Nitric Oxide Might Reduce the Need for Extracorporeal Support in Children With Critical Postoperative Pulmonary Hypertension

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Background. **Postoperative pulmonary hypertension is a life-threatening, yet reversible complication of congenital heart operations. Although inhaled nitric oxide (iNO), a selective pulmonary vasodilator, has been shown extensively to improve short-term oxygenation and hemodynamic indices in these patients, its influence on patient outcome has not been evaluated. The purpose of this study was to assess retrospectively whether patients who fulfilled our criteria for extracorporeal life support (ECLS) for critical postoperative pulmonary hypertension still required ECLS after the administration of iNO therapy.**

Methods. **Since January 1992, 10 patients (age 3 days to 10 months) fulfilled the criteria at our institution for ECLS for postoperative pulmonary hypertension. Of these, 5 could not be separated from cardiopulmonary bypass because of pulmonary hypertension, and 5 had critical pulmonary hypertension (pulmonary arterial pressure approaching systemic arterial pressure) causing severe cardiopulmonary compromise.**

Results. **Six of the 10 ECLS candidates had a sustained response to iNO and survived to discharge from the hospital, without the need for rescue ECLS. Three patients still required ECLS after 30 minutes, 4 hours, and 8 hours of beginning iNO because of failing cardiac output, and 2 survived. The remaining patient died after 5 days of iNO therapy, but was no longer a candidate for ECLS because of sepsis and multiorgan system failure.**

Conclusions. **Children with critical pulmonary hypertension unresponsive to maximal conventional treatment may be managed successfully with iNO without the need for rescue ECLS. A trial of iNO should therefore be given before the use of ECLS in these patients.**

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Severe reactive pulmonary hypertension (PH) is still an important cause of morbidity and mortality in children after corrective operations for congenital heart disease [1]. This complication may occur despite a technically successful operation and active conventional management, including the administration of high inspired oxygen, hyperventilation, sedation, neuromuscular blockade, and support with inotropic and vasodilator drugs [1]. When these therapies fail, patients can be considered for extracorporeal life support (ECLS) [2–5], which ensures adequate oxygenation and systemic perfusion in the face of a markedly elevated pulmonary vascular resistance and may allow time for the PH to resolve. However, ECLS is costly, invasive, and associated with substantial morbidity [3–7], and therefore should be offered only to infants in whom less invasive therapies have failed.

Inhaled nitric oxide (iNO) has emerged as a promising selective pulmonary vasodilator for infants and children with PH after cardiac operations [8–10]. It has repeatedly been shown to improve hemodynamic status and oxygenation in the short term [8–10], but the influence of iNO on patient outcome or on the need for rescue ECLS has not been assessed. Randomized clinical trials evaluating the role of iNO in congenital heart disease patients with postoperative PH may not be feasible because of the potential difficulty in recruiting sufficient numbers of patients and the ethical question of withholding a potentially life-saving treatment.

The purpose of this study was to review retrospectively whether patients with critical postoperative PH, who would have ordinarily received ECLS, still required ECLS after the administration of iNO therapy.

Material and Methods

Patient Population

Between January 1992 and October 1995, 1,700 infants and children underwent operations for congenital heart disease with cardiopulmonary bypass (CPB) at our institution. Seven hundred ninety-five of these patients were at risk of postoperative PH by virtue of having either high-flow left-to-right shunt lesions or lesions causing obstruction to pulmonary venous drainage. Inhaled nitric oxide was administered to 35 of these at-risk patients for postoperative PH (pulmonary arterial pressure to systemic arterial pressure [PAP/SAP] ratio >0.5).

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Ten of these 35 patients were identified retrospectively as meeting our institutional criteria for ECLS for critical postoperative PH (Table 1). Five (3 boys and 2 girls; age 3 days to 8 months) could not be weaned from CPB because of documented PH, despite maximal conventional therapy and an apparently adequate operative repair. Inhaled nitric oxide treatment began in these patients on the second attempt at weaning from CPB when failure to respond to iNO would have required ECLS. The mean PAP/SAP ratio before iNO in these 5 patients was 0.86 ± 0.09.

In the other 5 ECLS candidates (4 girls and 1 boy; age 3 days to 10 months), critical PH (PAP approaching SAP) developed in all within 5 days of their corrective congenital heart operation. These patients were all having recurrent (more than two) life-threatening PH crises, during which the PAP was suprasystemic and unresponsive to maximal conventional treatment. All had failed to respond to high inspired oxygen, hyperventilation, sedation with morphine (20 to 40 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and midazolam (2 to 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$), neuromuscular blockade with vecuronium, and at least one intravenous vasodilator (see Table 1). Inhaled nitric oxide was begun in these patients between 1 and 72 hours (median, 24 hours) after operation. Two required cardiopulmonary resuscitation during PH crises, and 1 needed repeated bolus doses of epinephrine (0.1 mL/kg) before iNO. Although 1 patient did not have a pulmonary arterial line and the PAP could not be estimated by echocardiography, this patient had all the other classic features of PH crisis, with a dramatic fall in oxygen saturation in arterial blood and systemic blood pressure, intermittently reversed by high-pressure, high inspired oxygen hand-bag ventilation.

Extracorporeal life support was introduced in our institution at approximately the same time as iNO (May 1992). Our two principal indications for ECLS in the postcardiotomy patient are severe ventricular failure refractory to maximal conventional therapy (despite an apparently adequate operative repair) and life-threatening, yet potentially reversible postoperative PH causing severe cardiocirculatory compromise. Patients are excluded from ECLS if they have irreversible cardiopulmonary disease, severe neurologic impairment, lethal congenital abnormalities, or multiple organ system failure.

Twenty-two patients (excluding those in the present study) have been supported at our institution with ECLS after open heart operations, with a survival rate of approximately 60%. These patients are distinct from the patients included in this study in that they received ECLS postcardiotomy for severe ventricular failure not associated with postoperative PH.

Inhaled Nitric Oxide Administration Protocol

A trial dose of iNO (20 ppm) was administered for 15 minutes to all the patients in this study, during which other treatment was not altered. Nitric oxide (NO) gas obtained in a mixture of nitrogen (N_2) at 1,000 ppm NO (BOC-Special Gases, Surrey, England) was delivered through a calibrated N_2 flow meter (KDG Instruments, Surrey, England) into the inspiratory limb of a mechanical ventilator, as described previously [11]. The concentrations of inspired NO and its oxidative product nitrogen dioxide (NO_2) were analyzed by chemiluminescence (model 42; Thermo Environmental Instruments, Franklin, MA) or electrochemical analysis (Bedfont Scientific, Kent, England) from samples of circuit gas obtained from a point 25 cm distal to the patient. The analyzers were calibrated at 0 and 10 ppm NO and 0 and 4 ppm NO_2 before each study.

The following variables were recorded at baseline and after exposure to 15 minutes of iNO: mean PAP, mean SAP, mean PAP/SAP ratio, mean oxygen saturation in arterial blood, mean partial pressure of oxygen in arterial blood, mean partial pressure of carbon dioxide in arterial blood, and mean arterial pH. The PAP was monitored in 9 of the 10 patients by an indwelling pulmonary arterial catheter (3 F), which had been inserted under direct vision into the proximal main pulmonary artery at the completion of the operative repair. The SAP was monitored continuously with an indwelling arterial catheter. Both the pulmonary and arterial catheters were connected to high-pressure tubing, fluid-filled transducers, and the Merlin Component Monitoring System (Hewlett-Packard, Böblingen, Germany). Arterial samples for blood gas analysis were withdrawn from indwelling arterial catheters. Methemoglobin levels were measured with a co-oximeter (model 482; Instrumentation Laboratory, Lexington, MA) after 30 minutes and 3 hours of exposure to iNO. Subsequently, levels were monitored every 12 to 24 hours during ongoing iNO therapy or more frequently if levels increased by more than 4%.

Ongoing Inhaled Nitric Oxide Therapy

Patients who showed greater than 20% improvement in oxygenation or PAP/SAP ratio during the initial phase of iNO administration and who were no longer ECLS candidates were continued on low-dose iNO therapy (1 to 20 ppm). Daily reverse dose response weaning allowed gradual reduction of the iNO as the situation improved. Neuromuscular blockade and deep sedation were continued until the patients had at least a 24-hour period of stability (no cardiopulmonary compromise or PH crisis) on low-dose iNO (<10 ppm). All patients were weaned from iNO before tracheal extubation.

Patients who failed to respond to the trial dose of iNO and who still met ECLS criteria were given a further 10 minutes of 70 ppm iNO (this is the maximum dose of iNO administered in a high concentration of oxygen, inspired oxygen fraction >0.85, at our institution). If they failed this dose, the iNO was discontinued and the patients were placed on ECLS.

Patient mortality and morbidity data were evaluated up to discharge from the hospital.

Statistical Analysis

Data are presented as mean ± standard error of the mean.

The Wilcoxon sign test was used to compare the hemodynamic and oxygenation indices recorded at base-

Table 1. Baseline Characteristics and Outcome of the 10 Patients Who Met Extracorporeal Life Support Criteria Before the Administration of Inhaled Nitric Oxide

Patient No.	Age	Diagnosis	Operation	Indication for ECLS	SAP (mm Hg)	PAP/SAP	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	Baseline pH/BE	Inotropes/ vasodilators	ECLS	Outcome	Comments
1	3 days	IAA^B, VSD	IAA repair	Failure to wean CPB	28	1.07	79	···	7.07/−17	Epi, Dob, Dop, NTG	Yes, 30 min	Survived	···
2	7 wk	TAPVD	TAPVD repair	Failure to wean CPB	35	0.9	76	31	7.08/−12	Dob, Dop, NTG	No	Survived	···
3	10 days	TGA, VSD	Arterial switch	Failure to wean CPB	48	1.0	88	39	7.38/−2.3	Dob, Dop, Enox	No	Survived	···
4	7 mo	AVSD	AVSD repair	Recurrent PH crises	59	0.91	61	45	7.32/−1.5	Epi, Dop, NTG, Pc	No	Survived	···
5	3 days	TAPVD	TAPVD repair	Recurrent PH crises	50	1.02	88	30	7.45/−2.0	Dob, Pc, Phenoxy	No	Survived	Required CPR
6	3 mo	AVSD, Down	AVSD repair	Recurrent PH crises	29	No line	41	32	7.45/−2.0	Dop, Enox, NTG	No	Survived	···
7	10 mo	AVSD, Down	AVSD repair	Recurrent PH crises	40	1.1	62	29	7.30/−9.6	Epi, Dop, Enox, NTG	No	Survived	Epi boluses
8	2 wk	Truncus type 1	Truncus repair	Recurrent PH crises	49	1.16	43	50	7.23/−5.5	Dob, Dop, NTG	Yes, 4 h	Survived	Neurologic Impairment
9	9 mo	LV infarct after TOF repair	Heart transplantation	Failure to wean CPB	50	0.54	75	64	7.07/−12	Epi, Dop, NTG, Isop	Yes, 8 h	Died	Sepsis
10	2 mo	AVd, TGA, $AVVA^L$, $hypo^{AA}$	Arterial switch	Failure to wean CPB	35	0.78	30	43	7.38/−3	Epi, Dop, Enox, NTG	No	Died after 5 d on iNO	Not offered ECLS, MOSF

AVd = atrioventricular discordance; AVSD = atrioventricular septal defect; $AVVA^L$ = left atrioventricular valve atresia; BE = base excess from arterial blood gas; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; Dob = dobutamine; Dop = dopamine; ECLS = extracorporeal life support; Enox = enoximone; Epi = epinephrine; $hypo^{AA}$ = hypoplastic aortic arch; IAA^B = interrupted aortic arch, type B; Isop = isoprenaline; LV infarct = left ventricular infarction; MOSF = multiorgan system failure; NTG = intravenous nitroglycerin; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PaO_2 = partial pressure of oxygen in arterial blood; PAP = mean pulmonary arterial pressure; Pc = prostacyclin; PH = pulmonary hypertension; Phenoxy = phenoxybenzamine; SAP = mean systemic arterial pressure; TAPVD = total anomalous pulmonary venous drainage; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; Truncus = truncus arteriosus; VSD = ventricular septal defect.

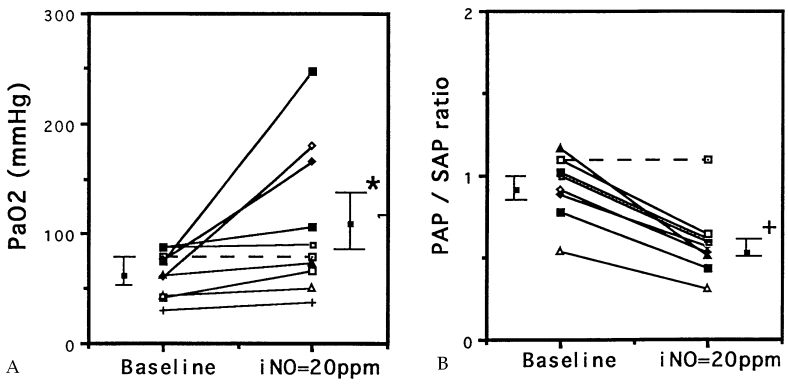

Fig 1. Changes in mean arterial partial pressure of oxygen (PaO2) *(A) and mean pulmonary to systemic arterial pressure ratio* (PAP/SAP) *(B) from baseline with exposure to inhaled nitric oxide* (iNO) *(20 ppm for 10 minutes) in all patients.* Dashed line *represents the patient who did not respond to the initial trial of iNO and who was immediately placed on extracorporeal life support;* solid lines *indicate patients who responded to iNO and who were continued on this therapy. Pulmonary to systemic arterial pressure ratio was missing in 1 patient because of absence of the pulmonary arterial line. (*Baseline compared with initial trial of iNO in the responders,* $p < 0.01$. $^{+}$*Baseline compared with initial trial of iNO in the responders,* $p < 0.02$.)

line with those obtained after the trial dose of iNO. A p value <0.05 was considered significant. The relation between the time after operation when the iNO was begun and the response to iNO, in terms of the percentage change in PAP/SAP ratio, was calculated by linear regression.

Results

Hemodynamic and oxygenation data for the 10 patients in this study who met the ECLS criteria are shown for individual patients in Table 1 and Figure 1 and for grouped data in Table 2.

Trial Dose of Inhaled Nitric Oxide—20 ppm for 15 Minutes

Nine of the 10 patients responded to the trial dose of iNO, as defined earlier, and were initially managed without ECLS support. Exposure to iNO in these patients was associated with a significant increase in partial pressure of oxygen in arterial blood ($p < 0.01$) and mean SAP ($p < 0.05$), as well as a significant fall in mean PAP ($p < 0.02$) and mean PAP/SAP ratio ($p < 0.02$) (see Fig 1; Table 2). There was no significant correlation between the time after operation when iNO was begun and the response to iNO, as measured by percentage change in PAP/SAP ratio ($r = 0.168$).

Patient Outcome

The patient who did not respond to the trial dose of 20 ppm iNO (case 1; see Table 1) also did not respond to 70 ppm, could not be weaned from CPB, and therefore was placed on ECLS. This patient survived to discharge from the hospital without neurologic morbidity. Results of echocardiography showed normal PAP after weaning from ECLS.

Six of the 9 patients who responded to the trial dose of iNO, as defined earlier, had a sustained response to ongoing iNO therapy (lasting between 4 and 13 days; median, 8 days) and survived to discharge from the hospital at a mean of 33 ± 8 days (patients 2 to 7; see Table 1). These 6 patients included 2 who could not be separated from CPB (patients 2 and 3) and 4 with recurrent PH crises (patients 4 to 7). Patient 5 had a short cardiopulmonary arrest before iNO during a crisis. The PAP remained low in all of these patients after weaning from iNO. There were no neurologic sequelae in these 6 patients.

Two of the 9 patients who initially responded to iNO again met ECLS criteria after 4 and 8 hours of iNO therapy. The first (patient 8), with a truncus arteriosus type I defect, was given iNO first in the operating room shortly after weaning from CPB when the patient had two consecutive life-threatening PH crises. This patient suffered a further crisis 4 hours after iNO was begun, during an emergency reintubation in the cardiac intensive care unit. This culminated in a cardiac arrest requiring 15 minutes of cardiopulmonary resuscitation. Extracorporeal life support was instituted 4 hours after the arrest because the patient continued to have low cardiac output with persistent metabolic acidosis, even though the PAP was not elevated at this time on iNO. The patient survived to discharge from the hospital but had signs of

Table 2. Changes in Hemodynamic and Arterial Blood Gas Indices From Baseline After Exposure to Inhaled Nitric Oxide (20 ppm for 15 Minutes) in All Patients

Measurement	PAP	SAP	PAP/SAP	PaO_2	$PaCO_2$	pH
Baseline	44 ± 3.2	47 ± 3.6	0.94 ± 0.06	64 ± 6.5	40 ± 3.9	7.29 ± 0.05
iNO, 20 ppm	31[b] ± 3.1	55[b] ± 4.3	0.59[b] ± 0.07	109[c] ± 21	33[b] ± 2.4	7.35 ± 0.06

[a] Values are expressed as mean ± SEM. [b] Baseline compared with initial trial of iNO, $p < 0.05$. [c] Baseline compared with initial trial of iNO, $p < 0.01$.

iNO = inhaled nitric oxide; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PaO_2 = partial pressure of oxygen in arterial blood; PAP = mean pulmonary arterial pressure; SAP = mean systemic arterial pressure.

severe neurologic impairment both clinically and on electroencephalographic examination. There was no evidence of PH after weaning from ECLS. In the second patient (patient 9), severe myocardial failure developed from overwhelming sepsis 8 hours after the iNO had facilitated weaning from CPB after a heart transplantation. Adequate systemic perfusion could not be achieved despite high-flow ECLS (200 $mL \cdot kg^{-1} \cdot min^{-1}$) and high-dose vasoconstrictor therapy (epinephrine 1.85 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Extracorporeal life support was discontinued 2 days later after the development of multiorgan system failure and brain death.

The remaining patient (patient 10), who responded to the trial dose of iNO, died after 5 days of iNO therapy of *Streptococcus pneumoniae* septicemia and multiorgan system failure. This patient was begun on iNO in the operating room because of failure to wean from CPB after an arterial switch operation. At the time of clinical deterioration, the patient was no longer deemed to be an ECLS candidate because of multiorgan failure and sepsis.

In all of the patients who initially responded to iNO but who later required ECLS or died, PH had remained controlled with iNO therapy.

In summary, 6 of the 10 patients (60%) who had met the ECLS criteria for postoperative PH were managed successfully with ongoing iNO treatment and survived to discharge from the hospital, without the need for rescue ECLS. Three patients received ECLS and 2 survived, 1 with neurologic impairment. One patient died despite ongoing iNO therapy, but was no longer an ECLS candidate because of multiorgan failure (Fig 2).

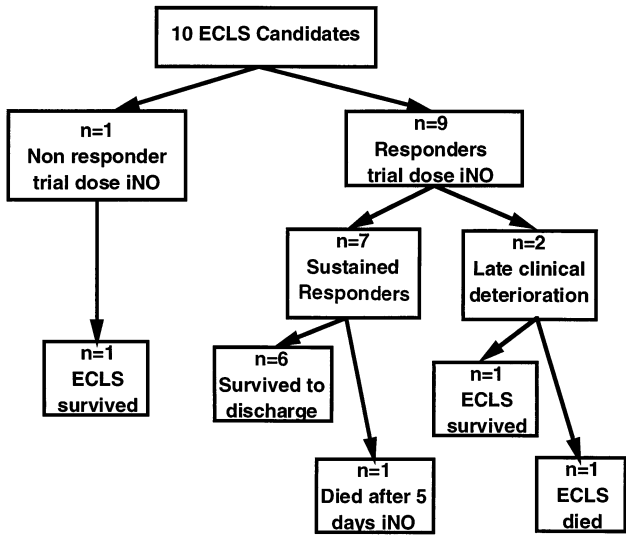

*Fig 2. Outcome of the 10 patients who met extracorporeal life support (*ECLS*) criteria for postoperative pulmonary hypertension during the period of study when inhaled nitric oxide (*iNO*) was available at our institution (January 1992 to November 1995).*

Toxicity

No clinical toxic effects were noted during iNO therapy.

Comment

This study shows that iNO might reduce the need for rescue ECLS in infants and children with critical PH after corrective congenital heart disease operations, without evidence of tolerance or toxicity.

Critical reactive PH occurring soon after operations for congenital heart disease fulfills the major selection criteria for ECLS because it is a life-threatening, yet reversible complication [1]. Widespread clinical experience has shown that postcardiotomy patients with intractable cardiorespiratory failure can be supported successfully with ECLS, with an overall survival rate of approximately 40% to 50% [3–7]. Dhillon and colleagues [2] confirmed recently that ECLS can be used specifically for critical PH after congenital heart disease operations. Our study supports these findings; however, because of its invasiveness, high morbidity, and high cost, ECLS should be reserved as a rescue therapy and used only when other less invasive therapies have failed.

Inhaled nitric oxide is a selective pulmonary vasodilator that has been administered with promising results to children with corrected [8–10] and uncorrected [12] congenital heart disease. The theoretic advantage of administering exogenous NO by inhalation directly to a potentially damaged pulmonary endothelium (because of the underlying congenital heart defect [13], compounded by the deleterious effects of CPB [14, 15]) has been shown repeatedly [8–10]. Inhaled nitric oxide has consistently been associated with improvements in hemodynamic status and oxygenation in congenital heart disease patients [8–10, 12] and appears, in the short term, to be superior to intravenous prostacyclin for postoperative PH [10].

The effect of iNO on clinical outcome and its influence on reducing the need for rescue ECLS in congenital heart disease patients with critical postoperative PH have not been evaluated. The ideal method for assessing the effect of a new treatment, such as iNO, on clinical outcome would be to conduct a large prospective randomized trial. Such a study, however, may not be feasible because of the difficulties in standardizing conventional treatment, patient selection criteria, the potential difficulty in recruiting sufficient numbers of patients, and the ethical problem of withholding a potentially life-saving treatment. The overlapping introduction of iNO and other therapies, such as ultrafiltration, at our institution made it impossible to review accurately whether iNO had altered morbidity, mortality, and the need for ECLS since its introduction in 1992.

We therefore chose to assess the clinical effect of iNO in those congenital heart disease patients who we believed had potentially treatable, yet life-threatening, postoperative PH and in whom other conventional treatments had failed. The only treatment option available to these patients was ECLS. Inhaled nitric oxide was administered before ECLS in an attempt to avoid this invasive form of life support.

The results of this study are encouraging, showing that 60% of these patients were managed successfully with

iNO and survived to discharge from the hospital, without requiring rescue ECLS. This compares favorably with the 40% to 50% ECLS survival rates in postcardiotomy patients in previous reports [3–7].

Three patients, however, still required ECLS despite iNO. Two of these patients failed to sustain their initial clinical improvement with iNO because of severe myocardial dysfunction secondary to a prolonged cardiac arrest or sepsis. Neither of these patients had PH during iNO treatment at the time of their clinical deterioration. The third patient who required ECLS failed to respond to the trial dose of iNO, probably because of associated severe myocardial dysfunction. The survival of 2 of these 3 patients with ECLS stresses the need for immediate availability of rescue ECLS for patients with critical postoperative PH complicated by myocardial dysfunction and sepsis.

It is impossible to speculate whether the patient who died of sepsis and multiorgan failure after 5 days of iNO would have benefited from the earlier institution of ECLS. This patient had a marked response to the trial dose of iNO and no longer met ECLS criteria. It would have been difficult to justify using an invasive therapy such as ECLS at this time. This patient did not have appreciable PH at the time of her death.

In conclusion, children with critical PH unresponsive to maximal conventional treatment may be managed successfully with iNO, without the need for rescue ECLS. These patients should therefore be given a trial of iNO before the use of ECLS.

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