealed that NO decreases the required time on mechanical ventilation ($P = 0.008$). In addition, the IL-6 level postoperatively and after 24 h was significantly reduced by NO ($P < 0.001$ for the two-time points). The reduction in TNF-α levels became significant after 24 h ($P = 0.05$). Furthermore, the reported side effects of NO were not different from those of the control ($P = 0.9$), indicating that NO can be safely administered to this population.

During CPB, several proinflammatory cytokines are released, and the neutrophils further amplify their release, resulting in the subsequent recruitment of monocytes and lymphocytes. As a result, an inflammatory reaction is initiated targeting different tissues[28]. IL-6 is
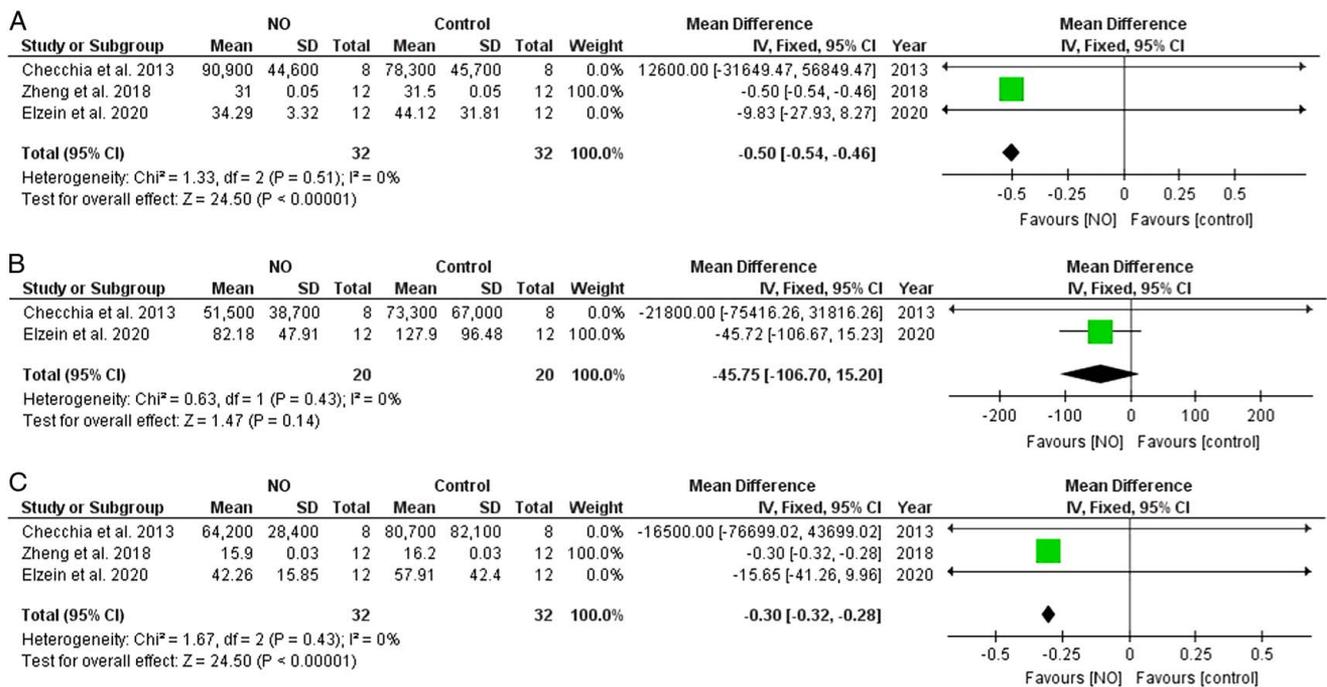

Figure 5. Forest plot of the analysis interleukin-6 (IL-6) level (pg/ml): (A) postoperatively, (B) after 12 h, and (C) after 24 h. NO, nitric oxide.
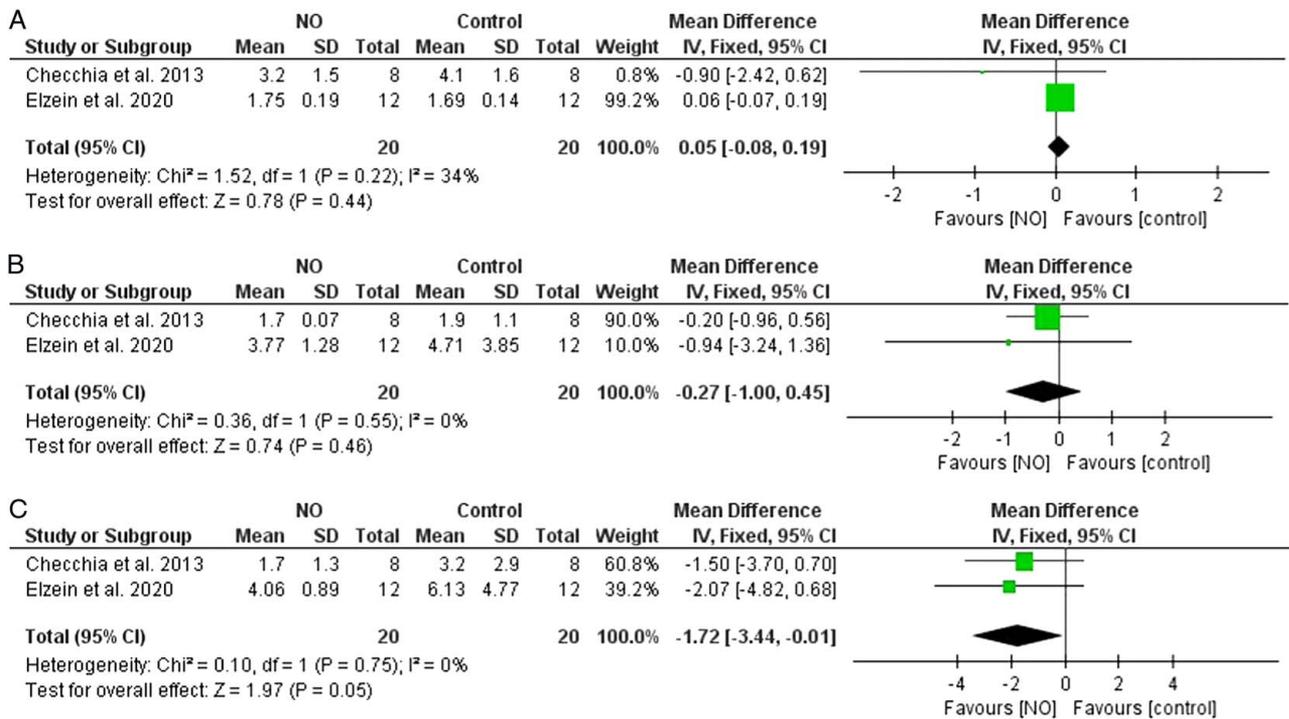
Elnaiem et al. Annals of Medicine & Surgery (2023)

Annals of Medicine & Surgery

Figure 6. Forest plot of the analysis tumor necrosis factor-alpha (TNF-α) level (pg/ml): (A) postoperatively, (B) after 12 h, and (C) after 24 h. NO, nitric oxide.

a proinflammatory cytokine that can be monitored to predict the clinical outcome of patients[29,30]. Among other consequences, patients with high levels of IL-6 mostly experience severe pulmonary dysfunction[31,32]. A study by Behr et al.[33] has reported elevated IL-6 levels after undergoing CPB. Our meta-analysis pooled data from three RCTs and concluded that administering NO during CPB significantly reduces the levels of IL-6 postoperatively and even after 24 h. Another analysis revealed a reduction of TNF-α levels at 24 h postoperatively, indicating a delayed effect on this pathway. However, the analysis of IL-8 levels revealed an insignificant effect at all studied time points. These findings suggest that NO primarily limits the inflammatory response that damages tissues by minimizing IL-6 release.

Clinically, the anti-inflammatory effect of NO was investigated through its impact on limiting postoperative pulmonary dysfunction. Our meta-analysis concluded that NO significantly reduces the required time for mechanical ventilation. This finding suggests a superiority of NO in recovering normal pulmonary function. Consequently, the administration of NO might minimize the financial burden on families and health systems. However, NO did not reduce the length of stay in the hospital significantly.

NO has also been used to minimize ischemia/reperfusion damage in different types of surgeries, including liver transplantation and knee surgeries[34,35]. A previous meta-analysis by Villarreal et al[36]. In 2020 investigated the use of NO postoperatively for pediatric patients who had undergone different cardiac surgeries. The findings of their study revealed a reduced duration of mechanical ventilation with NO as well. In addition, their findings were consistent with ours regarding the insignificant effect on shortening hospital stays. However, this study has not investigated the effect of NO on the release of proinflammatory mediators. The theory behind the efficacy of NO prefers the availability of NO at the time of CPB and reperfusion in order to limit the inflammatory process at its beginning rather than the delayed administration.
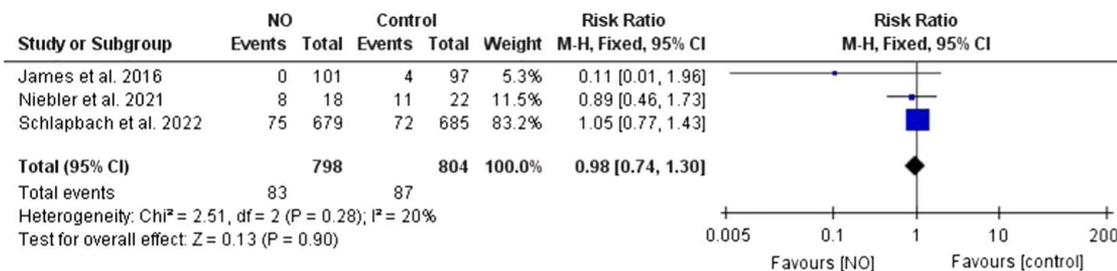

Figure 7. Forest plot of the analysis of adverse events. NO, nitric oxide.

To our knowledge, this is the first systematic review to investigate the application of NO in the CPB circuit for pediatric patients undergoing cardiac surgery. Our study is strengthened by pooling the data from RCTs only, providing the highest level of evidence. In addition, the included trials were of good to moderate quality. There is a paucity of RCTs investigating our review question; furthermore, the available RCTs included children of different age groups undergoing different cardiac surgeries. All these factors might have contributed to the discrepancy in the results. Because few RCTs were included, the resulting heterogeneity could not be solved by sensitivity or subgroup analyses in some of our outcomes. Moreover, the few number of included studies might have affected the power of the funnel plot used for evaluating publication bias. Therefore, further RCTs of a large scale are required to support the presented evidence in this review.

Ethical approval

Not applicable. The current study is a secondary analysis that did not involve patients.

Consent

Not applicable. The current study is a secondary analysis that did not involve patients.

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Author contribution

W.E.: conceptualization, data curation, formal analysis, investigation, project administration, supervision, visualization, original draft preparation, reviewing, and editing; A.M.E.: conceptualization, data curation, investigation, original draft preparation, reviewing, and editing; A.E.A.K.: data curation, original draft preparation, reviewing, and editing; M.M.: conceptualization, visualization, original draft preparation, and reviewing; L.H.: visualization, original draft preparation, and reviewing.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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Not applicable.

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References

[1] van der Bom T, Zomer AC, Zwinderman AH, et al. The changing epidemiology of congenital heart disease. Nat Rev Cardiol 2011;8:50–60.

[2] Schlapbach LJ, Gibbons KS, Horton SB, et al. 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.

[3] Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232–44.

[4] Larmann J, Theilmeier G. Inflammatory response to cardiac surgery: cardiopulmonary bypass versus non-cardiopulmonary bypass surgery. Best Pract Res Clin Anaesthesiol 2004;18:425–38.

[5] Kiaii B, Fox S, Swinamer SA, et al. The early inflammatory response in a mini-cardiopulmonary bypass system: a prospective randomized study. Innovations (Phila) 2012;7:23–32.

[6] Bennett M, Thuys C, Augustin S, et al. The safe addition of nitric oxide into the sweep gas of the extracorporeal circuit during cardiopulmonary bypass and extracorporeal life support. J Extra Corpor Technol 2018;50:260–4.

[7] Cheng T, Barve R, Cheng YWM, et al. Conventional versus miniaturized cardiopulmonary bypass: a systematic review and meta-analysis. JTCVS Open 2021;8:418–41.

[8] Zahler S, Massoudy P, Hartl H, et al. Acute cardiac inflammatory responses to postischemic reperfusion during cardiopulmonary bypass. Cardiovasc Res 1999;41:722–30.

[9] Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 2003;75:S715–20.

[10] Duval EL, Kavelaars A, Veenhuizen L, et al. Pro- and anti-inflammatory cytokine patterns during and after cardiac surgery in young children. Eur J Pediatr 1999;158:387–93.

[11] Domanski MJ, Mahaffey K, Hasselblad V, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA 2011;305:585–91.

[12] Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107:996–1002.

[13] Day JRS, Taylor KM. The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg 2005;3:129–40.

[14] Baehner T, Boehm O, Probst C, et al. Cardiopulmonary bypass in cardiac surgery. Anaesthesist 2012;61:846–56.

[15] Hu J, Spina S, Zadek F, et al. 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;9:129.

[16] Breuer J, Leube G, Mayer P, et al. Effects of cardiopulmonary bypass and inhaled nitric oxide on platelets in children with congenital heart defects. Eur J Pediatr 1998;157:194–201.

[17] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.

[18] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 2021;88:105906.

[19] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clin Res Ed) 2017;358:j4008.

[20] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

[21] Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[22] Niebler RA, Chiang-Ching H, Daley K, et al. Nitric oxide added to the sweep gas of the oxygenator during cardiopulmonary bypass in infants: a pilot randomized controlled trial. Artif Organs 2021;45:22–8.

Elnaiem et al. Annals of Medicine & Surgery (2023)

Annals of Medicine & Surgery

[23] Elzein C, Urbas C, Hughes B, *et al.* Efficacy of nitric oxide administration in attenuating ischemia/reperfusion injury during neonatal cardiopulmonary bypass. World J Pediatr Congenit Heart Surg 2020;11:417–23.

[24] Zheng S, Wang Q, Ji L, *et al.* Protective effects of ulinastatin combined with nitric oxide and prostaglandin E1 on lung injuries and coagulation in infants undergoing cardiopulmonary bypass. Int J Clin Exp Med 2018;11:13329–37.

[25] James C, Millar J, Horton S, *et al.* Nitric oxide administration during paediatric cardiopulmonary bypass: a randomised controlled trial. Intensive Care Med 2016;42:1744–52.

[26] Checchia PA, Bronicki RA, Muenzer JT, *et al.* Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children – a randomized trial. J Thorac Cardiovasc Surg 2013;146:530–6.

[27] Signori D, Magliocca A, Hayashida K, *et al.* Inhaled nitric oxide: role in the pathophysiology of cardio-cerebrovascular and respiratory diseases. Intensive Care Med Exp 2022;10:28.

[28] Checchia PA, Bronicki RA, Goldstein B. Review of inhaled nitric oxide in the pediatric cardiac surgery setting. Pediatr Cardiol 2012;33:493–505.

[29] Hauser GJ, Ben-Ari J, Colvin MP, *et al.* Interleukin-6 levels in serum and lung lavage fluid of children undergoing open heart surgery correlate with postoperative morbidity. Intensive Care Med 1998;24:481–6.

[30] Donati A, Battisti D, Recchioni A, *et al.* Predictive value of interleukin 6 (IL-6), interleukin 8 (IL-8) and gastric intramucosal pH (pH-i) in major abdominal surgery. Intensive Care Med 1998;24:329–35.

[31] Wang W, Huang HM, Zhu DM, *et al.* Modified ultrafiltration in paediatric cardiopulmonary bypass. Perfusion 1998;13:304–10.

[32] Cremer J, Martin M, Redl H, *et al.* Systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg 1996;61:1714–20.

[33] Behr D, Hernvann A, Pouard P, *et al.* Interleukin-6 and C-reactive protein during pediatric cardiopulmonary bypass. Clin Chem 1995;41:467–9.

[34] Lang JD, Smith AB, Brandon A, *et al.* A randomized clinical trial testing the anti-inflammatory effects of preemptive inhaled nitric oxide in human liver transplantation. PLoS One 2014;9:e86053.

[35] Mathru M, Huda R, Solanki DR, *et al.* Inhaled nitric oxide attenuates reperfusion inflammatory responses in humans. Anesthesiology 2007;106:275–82.

[36] Villarreal EG, Aiello S, Evey LW, *et al.* Effects of inhaled nitric oxide on haemodynamics and gas exchange in children after having undergone cardiac surgery utilising cardiopulmonary bypass. Cardiol Young 2020;30:1151–6.