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Inhaled Nitric Oxide and Related Therapies

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Abstract

Children with congenital heart defects are at risk for perioperative pulmonary hypertension if they require corrective or palliative surgery in the first week of life or if they have defects associated with significant pulmonary over circulation. In addition children undergoing cavopulmonary connections for single ventricle lesions require low pulmonary vascular resistance for surgical success. Treatment of perioperative pulmonary hypertension with inhaled nitric oxide has become standard therapy in many centers. Related drugs that increase nitric oxide synthesis including arginine and citrulline have also been studied in the perioperative period. In this article, previous clinical trials of inhaled nitric oxide, intravenous arginine, and intravenous and oral citrulline in children with perioperative pulmonary hypertension or elevated pulmonary vascular resistance after a cavopulmonary connection are reviewed. In addition, recommendations are presented for each agent on the clinical use in the perioperative setting including clinical indications, assessment of clinical effect, and length of therapy.

Keywords

Pulmonary hypertension; congenital cardiac surgery; inhaled nitric oxide; arginine; citrulline

Inhaled Nitric Oxide

As with many drugs and therapies utilized in the postoperative care of children undergoing surgical repair of congenital heart defects, inhaled nitric oxide is not specifically approved by the US Food and Drug Administration to treat postoperative pulmonary hypertension. In fact, inhaled nitric oxide is only approved to treat persistent pulmonary hypertension of the newborn in term neonates and all other uses are considered off label. That being said, inhaled nitric has been both extensively studied and even more extensively used to treat postoperative pulmonary hypertension. Therefore it is important to detail some of the clinical evidence supporting its use and make recommendations for both initiation and weaning of inhaled nitric oxide, updating advice contained in a European consensus document on the use of inhaled nitric oxide in children from 2004 (1).

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Early Clinical Studies of Postoperative Inhaled Nitric Oxide

One of the earliest clinical studies of inhaled nitric oxide after congenital cardiac surgery was performed by Wessel et al at Boston Children's Hospital in 1992 (2). In that landmark study, the authors studied endothelium dependent vasodilatation by administering preoperative and postoperative acetylcholine at a dose of 10-6 M to children. In the preoperative group, 12 children with known pulmonary hypertension were studied in the cardiac catheterization laboratory and during their procedure were administered acetylcholine and hemodynamic responses monitored. They noted a significant decrease in mean pulmonary artery pressure, pulmonary vascular resistance, mean systemic blood pressure, systemic vascular resistance, and right atrial pressure (Table 1). Nine patients with postoperative pulmonary hypertension were subsequently given both a single dose of acetylcholine (10-6 M) and inhaled nitric oxide at 80 ppm. Compared to the preoperative response, the postoperative response to acetylcholine was attenuated but the response to inhaled nitric oxide was more pronounced (Table 2). The authors concluded that endothelial dysfunction was responsible for the attenuated response to acetylcholine in the postoperative period compared to the preoperative response. They also conclude that inhaled nitric oxide at 80 ppm was quite effective at reducing both pulmonary artery pressure and pulmonary vascular resistance without significant effects on the systemic circulation and should be further investigated in clinical trials.

Miller et al reported the short term hemodynamic effects of the administration of 2, 10 and 20 ppm inhaled nitric oxide to 10 infants studied in the intensive care unit immediately after corrective cardiac operations (3). Measurements were facilitated by the use of thermistor-tipped pulmonary artery catheters. Even at the lowest dose, inhaled nitric oxide caused selective pulmonary vasodilatation. The pulmonary artery/systemic arterial pressure ratio was a predictor of response to nitric oxide with a greater response being seen in those infants with higher ratios (> 0.5). In this group of infants pulmonary vascular resistance fell by between 37 and 42%.

In 1995, Curran et al at Children's Memorial Hospital in Chicago used inhaled nitric oxide in 15 postoperative children with severe refractory pulmonary hypertension unresponsive to conventional therapy (4). The cardiac lesions and surgical procures in these 15 patients was quite varied and ranged from repair of an atrioventricular septal defect to a modified Norwood procedure or cardiac transplantation for hypoplastic left heart syndrome. Conventional therapy included mechanical ventilation with sedation and paralysis, a FiO_2 of 0.8 to 1.0 and inotropic support. Eleven of the children had a good response to inhaled nitric oxide utilizing doses as low as 10 to 20 ppm and were treated until their pulmonary hypertension resolved. Treatment length ranged from 1 to 10 days. Four of the 15 patients did not respond clinically to inhaled NO and it is notable that all 4 patients subsequently died. In the patients who responded the mean PA pressure decreased from 30.9 ± 5.8 mmHg to 23.1 ± 5.4 mm Hg ($p < .01$). The authors conclude that in the setting of refractory postoperative pulmonary hypertension, inhaled nitric oxide was not only effective but potentially life saving.

These 2 important early clinical trials indicated that inhaled nitric oxide should be studied in a randomized placebo controlled fashion to determine if it improved postoperative outcomes in children with postoperative pulmonary hypertension.

Randomized Clinical Trials of Postoperative Inhaled Nitric Oxide

Although postoperative pulmonary hypertension is a significant clinical problem with poor associated clinical outcomes, it is a rare enough event that adequately powered single center studies are difficult to perform. Several single center randomized placebo controlled clinical trials have been performed in the past 10 years, all with fairly small sample sizes. The first reported RCT was conducted by Russell et al at the University of California, San Francisco

(5). They prospectively enrolled 35 patients undergoing cardiopulmonary bypass for surgical correction of specific congenital heart defects with documented preoperative pulmonary hypertension by either preoperative echocardiography or cardiac catheterization. Preoperative pulmonary hypertension was defined as a mean PAP > 50% systemic mean arterial pressure. The majority of the patients had large unrestrictive right to left shunts at the ventricular level with an atrioventricular septal defect being then most common diagnosis. The study protocol included a 20 minute administration of either inhaled nitric oxide at 80 ppm or placebo- in this case nitrogen- combined with a FiO₂ of 90% and adequate ventilation. The protocol was performed in the operating suite immediately after discontinuation of cardiopulmonary bypass and assessment of adequacy of the repair by transesophageal echocardiography.

Of the 35 patients studied, 13 patients had documented postoperative pulmonary hypertension. In this group of 13 patients, 5 received inhaled nitric oxide and 8 received the placebo gas. In the 5 patients who received inhaled nitric oxide, the response was fairly dramatic with a rapid and sustained 20 % reduction in PA pressure compared to baseline values (Figure 1). Patients treated with placebo had a small increase in PA pressure over the 20 minute study period that was not significant. The remaining 22 patients did not develop postoperative pulmonary hypertension and there were no differences in PA pressure in this subgroup between those who received inhaled NO and those that received placebo. Major limitations of the study include the relatively small sample size which was compounded by the relatively low incidence (37%) of postoperative pulmonary hypertension despite a requirement of preoperative pulmonary hypertension for study entry. Randomization issues further restricted the most interesting group of patients to the 5 children who both developed postoperative pulmonary hypertension and were treated with inhaled nitric oxide. Nonetheless, this was the first published randomized, blinded, placebo controlled study of inhaled nitric oxide for treatment of postoperative pulmonary hypertension and certainly led the way for further investigation.

Standard therapy for postoperative pulmonary hypertension has historically included induction of respiratory alkalosis due to known effects of pH on pulmonary artery pressure and pulmonary vascular resistance. In an unblinded but randomized crossover study, Morris et al at the Hospital for Sick Children in Toronto attempted to assess the effects of hyperventilation and inhaled nitric oxide as potential treatments for postoperative hypertension (6). Their study group included 12 children who had undergone biventricular repair of congenital heart defects and had a documented postoperative pulmonary artery pressure > 25 mm Hg by indwelling PA catheter. Respiratory alkalosis was achieved by adjustment of the ventilator rate at a fixed tidal volume to achieve an arterial pH of 7.50 or greater. Two doses of inhaled NO were utilized to assess for a possible dose effect: inhaled NO at 5 ppm for 15 minutes followed by an increase to 40 ppm for an additional 15 minutes. Since this was a randomized crossover study, each patient received both treatments (hyperventilation and inhaled nitric oxide) in a randomized order with a 30 minute recovery period between treatments. The results of the study were intriguing. Hyperventilation to a pH of 7.50 definitely reduced PA pressure and pulmonary vascular resistance but at the expense of a subsequent decrease in cardiac output and an increase in systemic vascular resistance, both undesirable effects in the immediate postoperative period. Inhaled nitric oxide was equally effective at reducing PA pressure and pulmonary vascular resistance but without the untoward effects on cardiac output and systemic vascular resistance. Furthermore, there was no significant difference between the effect of inhaled NO at the 5 ppm and 40 ppm doses. The authors concluded that inhaled NO at fairly low doses was both safe and efficacious as a selective pulmonary vasodilator and had inherent advantages over other therapies such as hyperventilation.

Prevention of a postoperative pulmonary hypertensive crisis was the target outcome of a subsequent randomized clinical trial of inhaled nitric performed by Day et al at Primary Children's at the University of Utah (7). This study was more selective in that for study entry,

patients had to have postoperative pulmonary hypertension as defined by a systolic pulmonary artery pressure greater than 50% of systolic systemic artery pressure as measured by indwelling pulmonary and systemic arterial catheters. Thirty eight patients were randomized to inhaled nitric oxide vs. conventional therapy. The primary outcome was the frequency of postoperative pulmonary hypertensive crises in each group. However, the study was not blinded and control patients could cross over to receive inhaled nitric oxide if they had a sustained pulmonary hypertensive crisis that did not respond to conventional therapy. Hemodynamics before and 1 hour after initiation of treatment showed no significant differences between the conventional treatment and inhaled NO groups, although the systolic PAP to systolic SAP ratio dropped slightly in the inhaled NO group. There were 4 patients in the conventional therapy group and 3 patients in the inhaled NO group who developed a pulmonary hypertensive crisis. The conventional therapy patients who developed a pulmonary hypertensive crisis were all subsequently treated with inhaled NO and had marked improvement in oxygenation and hemodynamics. The authors concluded that inhaled NO did not significantly improve postoperative hemodynamics or prevent postoperative pulmonary hypertensive crises compared to conventional therapy but was effective as a rescue therapy for patients who failed conventional therapy.

The largest study to date evaluating inhaled nitric oxide in the postoperative period was performed by Miller et al at the Royal Alexandra Hospital for Children in Sydney Australia (8). The authors enrolled 124 patients undergoing an AVSD or unrestrictive VSD repair who had preoperative evidence of high pulmonary artery pressure or flow. In this blinded study, patients were randomized to receive inhaled iNO at 10 ppm vs placebo after surgery until extubation. The placebo treatment was inhaled nitrogen also at 10 ppm. Postoperative management as well as treatment of pulmonary hypertensive crises was driven by protocol for all patients. Compared to placebo, the patients in the nitric oxide group had a lower median pulmonary vascular resistance, had 30% fewer pulmonary hypertensive crises, and had a shorter median time to extubation readiness. The study was not powered to demonstrate a difference in actual length of mechanical ventilation or mortality. Nonetheless, this was a well executed study and as mentioned the largest to date that showed clear advantages of treatment with inhaled nitric oxide.

Cochrane Database of Systematic Reviews—A systematic review of the available data from randomized clinical trials was performed by Bizarro and Gross in 2008 (9). Utilizing Cochrane database procedures and guidelines, the authors evaluated published studies of inhaled nitric oxide in the postoperative setting. The methodologic quality of each published study was evaluated using established criteria including the method of randomization, concealment of allocation, blinding of treatment, completeness of follow-up, and blinded outcome assessment. Outcomes of interest included mortality, length of ICU stay or hospitalization, neurodevelopmental outcome, and physiologic variables. Utilizing preestablished inclusion and exclusion criteria, only the 4 randomized clinical trials that have been previously presented were included in the analysis (5, 6, 7, and 8). However, because each of these studies reported different outcomes, the number of patients included in the subsequent meta-analysis of each outcome was severely restricted and did not add much to the previously published literature. For example, only the studies by Day and Miler reported mortality and the subsequent meta-analysis was done on a cohort of 162 patients, hardly an adequate sample size in a population where postoperative mortality is a fairly rare event. Analysis of the incidence of postoperative pulmonary hypertensive crisis was limited to the study by Day and thus included data on only 38 patients. Analysis of physiologic outcomes was likewise quite restrictive. The authors concluded that there were no differences in the use of inhaled NO in the outcomes that were reviewed while acknowledging the limitations of the review due the concerns over methodological quality, sample size, and heterogeneity of

patients in the four studies. These limitations severely restrict any conclusions that can be drawn from this Cochrane review.

Inhaled nitric oxide in cavopulmonary circulations

Inhaled nitric oxide has also been investigated or recommended as a potential therapeutic tool in the management of patients with raised pulmonary vascular resistance in the context of cavopulmonary circulations and right ventricular failure. Goldman et al studied a group of patients following the Fontan operation in whom small inter-atrial communications were present (10). Responses to iNO 20 ppm were assessed in 10 consecutive children with SaO₂ ≤ 85% and compared with 5 children with SaO₂ > 85%. In patients with baseline SaO₂ < or = 85% exposure to iNO resulted in a significant increase in SaO₂ from a mean of 64% to 82% and a reduction in transpulmonary pressure gradient 12.2 to 9.6 mmHg. Baseline saturation was a predictor of response to iNO, with a greater response in those with lower saturations. The authors concluded that iNO improved both oxygenation and lowered trans-pulmonary gradient in desaturated patients after fenestrated Fontan operations, possibly by counteracting hypoxemia-induced pulmonary vasoconstriction. They asserted that a trial of iNO could be considered in clinically unstable patients with cavopulmonary connections if pulmonary vasoconstriction causing raised transpulmonary gradients occurred. Gamillsheg et al evaluated the effects of inhaled nitric oxide in patients with critical pulmonary perfusion after Fontan-type procedures and bidirectional Glenn anastomosis (11). Inhaled nitric oxide at doses of between 1.5 and 10 ppm was administered in 13 children (mean age 5.6 ± 1.6 years, 1.5 to 17 years) with critical pulmonary perfusion (central venous pressure > 20 mm Hg or transpulmonary pressure gradient > 10 mm Hg) in the early postoperative period after total cavopulmonary connection (n = 9) or after bidirectional Glenn anastomosis (n = 4). In patients after total cavopulmonary connection inhaled nitric oxide therapy decreased central venous pressure by 15.3% ± 1.4% (p = 0.0001) and transpulmonary pressure gradient by 42% ± 8% (p = 0.0008). In patients after bidirectional Glenn anastomosis, inhaled nitric oxide therapy resulted in a decrease of central venous pressure by 22% ± 1% and of the transpulmonary pressure gradient by 55% ± 6%. Arterial and venous oxygen saturations were also improved in both total cavopulmonary and Glenn groups. In a prospective randomized study, Cai et al have recently shown that inhaled nitric oxide 20 ppm resulted in significant falls in transpulmonary gradient (TPG) in children with high transpulmonary gradients (>10 mmHg) or central venous pressure (>15 mmHg) after the Fontan operation (mean reduction in TPG 2.4 mmHg) (12). However these authors also showed that the addition of milrinone 0.5 micrograms/kg/min to iNO resulted in a synergistic effect with a greater fall in TPG (mean reduction of 4 mmHg).

Use of inhaled nitric oxide in preoperative assessment of PVR

The evaluation of pulmonary vascular resistance is critical in decisions making when assessing operability for corrective surgery or cardiac transplantation and in the assessment of prognosis in pulmonary hypertensive patients (13,14). Atz et al compared the ability of inhaled nitric oxide (NO), oxygen (O₂) and nitric oxide in oxygen (NO+O₂) to identify reactive pulmonary vasculature in pulmonary hypertensive patients during acute vasodilator testing at cardiac catheterization (15). In a group of 46 patients they studied hemodynamic measurements in room air (RA), 100% O₂, return to RA and then NO (80 ppm in RA). In a second group of 25 patients, they studied response to RA, 100% O₂ and 80 ppm NO in oxygen (NO+O₂). Inhaled NO and O₂ individually produced similar reductions in PVR. A response of 20% or more reduction in PVR was seen in 22 of the 25 patients treated with NO+O₂ compared with 16 of 25 treated with O₂ alone (p = 0.01). The authors concluded that combination testing with NO + O₂ provided additional pulmonary vasodilatation in patients with a reactive pulmonary vascular bed and that the combination of NO+O₂ identified patients with significant pulmonary

vasoreactivity who might not be recognized if O₂ or NO were used separately. In a multi-institutional study, Balzer et al. extended on the study of Atz reporting the effects of iNO and O₂ in the evaluation of 124 patients with heart disease and severe pulmonary hypertension (13). The ratio of pulmonary and systemic vascular resistance (Rp:Rs) was determined at baseline while breathing approximately 21% to 30% oxygen, and then in approximately 100% oxygen and approximately 100% oxygen with 10 to 80 parts per million nitric oxide to evaluate pulmonary vascular reactivity. Surgery was performed in 74 patients. Twelve patients died or developed right heart failure secondary to pulmonary hypertension following surgery. An Rp:Rs ratio of <0.33 and a 20% decrease in Rp:Rs from baseline were chosen as 2 criteria for operability to determine, in retrospect, the efficacy of preoperative testing in patient selection. In comparison to an evaluation with oxygen alone, sensitivity (64% versus 97%) and accuracy (68% versus 90%) were increased by an evaluation with oxygen and nitric oxide when Rp:Rs<0.33 was used as the criterion for operability. The authors concluded that through the use of a combination of oxygen and inhaled nitric oxide during preoperative testing, a greater number of appropriate candidates for corrective cardiac surgery or transplantation could be identified.

Recommendations for Use of Inhaled Nitric Oxide in the Perioperative Setting

1. Evidence from available clinical trials and expert opinion supports the use of inhaled nitric oxide for treatment of pulmonary hypertension (Class I, Level B) There is evidence and/or general agreement that inhaled nitric oxide is useful and effective (Class I) and that the data is derived from a single randomized trial, or non-randomized studies (Level B). The level of evidence is not at level A because the study by Miller et al is the only study of sufficient size to address clinical outcomes other than purely physiologic outcomes. The initial dose of inhaled nitric oxide should be 20 ppm on the basis of weight of opinion and evidence from non-randomized studies (Class I, Level B).
2. There are no adequate clinical trials on the use of iNO in the setting of cavopulmonary circulations. However evidence from case series and expert consensus favors a trial of iNO in children with a high transpulmonary gradient in the immediate postoperative period following cavopulmonary procedures (Class II, Level B).
3. However, clinical recommendations should provide guidance as to not only whether to use a therapy but also how to use and discontinue that therapy. If possible, inhaled nitric oxide should be utilized only when there is clear evidence of pulmonary hypertension utilizing echocardiographic or pulmonary artery catheter data. The qualification of "*if possible*" is important because pulmonary artery catheters are not routinely utilized in the postoperative period in most centers and echocardiographic data often cannot be obtained emergently. In those instances, inhaled nitric oxide should be utilized and the physiologic response noted while waiting for echocardiographic measurements.
4. Once inhaled nitric oxide has been started, reasonable attempts to wean it off should be made every 12 to 24 hours utilizing an objective weaning protocol that measures the physiologic response to both the decrease in dose as well as the discontinuation of inhaled NO. As an example, the inhaled NO weaning protocol utilized at Vanderbilt Children's Hospital is depicted in Figure 2.
5. Inhaled nitric oxide should be discontinued after a 30 minute trial if no beneficial effect has been documented (i.e., improvement in cyanosis, transpulmonary gradient and/or cardiac output).

Recommendations for the use of iNO in acute pulmonary vasodilator testing

There is some evidence from acute studies and case series that the use of inhaled nitric oxide in addition to oxygen can identify a greater number of appropriate candidates for corrective cardiac surgery or transplantation than oxygen alone. Expert consensus supports the use of iNO in addition to oxygen during pulmonary reactivity testing in children with pulmonary hypertension being considered for surgical correction or transplantation (Class I, Level B).

Intravenous Arginine

Arginine is the substrate for nitric oxide synthase and therefore it would be logical that arginine would be an effective postoperative treatment for pulmonary hypertension. However, in the postoperative period there is relative decreased availability of arginine (16). Hemolysis of red blood cells during cardiopulmonary bypass releases arginase which further decreases plasma arginine levels. In addition, pulmonary endothelial dysfunction in the postoperative period, conventionally defined as a loss of vasodilator response to acetylcholine, may also result in decreased synthesis of nitric oxide despite adequate substrate. Arginine supplementation was the focus of an interesting clinical study by Schulze-Neick, et al in London published in 1999 (17). The authors studied 20 patients with known pulmonary hypertension and left to right shunting due to ASD, VSD, and AVSD cardiac lesions. Ten patients were studied preoperatively in the cardiac catheterization lab and an additional 10 patients were studied postoperatively 2 hours after separation from cardiopulmonary bypass. All patients received an infusion of arginine at 15 mg/kg/min after being ventilated with a FiO₂ of 0.65 for 15 minutes. Of note, the PVRI was 50% higher in the postoperative group compared to the preoperative group at baseline. In both patient groups, increasing the FiO₂ to 0.65 resulted in a dramatic decrease in pulmonary vascular resistance index. However, an additional decrease in PVRI with the arginine infusion was only seen in the postoperative group. Furthermore, the drop in PVRI was also not as impressive as that provided by oxygen alone.

Recommendations

Arginine chloride is available on most hospital formularies as a treatment for severe metabolic alkalosis and hyponatremia. However, its use as a postoperative pulmonary vasodilator is not well supported in the literature with adequate randomized clinical trials and it is therefore there is only a Class IIa, Level B recommendation indicating conflicting evidence or a divergence of opinion but leaning towards efficacy (IIa), and level of evidence B indicating that the evidence is derived from a single randomized trial or unrandomized trials. Clearly further research is needed in this area.

Citrulline Therapy

Investigators at Vanderbilt Children's Hospital in Nashville have performed a series of studies investigating the role of the hepatic urea cycle in postoperative pulmonary hypertension. The urea cycle generates both citrulline and arginine and is therefore critical to nitric oxide synthesis (Figure 3). In observational studies of urea cycle function, Barr et al noted that both plasma citrulline and arginine levels were significantly decreased after congenital cardiac surgery (16).

Oral citrulline clinical trial

This observation led to a study of oral citrulline which is clinically used for treatment of children with urea cycle defects. Smith et al performed a randomized double blind placebo controlled trial of oral citrulline in 40 patients undergoing repair of congenital cardiac defects (18). Patients were randomized to receive 5 doses of oral citrulline (1.9 grams/kg) vs. placebo. The 1st dose was administered immediately prior to surgery and the 2nd dose immediately on arrival

in the Pediatric ICU after surgery followed every 12 hours $\times$ 3 doses. No adverse side effects were noted. Plasma citrulline levels were significantly higher in the citrulline group (36 vs. 26 $\mu\text{mol/l}$ $p=0.013$) demonstrating adequate absorption. The study was not adequately powered to detect an effect on the *incidence* of postoperative pulmonary hypertension, however it was noted that patients with a plasma citrulline level $> 37 \mu\text{mol/L}$ did not develop pulmonary hypertension (Table 3).

Intravenous citrulline clinical trial

Barr et al at Vanderbilt then investigated the pharmacokinetics of intravenous citrulline in preparation for a clinical efficacy trial (19). Using a dose escalation trial design, a total of 17 patients were studied before a final protocol was derived to include a preoperative citrulline bolus of 150 mg/kg followed 4 hours later postoperatively with a continuous infusion of 9 mg/kg/hr for 48 hours. No adverse side effects or adverse events related to the administration of intravenous citrulline were noted. This pharmacokinetic study laid the groundwork for an ongoing randomized placebo controlled double blind clinical trial of intravenous citrulline in children at risk for postoperative pulmonary hypertension after congenital cardiac surgery.

Recommendations

Oral citrulline is available on most hospital formularies as a treatment for urea cycle defects. However therefore there is only a Class IIa, Level B recommendation indicating a divergence of opinion for its use but leaning towards efficacy as a pulmonary vasodilator (IIa), and level of evidence B indicating that the evidence is derived from a single randomized trial or unrandomized trials. Absorption from the gastrointestinal tract is also a potential issue in the perioperative period. Further research with both oral and intravenous citrulline is needed.

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References

1. Macrae DJ, et al. Inhaled nitric oxide therapy in neonates and children: reaching a European consensus. *Intensive Care Med* 2004;30(3):372–80. [PubMed: 14722629]
2. Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation* 1993;88:2128–2138. [PubMed: 8222107]
3. Miller OI, et al. Very-low-dose inhaled nitric oxide: A selective pulmonary vasodilator after operations for congenital heart disease. *J Thorac Cardiovasc Surg* 1994;108(3):487–494. [PubMed: 8078341]
4. Curran RD, Mavroudis C, Backer CL, Sautel M, Zales VR, Wessel DL. Inhaled Nitric Oxide for Children With Congenital Heart Disease and Pulmonary Hypertension. *Ann Thorac Surg* 1995;60:1765–71. [PubMed: 8787478]
5. Russell IAM, Zwass MS, Fineman JR, Balea M, Rouine-Rapp K, Brook M, Hanley FL, Silverman Norman H, Cahalan MK. The Effects of Inhaled Nitric Oxide on Postoperative Pulmonary Hypertension in Infants and Children Undergoing Surgical Repair of Congenital Heart Disease. *Anesth Analg* 1998;87:46–51. [PubMed: 9661544]
6. Morris K, Beghetti M, Petros A, Adatia I, Bohn D. Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease. *Crit Care Med* 2000;28:2974–2978. [PubMed: 10966281]
7. Day RW, Hawkins JA, McGough EC, Crezéé KL, Orsmond GS. Randomized Controlled Study of Inhaled Nitric Oxide After Operation for Congenital Heart Disease. *Ann Thorac Surg* 2000;69:1907–13. [PubMed: 10892945]

8. Miller OI, Tang SF, Keech A, Pigott NB, Beller E, Celermajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomized double-blind study. *Lancet* 2000;356:1464–69. [PubMed: 11081528]
9. Bizzarro, M.; Gross, I. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease (Review). JohnWiley & Sons, Ltd; Copyright © 2008 The Cochrane Collaboration
10. Goldman AP, et al. Pharmacological control of pulmonary blood flow with inhaled nitric oxide after the fenestrated Fontan operation. *Circulation* 1996;94(9 Suppl):II44–8. [PubMed: 8901718]
11. Gamillscheg A, et al. Inhaled nitric oxide in patients with critical pulmonary perfusion after Fontan-type procedures and bidirectional Glenn anastomosis. *J Thorac Cardiovasc Surg* 1997;113(3):435–42. [PubMed: 9081087]
12. Cai J, et al. Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study. *Ann Thorac Surg* 2008;86(3):882–8. discussion 882–8. [PubMed: 18721577]
13. Balzer DT, et al. Inhaled Nitric Oxide as a Preoperative Test (INOP Test I): the INOP Test Study Group Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *Circulation* 2002;106(12 Suppl 1):I76–81. [PubMed: 12354713]
14. Adatia I, et al. Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation. *J Am Coll Cardiol* 1995;25(7):1656–64. [PubMed: 7759720]
15. Atz AM, et al. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *J Am Coll Cardiol* 1999;33(3):813–9. [PubMed: 10080486]
16. Barr FE, Beverley H, VanHook K, Cermak E, Christian K, Drinkwater D, Dyer K, Raggio N, Scott N, Moore J, Christman B, Summar M. Effect of Cardiopulmonary Bypass on Urea Cycle Intermediates and Nitric Oxide Levels after Congenital Heart Surgery. *J Pediatrics* 2003;142:26–30.
17. Schulze-Neick I, Penny DJ, Rigby ML, Morgan C, Kelleher A, Collins P, Li J, Bush A, Shinebourne EA, Redington AN. L-Arginine and Substance P Reverse the Pulmonary Endothelial Dysfunction Caused by Congenital Heart Surgery. *Circulation* 1999;100:749–755. [PubMed: 10449698]
18. Smith HAB, Canter JA, Christian KG, Drinkwater DC, Scholl FG, Christman BW, Barr FE, Summar ML. Nitric Oxide Precursors and Congenital Heart Surgery: A Randomized Controlled Trial of Oral Citrulline. *Journal of Thoracic and Cardiovasc Surg* 2006;132:58–65.
19. Barr FE, Tirone RG, Taylor MB, Rice G, Arnold J, Cunningham G, Smith HAB, Campbell A, Canter JA, Christian KG, Drinkwater DC, Scholl F, Kavanaugh-McHugh A, Summar ML. Pharmacokinetics and Safety of Intravenous Citrulline in Children Undergoing Congenital Heart Surgery: A Potential Therapy for Postoperative Pulmonary Hypertension. *Journal of Thoracic and Cardiovascular Surgery* 2007;134:319–326. [PubMed: 17662768]

Figure 1.

Russel et al noted a significant decrease in pulmonary artery pressure compared to baseline in patients who received inhaled nitric oxide at 80 ppm compared to placebo during the 20 minute postoperative study period.

PCCU iNO Weaning Protocol

Figure 2.

Nitric oxide weaning protocol utilized at Vanderbilt Children's Hospital. If inhaled nitric oxide is initiated, then attempts to wean the nitric oxide are made to achieve the lowest therapeutic dose using changes in oxygenation or mean arterial pressure as outcomes. Further attempts at weaning are made every 12 hours until the nitric oxide can safely be discontinued.

Figure 3.

The hepatic urea cycle is primarily known for processing of nitrogen waste but it is also the major source of the amino acids arginine and citrulline- key intermediates in nitric oxide synthesis.

Table 1

Acetylcholine caused significant pulmonary vasodilatation, demonstrating an intact endothelial response (study by Wesel et al.)

Preoperative measurements	Baseline	10-6 M ACH	P
Mean PA pressure, mm Hg	42.8 ± 4.1	31.6 ± 3.6	.001
Pulmonary vascular resistance, U*m2	5.6 ± 1.0	3.0 ± 0.7	.0005
Mean systemic pressure, mm Hg	70.1 ± 4.3	57.0 ± 5.2	.005
Systemic vascular resistance, U*m2	18.0 ± 1.8	14.2 ± 2.2	.03
Right atrial pressure, mm Hg	7.0 ± 0.5	6.3 ± 0.5	.03

Postoperative response to inhaled nitric oxide demonstrating moderate postoperative endothelial dysfunction but a robust endothelial independent response (study by Wessel et al)

Table 2

Postoperative measurements	Baseline	10-6 M ACH	P	Baseline	iNO 80 ppm	P
Mean PA pressure, mm Hg	32.9 ± 3	30.0 ± 2.7	.005	34.4 ± 2.6	25.8 ± 2.4	.0001
Pulmonary vascular resistance, U*m2	5.8 ± 0.9	5.1 ± 0.8	.05	6.8 ± 1.2	4.5 ± 0.8	.005
Right atrial pressure, mm Hg	10.0 ± 0.8	10.4 ± 1.0	NS	9.8 ± 0.9	8.9 ± 0.9	.04

Table 3

Patient plasma citrulline levels and postoperative pulmonary hypertension (study by Smith et al)

Citrulline level @ 12 h postop	No PHTN	+ PHTN
<37 umol/L	18 patients	9 patients
>37 umol/L	12 patients	0 patients

p value= 0.036 (Fisher's exact)