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REVIEW ARTICLE

Review of Inhaled Nitric Oxide in the Pediatric Cardiac Surgery Setting

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Abstract Surgical intervention for congenital heart disease (CHD) can be complicated by pulmonary hypertension (PH), which increases morbidity, mortality, and medical burden. Consequently, postoperative management of PH is an important clinical consideration to improve outcomes. Inhaled nitric oxide (iNO) is a widely accepted standard of care for PH and has been studied in the context of cardiac surgery for CHD. However, large randomized, double-blind, placebo-controlled, multicenter clinical trials in pediatric patients are limited. This review will provide an overview of the clinical studies in this setting and will discuss general treatment considerations to facilitate a better understanding of the clinical use of iNO for PH after pediatric cardiac surgery.

Keywords Nitric oxide · Inhalation · Congenital heart disease · Pulmonary hypertension · Cardiopulmonary bypass · Pediatric cardiac surgery

Introduction

Congenital heart disease (CHD) poses a significant medical burden and is the primary reason for cardiac surgical interventions in neonatal and pediatric patients. Mortality among infants with diseases of the circulatory system is 2.1%, and mortality among 1- to 4-year-olds with diseases of the heart is 3.5%, making this the fifth leading cause of death in this age group [30]. The incidence of severe forms of CHD is approximately 3/1,000 live births [32]. Although surgical interventions to correct associated defects have improved, they may be complicated by postoperative pulmonary hypertension (PH). Studies in children have demonstrated that PH in cardiac surgery patients increases morbidity and mortality [33, 34]. Addressing this serious condition both before and after surgery may be crucial to operative success.

PH may be due to either increased pulmonary blood flow (PBF), increased pulmonary vascular resistance (PVR), or a combination of both. In children with CHD, most instances of PH are benign secondary to increased PBF (e.g., large patent ductus arteriosus or ventricular septal defect), are easily corrected with surgery and do not exhibit residual PH during the postoperative period. In some instances, long-standing or excessive increased PBF or obstructive lesions result in increased PVR, which may not resolve after surgical correction or palliation of the underlying anatomic lesion, especially after cardiopulmonary bypass (CPB). Table 1 lists the most common lesions and conditions associated with increased PVR and PH during the postoperative period. In these instances, PH may be a significant clinical problem and requires treatment. This review will focus primarily on PH associated with an increased PVR in the postoperative period and its management.

The exact incidence of PH in children undergoing surgical interventions remains unclear. In a study monitoring 20 infants and neonates at high risk for postoperative PH, 11 developed significant major pulmonary hypertensive crises, and 6 ultimately died [33]. When patients with episodic PH were included in the analysis, the rate of PH was 75%. This risk is not limited to corrective repair or palliation of CHDs. Among pediatric patients undergoing cardiac transplantation,

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Table 1 The most common anatomic lesions and conditions associated with PH after definitive surgical repair with CPB in children

Unrestrictive VSD in children >6 months old
Atrioventricular canal in children >6 months old
Transposition of the great arteries with VSD in children >6 months old
Double-outlet right ventricle in children >6 months old
TAPVR in infants <8 weeks old
TAPVR with obstruction
Schoen's syndrome
Truncus arteriosus
Hemitruncus arteriosus
Aortopulmonary window
Scimitar syndrome in neonates <1 month old
Cardiac transplantation

VSD Ventricular septal defect, *TAPVR* total anomalous pulmonary venous return

increased preoperative PVR has been shown to be associated with long-term adverse outcomes, such as right-ventricular failure and eventual mortality [10, 21]. In addition, PH affects morbidity as well as mortality [34]. Among those infants undergoing CPB, postoperative PH has been identified as a significant risk factor associated with longer duration of stay in an intensive care unit [8, 53]. Increased PVR in infants has also been correlated with increased time on mechanical ventilation and in recovery after surgery for CHD with CPB [61].

Given the impact of both preoperative and postoperative PH on mortality and morbidity in pediatric cardiac patients, its management remains an important clinical goal. Treatment with inhaled nitric oxide (iNO) has been studied for postoperative PH in a number of pediatric cardiac surgery indications, including patients with high-risk CHD [15, 37, 49], Fontan procedures [23, 39, 71], and orthotopic heart transplantation [12, 13]. Randomized trials [49, 59], observational studies [23, 38], and case reports [12, 66, 69, 72] have documented the effects of this treatment in the pediatric cardiac surgery setting. The objective of this review is to provide a central resource summarizing these results as well as a discussion of the mechanisms and clinical considerations of iNO use in the pediatric cardiac surgery setting.

Pediatric Hypertension in Postoperative Cardiac Surgery

Definition and Pathophysiology

Pulmonary arterial hypertension is generally defined as a resting mean pulmonary arterial pressure >25 mmHg, a pulmonary wedge pressure ≤15 mmHg, and a PVR >3 Wood units [45, 63]. This definition, however, is more accurately applied to adult patients. In pediatric patients, PH may be more commonly defined as a systolic pulmonary arterial pressure of more than half of the systemic blood pressure [26, 65].

The general mechanism of PH is a complex process of pathophysiologic changes to the pulmonary vascular bed, including vasoconstriction, vascular remodeling, endothelial dysfunction, and thrombus formation. PH in infants and children is often caused by CHD, specifically by associated defects involving left-to-right shunt, transposition of the great arteries, and obstructive lesions [26, 65]. This process may be exacerbated immediately after surgery for CHD through increased vasoreactivity and vasospastic stimuli, which may cause sudden increases in pulmonary arterial pressure and resistance [1]. This can result in potentially lethal episodic pulmonary hypertensive crises that can result in acute right heart failure, tricuspid regurgitation, systemic hypotension, myocardial ischemia, and/or increased airway resistance [1].

A key factor in the etiology of postoperative PH is endothelial dysfunction characterized by increased production of vasoconstrictive signals, decreased production of vasodilatory signals, and a procoagulant state [45]. Clinical research has demonstrated that CPB causes endothelial injury [69]. Wessel et al. [69] administered infusions of acetylcholine, an endothelium-dependent vasodilator, both before and after surgery, in children with PH undergoing surgery with CPB for CHD. Results showed that pulmonary vasodilation was potentiated after preoperative administration of acetylcholine (decreases of 46% and 27% in PVR and pulmonary artery pressure, respectively) but less so (decreases of 11% and 9%) after postoperative administration (Fig. 1). Conversely, postoperative inhalation of NO, which does not require an intact endothelium to exert its action, resulted in similar degrees of pulmonary vasodilation as preoperative acetylcholine. These results support the conclusion that CPB damages pulmonary endothelial cells in children, resulting in failure of endothelium-dependent pulmonary vasodilation and subsequent development of PH [69]. Beghetti et al. [5] measured exhaled NO levels before and 30 minutes after CPB in 30 children with acyanotic heart repair and left-to-right intracardiac shunts. Results showed decreases in exhaled NO levels in all but three patients (27.6% mean decrease (Fig. 2)). A correlation was found between exhaled NO levels and both aortic cross-clamp and bypass time, further supporting the conclusion that decreased exhaled NO levels are a result of pulmonary vascular injury rather than decreased PBF flow [5].

Treatment Options in Postoperative PH

Traditional management of postoperative PH includes alkalinization, hyperventilation, oxygenation, and muscle relaxation with sedation. Fentanyl is used to suppress the vasoconstriction induced by tracheal suctioning and other postoperative stress responses [1]. Mechanical ventilation

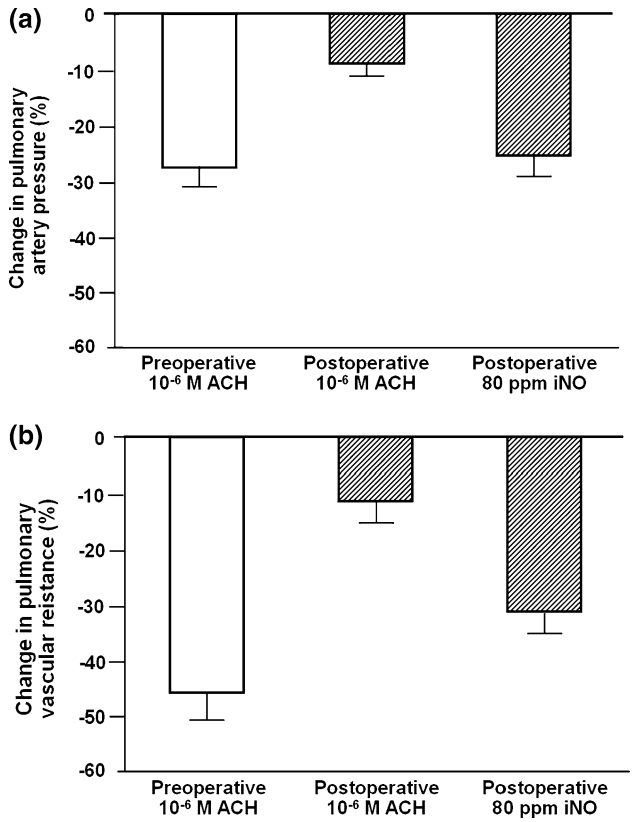

Fig. 1 Changes in **a** pulmonary arterial pressure and **b** pulmonary vascular resistance index in children with CHD before and after cardiopulmonary bypass. *ACH* Acetylcholine. Reprinted with permission from Circulation, Vol. 88, David L. Wessel, Ian Adatia, Therese M. Giglia, John E. Thompson, and Thomas J. Kulik, Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass, pages no. 2128–2138, Copyright © 1993, with permission from the American Heart Association [69]

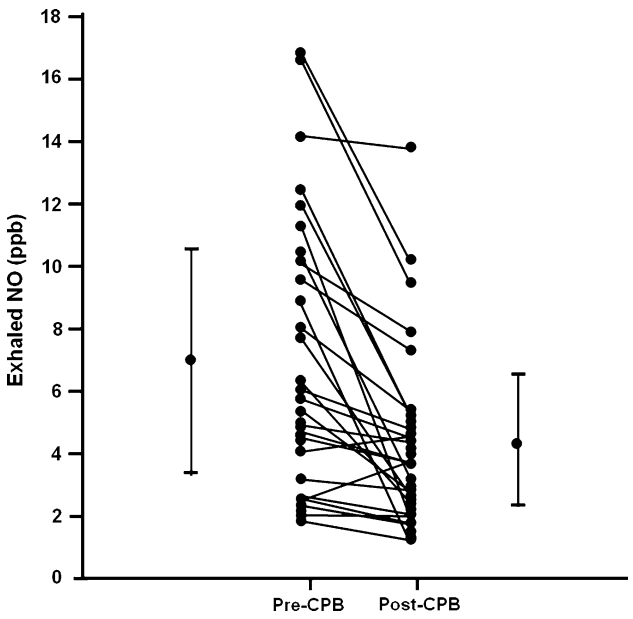

Fig. 2 Exhaled NO concentrations before and after CPB. Reprinted from The Annals of Thoracic Surgery, Vol. 66, Maurice Beghetti, Philip E. Silkoff, Marlova Caramori, Helen M. Holtby, Arthur S. Slutsky, and Ian Adatia, Decreased exhaled nitric oxide may be a marker of cardiopulmonary bypass–induced injury, pages no. 532–534, Copyright © 1998, with permission from The Society of Thoracic Surgeons [5]

with supplemental oxygen is used to mitigate hypoxic vasoconstriction, and alkalinization can counteract vasoconstriction induced by acidosis [1]. Newer pharmacologic interventions include treatment with vasodilators, such as phosphodiesterase-5 inhibitors, and prostaglandins [58]. Each of these approaches, however, is problematic due to systemic effects. Other disadvantages of these systemic agents are that they may impair oxygenation by releasing hypoxic pulmonary vasoconstriction, as well as potentially precipitating systemic hypotension, if systemic vascular resistance falls to a much greater extent than PVR.

Inhaled NO

Vasodilatory Effects of NO

NO decreases vascular tone by way of the guanylate cyclase signal transduction pathway [40]. It is produced endogenously by vascular endothelial cells and diffuses readily to adjacent vascular smooth muscle cells where it binds to guanylate cyclase [40]. This results in the production of cyclic guanosine monophosphate (cGMP), which leads to vasodilation by way of intracellular calcium signaling [40].

Inhaled NO diffuses rapidly through the alveoli to the pulmonary vascular arteries, causing local vasodilation. Excess NO that reaches the intravascular space binds to hemoglobin and is readily converted to nitrate and methemoglobin [35, 40]. Thus, iNO selectively relaxes the pulmonary vasculature with few effects on the systemic vasculature [35].

Clinical Systemic Effects of NO: Inflammation

NO has been used for PH for more than a decade. Its role in inflammation, tissue injury, apoptosis, and cell defense is currently being investigated [11, 16, 17, 41, 64]. NO appears to be a key link between ischemia/reperfusion injury and the rate of tissue repair [7, 42, 46]. In fact, alterations in NO generation appear to underpin the interrelationship of endothelial function and inflammation, with several potential protective roles in inflammatory response and ischemia. It has been demonstrated that NO inhibits platelet adhesion and aggregation [55] and blocks monocyte adherence and migration [44]. Furthermore, NO is an inhibitor of leukocyte activation, which leads to

neutrophil–endothelium adhesion and to the generation of oxygen-free radicals. NO may also act to arrest the release of products with cytotoxic and vasoconstrictive properties (leukotrienes, cytokines, prostaglandins) and may have a direct cytoprotective effect on the endothelial cell during the inflammatory reaction [68].

NO and the Neutrophil

Interaction between neutrophils and activated endothelium follow multiple distinct, consecutive phases. The inflammatory injury after CPB is known to be neutrophil-mediated. Pro-inflammatory cytokines (e.g., tumor necrosis factor-α and interleukin [IL]-1, IL-6, and IL-8), generated during CPB and amplified by neutrophils, modulate the immune response and recruit leukocytes and monocytes to target tissues. The use of exogenous NO is based on data that have demonstrated NO as a potent cardioprotective agent that decreases neutrophil-mediated damage. Accordingly, NO has been shown to attenuate neutrophil function and neutrophil–endothelial cell interactions, which initiate the inflammatory cascade and sequelae of contractile dysfunction and infarction [60, 68].

NO and CPB

Increasingly, convention argues that NO added to the bypass circuit has an effect distal to the entry site. This goes against current dogma regarding NO metabolism. However, there is mounting evidence that NO or an NO donor compound, given to patients with compromised endogenous NO production, results in decreased vascular resistance, increased blood flow, and decreased inflammation, thereby resulting in decreased tissue damage.

This has been modeled in disease states involving hemolysis, such as sickle cell disease [56]. It is speculated that an acute scavenging of NO by oxyhemoglobin liberated by hemolysis during CPB may produce the required vasoconstriction, platelet activation, leukocyte adhesion, and oxygen-free radical generation necessary to explain the clinical phenomenon associated with CPB [22]. Alternatively, NO added to the bypass circuit may have anti-inflammatory effects on leukocytes that filter through the bypass gas exchanger. Through this mechanism, NO could have anti-inflammatory benefits and still act primarily as a local mediator in the bypass exchanger only [16, 22]. Although the use of NO within bypass circuits is currently experimental, clinical trials are underway to assess the feasibility of this method in clinical practice.

Pharmacokinetics and Drug Interactions

Pharmacokinetic studies of iNO have been based on adult populations. After inhalation, NO is absorbed systemically and combines predominately with oxyhemoglobin to form methemoglobin and nitrate, or it combines with deoxyhemoglobin to produce nitrosyl hemoglobin, which is transient and converts readily to methemoglobin when exposed to oxygen. In the lungs, exposure of iNO to oxygen and water produces nitrogen dioxide and nitrite, which are also converted to methemoglobin and nitrate [35].

Formal drug-interaction studies have not been performed, but NO donor compounds and agents that oxidize hemoglobin to methemoglobin, such as nitroprusside, nitroglycerin, and prilocaine, may have additive effects with iNO with respect to the risk of methemoglobinemia [35].

Dosage

The recommended dose of iNO is 20 ppm for the approved indication of hypoxic respiratory failure associated with PH in term and near-term neonates [35]. In children with congenital heart defects, long-term use (i.e., days to weeks) of iNO, 5–40 ppm, after cardiac surgery, the maximum observed methemoglobin levels were ≤4% [29]. To minimize potential adverse effects, the lowest effective dose of iNO should be used [29, 35].

Investigations of iNO in Pediatric Cardiac Surgery

iNO has also been investigated for the treatment of PH associated with cardiac surgery. Studies of iNO in adults undergoing cardiac surgery have confirmed the benefit of this agent in decreasing PVR and pulmonary arterial pressure without decreasing systemic arterial pressure and systemic vascular resistance [9, 18, 20, 57]. Similar results have been demonstrated in the perioperative period as well [20]. It has also been suggested that iNO may be beneficial in patients with right-ventricular dysfunction because it selectively decreases right-ventricular afterload and improves right-ventricular function [18]. Furthermore, use of iNO before, during, and after cardiac surgery may attenuate the release of markers of myocardial injury, endothelial cell activation, and left-ventricular dysfunction [20].

High-Risk CHD

iNO therapy in pediatric patients after surgery for CHD has been reported in a variety of clinical trials, including case reports, pilot studies; prospective and retrospective investigations, randomized, controlled clinical studies, and cross-over studies [4, 12, 15, 24, 27, 37, 38, 47, 49, 50, 59, 62, 66, 69, 72]. Table 2 lists these 15 studies, which included 412 patients ranging in age from 1 day to 20 years. Thirteen of the 15 studies measured pulmonary

arterial pressure, systolic arterial pressure, and/or the ratio of pulmonary arterial pressure to systemic arterial pressure and showed that iNO decreased all of these values [4, 15, 24, 27, 37, 38, 47, 49, 50, 59, 62, 66, 69]. Four trials reported PVR, or the ratio of PVR to systemic vascular resistance, and found it to be decreased after iNO use [47, 49, 50, 69]. Increased oxygenation, as demonstrated by arterial oxygen saturation, arterial oxygen pressure, pulmonary artery oximetry, or pulse oximetry, was reported in 7 of the studies [15, 24, 27, 37, 62, 66, 72]. Inhaled NO has also been shown to be effective in preventing transient episodes of postoperative pulmonary hypertensive crisis and to stabilize patients in hypertensive crisis [12, 49].

Studies by Miller et al. [47] and Russell et al. [59] compared responses with iNO in patients with ratios of pulmonary arterial pressure to systemic arterial pressure >0.50 or <0.50. They found that the group with the higher ratios responded to iNO, whereas the group with the lower ratios had no significant improvement or only a modest response. Turanlahti et al. [66] found that the preoperative response to iNO did not predict postoperative PH.

A randomized trial conducted by Day et al. [15] compared iNO with placebo given after corrective surgery for CHD. The study found no between-group differences in acute hemodynamic and blood gas measurements 1 hour after treatment, although the iNO group had significant differences ($P < 0.05$) compared with baseline in six of the eight parameters measured (whereas the placebo group had none). In addition, with sustained therapy, the iNO- and placebo-treatment groups showed no differences in the incidence of pulmonary hypertensive crises (15 vs. 20%, respectively), although the investigators noted that the study was substantially underpowered (due to small sample size) to detect such differences.

A recent retrospective study by Journois et al. [38] examined mortality in 64 patients and showed significant decreases in mortality in a patient group receiving iNO (24%) compared with a control group receiving conventional care (56%; $P = 0.02$). iNO also decreased mortality among patients with severe postoperative PH to a level comparable with that found among patients without postoperative PH [38]. In another randomized, placebo-controlled, double-blind study by Miller et al. [49], use of iNO was associated with fewer pulmonary hypertensive crises, shorter times to extubation, and shorter times on study gas. Among the largest investigations ($n = 124$) of iNO in postoperative pediatric cardiac surgery, this study also demonstrated a significantly lower PVR index ($P < 0.001$) in the iNO group than in the placebo group (Fig. 3) [49]. Clinical experiences reported by Gothberg and Edberg [24] suggest that a postoperative regimen that includes iNO results in shorter stays in the pediatric intensive care unit after CPB surgery. Taken together, results of these studies show that in pediatric patients with PH after surgery for CHD, iNO effectively improved hemodynamics and postoperative outcomes.

Fontan Procedures

Studies of iNO in patients undergoing Fontan and bidirectional Glenn procedures are both prospective and retrospective in design and have included case reports, case series, and observational studies (Table 3) [19, 23, 31, 39, 67, 70–72]. All studies in which arterial oxygen saturation was measured showed that this hemodynamic parameter increased after iNO administration [19, 23, 31, 67, 71, 72]. An early prospective trial by Goldman et al. [23] found that arterial oxygen saturation before initiation of iNO therapy was a predictor of response (i.e., a lower baseline arterial oxygen saturation predicted a greater response) and an arterial oxygen saturation >85% predicted no improvement in hemodynamics. Similarly, a more recent retrospective study by Yoshimura et al. [71] found no significant hemodynamic improvement after iNO administration in a patient subset with baseline central venous pressure < 15 mm Hg and transpulmonary pressure gradient <8 mmHg. The investigators proposed that appropriate indications for iNO after Fontan-type procedures are a central venous pressure ≥15 mmHg and transpulmonary pressure gradient ≥8 mmHg [71].

When transpulmonary gradient or central venous pressure were reported, iNO was found to decrease these hemodynamic parameters [19, 23, 71, 72]. Systemic arterial pressure was reported to be increased after iNO in 2 studies [19, 71]. Khambadkone et al. [39] examined the long-term effect of iNO administration in 15 patients 9 years (median) after Fontan procedure. Results showed iNO to be effective in decreasing PVR, suggesting that some Fontan patients will benefit from treatments that enhance or replace endogenous NO. A case study in 2002 by Hofer et al. [31] reported that extracorporeal membrane oxygenation was avoided in a 4-year-old postoperative Fontan patient by use of iNO. These clinical results demonstrate that iNO may improve hemodynamics and patient outcome after Fontan-type procedures; the aforementioned study investigators propose that iNO use may be an important therapy in this pediatric surgical setting [19, 23, 31, 67, 70–72].

Orthotopic Heart Transplantation

Pre-existing PH is a well-recognized risk factor for increased mortality after orthotopic heart transplantation [13]. Studies of iNO in the pediatric heart transplant setting are limited (Table 4) [3, 12, 13]. A recent retrospective

Table 2 iNO use after pediatric surgery for CHD

Study	Design	*N*	Age	Diagnosis[a]	Dose and duration	Outcome in response to iNO
Haydar et al. [27]	Case study	1	18 months	TGA, VSD	5–20 ppm 10 days	PAP decreased; SpO_2, SvO_2 increased
Wessel et al. [69]	Prospective case series	9	1 day–11 years (median 15 months)	AVSD, VSD, PS, MS, CoAo	80 ppm 15 min	Mean PAP decreased 4.4–25.8 mmHg ($P < 0.0001$) and PVR 6.8–4.5 U·m^2 ($P < 0.005$)
Beghetti et al. [4]	Pilot study	7	6–168 months	VSD, PDA, TA, ECD	15 ppm 4–16 days (median 9.5)	Mean PAP decreased 51–31 mmHg ($P < 0.05$) but no change in mean SAP
Journois et al. [37]	Prospective case series	17	5 days–24 months (median 50 days)	APVR, VSD, IAA, AVCD, TA	20 ppm Hemodynamic measurement at 20 min Total 4–250 h (mean 44)	Systolic PAP decreased by 32%, diastolic PAP by 43% SaO_2 increased by 9.7%, SvO_2 by 37% ($P < 0.05$ for all)
Miller et al. [47]	Prospective case series	10	2–21 months (mean 8.0–8.3)	AVSD, TAPVD, VSD, TA, DORV/APW	2, 10, 20 ppm 10 min	Group with mean PAP/SAP ≥0.50: PVR/SVR ratio decreased by 33% and mean cardiac index increased by 14% Group with mean PAP/SAP <0.50: modest response Response correlated well with PVR/SVR ratio
Curran et al. [12]	Prospective case series	20	1 day–14 years (mean 0.9 years)	AVC, PA/IVS, HLV, AS, PDA, DORV, VSD, ASD, cardiomyopathy, RVOTO, MR, tracheal rings, PS, EA, TA, IAA, CorT, ToF, CoAo	20–80 ppm 1 h–10 days (mean 3.3)	Mean PAP decreased by 25% ($P < 0.01$) Five received intraoperative iNO
Shimpo et al. [62]	Prospective case series	10	1–108 months (median 11)	TGA, VSD, MR CAVC, SV, TAPVC	2–5 ppm 1–200 h (mean 38.6)	PAP decreased by 26% from 55–41 mmHg ($P < 0.05$) PaO_2 increased from 110 to 149 mmHg ($P < 0.001$)
Russell et al. [59]	Controlled, double-blind RCT	40	2 days–6.5 years	ASD, VSD, AVSD, TA, CorT, MS	80 ppm 20 min	Group with mean PAP/SAP ≥0.50: mean PAP decreased by 19 vs. 9% in control ($P = 0.008$) Group with mean PAP/SAP <0.50: no significant difference
Zobel et al. [72]	Prospective case series	37	5 days–16 years (mean 2.9 years)	VSD, AVCD, TAPVR, ToF, Fontan or Glenn circulation	2–20 ppm (lowest effective dose) 12–432 h (mean 112.6)	SaO_2 improved from 79.6 to 90.1% in entire group ($P < 0.01$) In patients with PAP/SAP >0.5: mean PAP decreased from 47.8 to 27.5 mmHg ($P < 0.01$)

Table 2 continued

Study	Design	*N*	Age	Diagnosis[a]	Dose and duration	Outcome in response to iNO
Day et al. [15]	Randomized, controlled trial	38	Control: 1 day–3 years (median 6 months) NO: 1 day–20 years (median 7 months)	AVSD, ASD, VSD, TAPVR, PAPVR, PVO, MVS, SV AH, AV/PV S	20 ppm (continuous until weaned from ventilation)	Decreased systolic pulmonary pressure 52–47 mmHg, left atrial pressure 12–11 mmHg, and $PaCO_2$ 39–36 mmHg Increased $Pa0_2/FIO_2$ from 141 to 179 mmHg ($P < 0.05$ for all) No difference in incidence of PH crises compared with controls but iNO-rescued crises
Gothberg and Edberg [24]	Prospective case series	12	1 days–12.6 months (mean 3.8 months)	AVSD, VSD, VSD + PDA, ASD or CoAo, TAPVR, ASD + PDA, TGA + VSD + ASD	3–80 ppm (measurements at 10 min)	Mean PAP decreased from 32 to 28 mmHg ($P < 0.01$) PaO_2 increased from 13.3 to 16.7 mmHg ($P < 0.05$)
Miller et al. [49]	Randomized, placebo-controlled, double-blind trial	124	NO: 1–5 months (median 3) Placebo: 1–4 months (median 2)	VSD, AVSD, TA, TAPVD	10 ppm Mean for 87 h for iNO and 117 h for control	PVR decreased in iNO group ($P < 0.001$) Fewer PH crises ($P < 0.001$) Shorter times to meet extubation criteria ($P = 0.019$) Shorter total time on study gas ($P = 0.023$)
Morris et al. [50]	Randomized cross-over	12	0.1–7.7 years	TA, AVSD, TGA, TAPVD, VSD, MS, SAS, MVS	5–40 ppm 15 min	Mean PAP decreased from 34.5 to 29.4 mmHg ($P < 0.01$) and PVRI from 8.1 to 6.1 WU/m^2 ($P < 0.001$)
Turanlahti et al. [66]	Case series	11	2.6–48 months (mean 9.6)	ASD, VSD, PDA, DORV, TA, AVSD	10–80 ppm Duration not specified, weaned when clinical condition permitted	Systolic PAP/SAP decreased by 0.35 ($P = 0.01$) and pulmonary artery oximetry increased by 15% ($P = 0.03$) Preoperative response to iNO did not predict postoperative PH
Journois et al. [38]	Retrospective, observational with historical controls based on multivariate confounder scores	64	Median 0.54 years	AVCD	Mean 25 ppm 0.25–17 days (median 5.2)	Mortality decreased iNO: 24% (95% CI 7–41) Controls: 56% (95% CI 37–75) ($P = 0.02$)

$Paco_2$ Arterial carbon dioxide tension, *Pao_2/FIo_2* ratio between arterial oxygen tension and fraction of inspired oxygen, *PAP* pulmonary arterial pressure, *PVRI* pulmonary vascular resistance index, *Sao_2* arterial oxygen saturation, *SAP* systemic arterial pressure, *Spo_2* peripheral oxygen saturation, *Svo_2* venous oxygen saturation, *SVR* systemic vascular resistance, *WU* Wood units, *RCT* randomized controlled trial

[a] Abbreviations for various congenital heart defects are given in Table 5

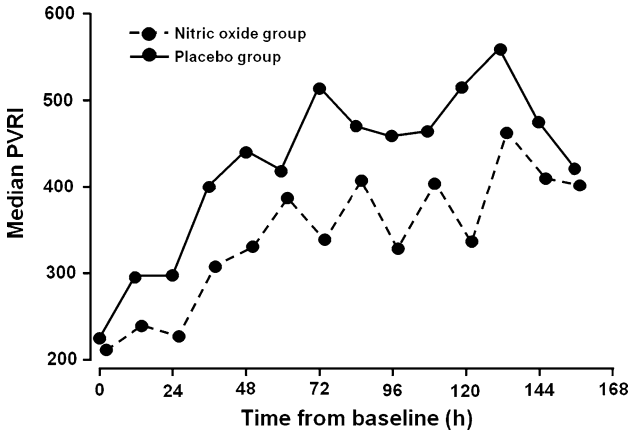

Fig. 3 Median pulmonary vascular resistance index (PVRI) after congenital heart surgery in infants at high risk of pulmonary hypertension. Reprinted from The Lancet, Vol. 356, Owen I. Miller, Swee Fong Tang, Anthony Keech, Nicholas B. Pigott, Elaine Beller, and David S. Celermajer, Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: A randomised double-blind study, pages no. 1464–1469, Copyright © 2000, with permission from Elsevier [49]

study examined the use of preoperative and postoperative vasodilators to improve morbidity in pediatric patients with increased PVR after transplantation. Daftari et al. [13] compared a group of patients with a mean preoperative PVR of 11 Wood units with a control group having a mean preoperative PVR of 3 Wood units ($P < 0.00001$). The group with the increased PVR received preoperative treatment with bosentan and/or sildenafil followed by postoperative treatment with iNO and sildenafil. The investigators found no significant differences in post-transplantation mortality, cardiac function, and PVR between the two groups. The investigators concluded that PVR >6 Wood units should not be an absolute contraindication to pediatric heart transplantation and adopted a prophylactic strategy of routine use of sildenafil along with iNO in the immediate post-transplantation period in patients with pre-existing PH.

In an earlier, prospective study of iNO in the pediatric cardiac surgical setting conducted by Curran et al. [12], 3 of the 20 patients studied underwent heart transplantation. One patient experienced transient post-transplant episodes of PH but stabilized with administration of iNO at 10–20 ppm. An additional 2 patients appeared to benefit clinically from iNO and responded with a decrease in mean pulmonary arterial pressure. One patient was unable to be weaned from CPB with conventional therapy for PH, but weaning was successful with iNO administration. The use of iNO in pediatric heart transplantation has not been studied extensively; however, the limited evidence to date suggests that future clinical research in this setting may provide additional insight.

Safety Considerations with iNO

Methemoglobinemia

Oxidation of hemoglobin to methemoglobin by NO is a concern with iNO. Methemoglobin is unable to reversibly bind oxygen, and concentrations of methemoglobin >10% result in clinical cyanosis [25]. Both Hamon et al. [25] and Hermon et al. [29] have documented increased levels of methemoglobin after iNO treatment, but doses <20 ppm rarely result in levels of 4–5%. Because methemoglobin levels have been shown to increase with increasing concentrations of iNO, the minimal effective dose of iNO is recommended to avoid potential methemoglobinemia, and doses >20 ppm should not typically be used [29, 35].

NO Withdrawal

Abrupt withdrawal from iNO may lead to rebound PH, which results from downregulation of endogenous NO production and increased levels of endothelin-1, a potent vasoconstrictor [48, 54]. A randomized clinical trial of iNO withdrawal by Davidson et al. [14] demonstrated a dose-dependent decrease in arterial oxygen tension (Pao_2) after acute iNO withdrawal and found that rebound hypertension could be avoided if the oxygenation index was <10 and the iNO dose was gradually decreased to 1 ppm before cessation. The adverse hemodynamic effects of rapid iNO withdrawal have been shown to be attenuated by increasing cGMP with dipyridamole and sildenafil [2, 36, 43, 51, 52] as well as through prostacyclin-mediated vasodilation [28].

In pediatric patients who previously failed to wean from iNO after surgery for CHD, sildenafil has been shown to facilitate weaning [43]. Behrends et al. [6] describe a case report of an adult with acute respiratory distress syndrome in whom iNO weaning was unsuccessful after extracorporeal membrane oxygenation. Sildenafil facilitated a decrease in iNO requirements, but complete withdrawal was possible only with a combination of sildenafil with the endothelin receptor antagonist bosentan.

When using iNO, it is important to consider that rapid weaning should be avoided after pediatric cardiac surgery. In situations where iNO-induced rebound hypertension occurs due to rapid weaning or discontinuation, other interventions, such as sildenafil, dipyridamole, prostacyclin, and bosentan, should be considered as potential means for managing this phenomenon.

Conclusion

Inhaled NO has become a standard of care for PH in many pediatric intensive care units, and clinical experience with

Table 3 iNO use after pediatric Fontan or Glenn procedure

Study	Design	*N*	Age	Diagnosis[a]	Dose and duration	Outcome in response to iNO
Yahagi et al. [70]	Case study	1	6 years	Fontan procedure	5–6 ppm	Mean PAP decreased from 20 to 13 mmHg and improved hemodynamics
				MA, PA, PDA	48 h	Conventional methods failed to improve low cardiac output syndrome
Goldman et al. [23]	Prospective, observational, all treated	15	Group 1: 1.5–15 y (median 3.5)	Fontan procedure	20 ppm	Group 1*:* baseline SaO_2 ≤85%, TPG decreased from 12 to 9 mmHg ($P < 0.01$) and CVP from 18 to 16 mmHg ($P < 0.01$); SaO_2 increased from 64 to 83% ($P < 0.01$)
			Group 2: 1.5–17 years (median 5.3)	DORV, MA, VSD, PA, AVSD, HLV, PS, TGA, TAPVD, DILV, HRV, TA, RVOTO, EA, MS	15 min	Group 2*:* postoperative SaO_2 >85%, no improvement in hemodynamics
Gamillscheg et al. [19]	Prospective, all treated	13	1.5–17 years (mean 5.6)	Fontan or Glenn procedure	1.5–10 ppm (mean 4.1)	Total cavopulmonary connection: CVP decreased by 15.3% ($P = 0.0001$) and TPG by 42% ($P = 0.0008$)
				PA, VSD, HLV, TGA, HRV, DILV, TriA, CCH, SA, SAV	Lowest effective dose	SAP increased by 12% ($P = 0.011$) and SaO_2 by 8.2% ($P = 0.005$)
					12–264 h (mean 106)	Glenn anastomosis: CVP decreased by 22% and TPG by 55%
						SAP increased by 13% and SaO_2 by 37%
Zobel et al. [72]	Prospective case series	16	Mean 5.2 years	Fontan or Glenn procedure (subset of a larger patient group)	2–20 ppm	SaO_2 improved from 81 to 90% ($P < 0.01$) and TPG pressure decreased significantly from 14.3 to 7.3 mmHg ($P < 0.01$)
					Lowest effective dose	
					Duration not specified for this patient group	
Hofer et al. [31]	Case report	1	4 years	Fontan procedure	25 ppm	SaO_2 improved to 87%, thereby avoiding ECMO use
				SV, TGA, CoAo	10 days	
Khambadkone et al. [39]	Observational, all treated	15	7–17 years (median 12)	Median 9 years after Fontan procedure	20 ppm	9 years after Fontan, supplemental iNO led to decrease in PVR
				TriA, DILV, PA, PA IVS, DORV, TGA	10 min	Some patients may benefit from treatments that enhance or replace pulmonary NO production or release
Urcelay et al. [67]	Case report	1	2 years	Fontan procedure	40 ppm	SaO_2 improved from <70 to 85%
				PAVMs	8.5 days	
Yoshimura et al. [71]	Retrospective	47	1–16 years (median 4)	Fontan procedure for UVH, TriA, DORV, MA, PA IVS, MVSD	5–30 ppm (median 10)	CVP decreased from 16.2 to 14.6 mmHg ($P < 0.0001$) and TPG from 9.9 to 8.4
					5 h–52 days (median 2 days)	($P = 0.0001$)
						SAP increased from 71.9 to 76.8 mmHg ($P < 0.05$)
						SaO_2 improved from 90.1% to 93.3% ($P < 0.01$)
						If CVP <15 mmHg or TPG <8 mmHg, no changes in hemodynamics
						CVP ≥15, TPG ≥8 mmHg or both are appropriate indications

ECMO Extracorporeal membrane oxygenation, *PAP* pulmonary arterial pressure, *SaO_2* arterial oxygen saturation, *SAP* systemic arterial pressure, *TPG* transpulmonary gradient

[a] Abbreviations for various CHDs are listed in Table 5

Table 4 iNO use after pediatric heart transplantation

Study	Design	*N*	Age	Diagnosis	Dose and duration	Outcome in response to iNO
Curran et al. [12]	Prospective case series (transplant was a subgroup of a larger study)	3	1 and 14 days, 14 years	Transplant	10–80 ppm 1.5–10 days	2 patients had decreased PAP, 1 patient had transient episodes of PH
Bacha et al. [3]	Case study	1	23 months	Transplant	10–20 ppm 14 days	After ECMO, SaO_2 improved from values in the 50% range to values in the 70% range
Daftari et al. [13]	Retrospective comparing patients with PVR >6 WU and controls with PVR <6 WU	27 months	1–19 years	Transplant	5–10 ppm Duration unspecified	PVR >6 WU should not be an absolute contraindication to cardiac transplant Postoperative use of vasodilators, such as iNO, may be used as a prophylactic measure

PAP Pulmonary arterial pressure, *SaO_2* arterial oxygen saturation, *WU* Wood units

iNO has led to advancements in delivery, dosing, and weaning that prevent or mitigate adverse effects, such as rebound hypertension, methemoglobinemia, or nitrogen dioxide exposure.

The main limitations of the aforementioned studies are small patient populations as well as variations in study design, standards of care, and underlying diagnoses. Although larger, randomized, controlled clinical trials would serve to further increase clinical confidence in iNO use in these settings, conducting such studies is challenging, if not impossible. Given the infrequent nature of some of these clinical events and the rapid nature in which a patient can enter a grave state, both recruitment and conduct of an adequately large clinical trial are problematic. In addition, the lack of clinical equipoise, particularly among clinicians with experience in iNO use, further precludes the ability to appropriately obtain sufficient patient cohorts, especially in placebo-controlled trials.

Clinical evidence, nevertheless, continues to emerge for the use of iNO in the treatment of PH after pediatric cardiac surgery. Much of this evidence reports improvement in hemodynamic measurements, recommends treatment with iNO, notes a positive experience with iNO therapy, and/or adopts iNO as a standard of care. Finally, the emerging understanding of the systemic effects of iNO on inflammation opens further possible therapeutic opportunities.

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Appendix

See Appendix Table 5.

Table 5 List of CHDs in studies of pediatric postoperative iNO use

Acronym	Definition
AH	Aortic hypoplasia
APVR	Anomalous pulmonary venous return
APW	Aortopulmonary window
AS	Aortic stenosis
ASD	Atrial-septal defect
AV/PV S	Aortic valve and pulmonary valve stenosis
AVC	Atrioventricular canal
AVCD	Atrioventricular canal defect
AVSD	Atrioventricular septal defect
CCH	Criss-cross heart
CoAo	Aortic coarctation
Cor T	Cor triatriatum
DILV	Double-inlet left ventricle
DORV	Double-outlet right ventricle
EA	Ebstein's anomaly
ECD	Endocardial cushion defect
HLH	Hypoplastic left heart
HLV	Hypoplastic left ventricle
HRV	Hypoplastic right ventricle
IAA	Interrupted aortic arch
IPA	Innominate artery–pulmonary artery
LAO	Left atrium obstruction (after Senning surgery)
MA	Mitral atresia

Table 5 continued

Acronym	Definition
MR	Supravalvular mitral ring
MR CAVC	Mitral regurgitation complete atrioventricular canal
MS	Mitral stenosis
MVS	Mitral valve stenosis
MVSD	Multiple ventricular septal defects
PA	Pulmonary atresia
PA/IVS	Pulmonary atresia with intact ventricular septum
PAB	Pulmonary artery band
PAPVR	Partial anomalous pulmonary venous return
PAVM	Pulmonary arteriovenous malformations
Patent ductus arteriosus	Patent ductus arteriosus
PS	Pulmonary stenosis
PVO	Pulmonary venous obstruction
RVOTO	Right-ventricular outflow tract obstruction
SA	Single atrium
SAS	Subaortic stenosis
SAV	Single atrioventricular valve
SV	Single ventricle
SV AH	Single ventricle with aortic hypoplasia
TA	Truncus arteriosus
TAPVC	Total anomalous pulmonary venous connection
TAPVD	Total anomalous pulmonary venous drainage
TAPVR	Total anomalous pulmonary venous return
TGA	Transposition of great arteries
ToF	Tetralogy of Fallot
Tri A	Tricuspid atresia
UVH	Univentricular heart
VSD	Ventricular septal defect

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