The Heart Surgery Forum #2004-1136
7 (6), 2004 [Epub November 2004]
doi:10.1532/HSF98.20041136

Online address: www.hsforum.com/vol7/issue6/2004-1136.html

Collective Review: Perioperative Uses of Inhaled Nitric Oxide in Adults

Dr. Oz

Mehmet C. Oz, MD,[1] Abbas Ardehali, MD[2]

[1]Columbia University College of Physicians and Surgeons, New York, New York; [2]David Geffen School of Medicine at UCLA, Los Angeles, California, USA

ABSTRACT

Pulmonary arterial hypertension and hypoxemia constitute a significant cause of postoperative right heart failure and mortality. Timely administration of inhaled nitric oxide (iNO) can improve hemodynamic parameters and oxygenation in patients undergoing heart and/or lung transplantation and various high-risk cardiac procedures involving coronary artery bypass grafting and/or left ventricular assist device placement. As a diagnostic tool, iNO can be used to identify heart transplant recipients at high risk of right ventricular failure and patients with primary pulmonary hypertension who may benefit from vasodilator therapy. In addition to its role as a potent and selective pulmonary vasodilator, iNO is a useful intraoperative adjunct in adult cardiac surgery patients that may reduce the need for right ventricular assist device placement. This review focuses on the multiple clinical applications of iNO in perioperative patient care.

INTRODUCTION

In the perioperative setting, pulmonary arterial hypertension (PAH) is common and, if persistent, can lead to right ventricular (RV) dysfunction and right-sided circulatory failure, jeopardizing survival. Thin walled and highly compliant in comparison with the left ventricle (LV), the RV is pathophysiologically more vulnerable to increases in intrathoracic and pericardial pressure, may dilate in response to minor variations in preload and afterload, and is restricted in its ability to increase contractility in response to increased preload. Positive inotropic support intended to augment RV output may have the deleterious effect of increasing PAH. Timely intervention with fast-acting and selective inhaled vasodilating agents, such as inhaled nitric oxide (iNO), can decrease pulmonary vascular resistance (PVR) without increasing pulmonary arterial shunting and systemic vasodilation, thereby reversing PAH, ameliorating RV failure, and preventing hypoxemia.

Received September 10, 2004; accepted September 15, 2004.

Address correspondence and reprint requests to: Mehmet C. Oz, MD, Vice-Chair of Surgery, Professor of Cardiac Surgery, Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital, 177 Fort Washington Ave, MHB-7GN-435, New York, New York 10032, USA; 1-212-305-4434; fax: 1-212-305-2439 (e-mail: mco2@columbia.edu).

NO, which is present endogenously in exhaled air, is delivered as a bolus dose with each breath from the nasopharynx to the lungs [Dweik 1998]. Intubation deprives patients of this bolus dose, suggesting that iNO administration in these contexts may rectify an iatrogenic deficiency state [Gerlach 1994, Hart 1999]. Initially characterized as endothelial cell–derived relaxing factor in the late 1980s, iNO has been used clinically since the early 1990s to improve the perfusion of well-ventilated lung regions, reduce intrapulmonary shunting, improve oxygenation, and decrease pulmonary artery pressure (PAP) and PVR in a variety of disease states [Hart 1999].

An endothelial cell product of L-arginine, NO promotes pulmonary vascular vasodilation by increasing intracellular levels of cyclic guanosine monophosphate [Hart 1999]. After diffusion into the vessel lumen, NO quickly binds to hemoglobin and is inactivated [Dweik 1998]. iNO is currently available in calibrated, closed-circuit systems that minimize nitrogen dioxide production, making safe administration possible, although continuous monitoring of inhaled nitrogen dioxide production as well as blood methemoglobin levels is required [Zapol 1994]. However, at the low doses commonly used (<20 ppm), methemoglobinemia, the most common adverse effect associated with prolonged high-dose therapy (>80 ppm), is not a clinically significant problem [Rossaint 1995, Roberts 1997, Dellinger 1998]. In the diagnostic and perioperative setting, iNO has the advantage of rapid onset of action locally and rapid inactivation by hemoglobin with minimal effects on systemic hemodynamics [Hart 1999].

CLINICAL EXPERIENCE WITH INO IN THE DIAGNOSTIC SETTING

Two populations of patients benefit from diagnostic testing with vasodilators: those with heart failure or valvular disease who may be candidates for surgery and those with primary PAH who are potentially eligible for therapy with calcium channel antagonists.

Following heart transplantation, patients with severe PAH are susceptible to acute RV failure for several reasons: (1) an inability of the smaller RV to adapt itself to an increased afterload; (2) low coronary blood flow per unit mass, which may lead to less cooling and perhaps less cardioplegia during the organ-harvesting process; and (3) tricuspid regurgitation due to annular distortion during implantation and a dilatory response to increased afterload [Bhatia 1987]. Therefore, inhaled or intravenous vasodilators are used before heart

transplantation or other cardiac surgery to screen for pulmonary reactivity in patients with heart failure (most of whom have secondary PAH) or valvular disease.

In conjunction with markedly elevated PVR (defined as greater than 6 Wood units), PAH was traditionally considered a contraindication to cardiac transplantation [Addonizio 1987, Bhatia 1987]. However, subsequent data demonstrated that the vasodilator-induced PVR index (PVRI) unit more accurately assessed the risk of RV failure than the Wood unit because it allowed for variations in body size [Addonizio 1987].

Intravenous nitroprusside challenge provided initial evidence that right heart hemodynamic measurements were predictive of postoperative mortality due to RV failure [Costard-Jackle 1992]. However, although nitroprusside accurately identified patients with reversible PAH, it was nonselective in that systemic vasodilation resulted from the doses required to achieve pulmonary vasodilation [Costard-Jackle 1992, Semigran 1994]. Additionally, nitroprusside has been associated with ventilation/perfusion mismatch and thiocyanate toxicity in the context of chronic use.

In contrast, iNO is a selective vasodilator that rapidly identifies patients with reversible pulmonary vasoconstriction without inducing systemic hypotension [Semigran 1994]. In a population of patients with severe heart failure who were referred for cardiac transplantation, Semigran and colleagues showed that iNO decreased PVR more robustly than intravenous nitroprusside, thereby identifying suitable surgical candidates with reversible (as opposed to fixed) PVR in whom nitroprusside caused systemic hypotension [Semigran 1994]. Significantly, the best response to iNO challenge (80 ppm) in another study was achieved by patients with the highest degree of pulmonary vasoconstriction, as determined by an elevated baseline PVRI [Loh 1994]. Atz and colleagues showed that combination testing with 100% oxygen and iNO not only enhanced the pulmonary vasodilatory response but also safely and accurately identified those patients with significant pulmonary vasoreactivity who otherwise might have been overlooked if either agent had been used alone [Atz 1999].

In patients with primary PAH, iNO testing reveals the probability of nonresponse to calcium channel antagonists, agents that can effectively prolong survival in hemodynamic responders [Rich 1992, Ricciardi 1998]. Reduction in PVR with iNO accurately and safely predicts hemodynamic response to nifedipine without the risk of the systemic hypotension and RV contractility associated with intravenously administered adenosine and nitroprusside [Ricciardi 1998, Cockrill 2001]. iNO screening is easily administered and spares patients with primary PAH the risk and expense associated with a trial of calcium channel antagonists in the intensive care unit [Ricciardi 1998].

In summary, iNO is a well-established, appropriate, and cost-effective diagnostic screening tool suitable for patients with PAH who are seeking to qualify for cardiac surgery or medical therapy [Ricciardi 1998].

HIGH-RISK CARDIAC SURGERY

Postoperative increases in PVR may seriously compromise RV afterload with consequent RV mismatch, reducing the cardiac output and ultimately causing RV failure. Table 1 delineates the perioperative management options for patients with RV dysfunction. Although intravenously administered pulmonary vasodilators reduce PVR, their efficacy is blunted by their hypotensive effects as well as by vasodilation of nonventilated lung regions, which increases shunt fraction [Maxey 2002]. Accordingly, the selective activity of inhalation agents, especially iNO, in reducing PVR without altering systemic blood pressure has rendered it the standard of care in the preservation of RV function following various cardiac procedures.

Table 1. Management of Patients with Right Heart Dysfunction

Preoperative	Diuresis
Operative	Deepening anesthesia
	Vasoactive drugs
Postoperative	Addressing primary pulmonary problems
	• Oxygen saturation <95% (check for a patent foramen ovale and left-to-right shunting)
	• Placement of a peak-end expiratory pressure valve up to 10 mm Hg
	Separating from bypass
	• Goal
	– Mixed venous saturation >50%
	– Central venous pressure <15 mm Hg
	– Cardiac index >1.8 L/min per m^2
	• Procedures
	– Patients should be sedated and paralyzed to reduce the reactive pulmonary bed
	– Core temperature should be warmed to reduce shivering and bleeding
	– pH should be normalized to reduce pulmonary vascular spasm
	– Hematocrit should be elevated to 30% to maximize oxygen-carrying capacity (especially if hypoxia is present)
	• In case of vasodilatory shock
	– Arginine vasopressin (Pitressin, 6 U/min)
	– Epinephrine
	– Dobutamine
	• Next step
	– Inhaled agents (eg, inhaled nitric oxide)

Evidence from small nonrandomized single-center studies suggests that iNO improves hemodynamics and oxygenation (decreasing the mean PAP [mPAP], the PVR, and the RV stroke work index [RVSWI] and increasing the cardiac index and the ratio of arterial blood oxygen tension to the fraction of inspired oxygen [PaO_2/FiO_2]), thereby preserving RV function [Fullerton 1996, Maxey 2002]. In 17 patients with modest PAH following coronary artery bypass grafting (CABG) and/or mitral valve replacement, iNO was shown to improve hemodynamics and significantly increase the PaO_2/FiO_2 ratio, possibly by ventilation/perfusion match enhancement, thus lowering RV afterload and RVSWI [Maxey 2002]. Another study evaluated 20 cardiac surgery patients who did not have severe PAH and showed that iNO at a dose of 20 ppm normalized PVR and PAP as effectively as higher 40-ppm doses

[Fullerton 1996]. A French study of 6 patients with mild PAH following mitral valve replacement showed that iNO (40 ppm) improved hemodynamics and oxygenation without altering systemic arterial or pulmonary wedge pressure and thereby preserved coronary perfusion of the RV [Girard 1992]. Generally, the dose of iNO should be initiated at 20 ppm in patients with postoperative PAH and increased to 40 ppm if warranted, because therapeutic benefit rarely occurs above this level [Argenziano 1998, Beck 1999, Schmid 1999].

Hypothetically, ventilation/perfusion mismatch, PAH, and hypoxemia may result from cardiopulmonary bypass–induced impairment of endothelial NO production [Bender 1997]. A study of 13 patients demonstrated that iNO decreased the ratio of mPAP to the mean systemic arterial pressure, increased the PaO_2/FiO_2 ratio, and decreased shunt fraction. The investigators concluded that iNO may be a valuable adjunctive therapy within the first 24 hours following CABG because it selectively increases ventilation/perfusion matching in patients with persistent PAH and hypoxemia and preserves RV function [Bender 1997]. A small randomized crossover study that enrolled 14 patients with severe pulmonary hypertension but a preserved RV function after cardiac surgery found that treatment with iNO was equivalent to prostaglandin in terms of cardiac index and RV performance [Schmid 1999].

A larger nonrandomized study by our group at Columbia University assessed iNO treatment in 34 patients (including 16 LV assist device [LVAD] recipients) who developed hemodynamically significant increases in PVR after various cardiothoracic procedures involving CABG [Beck 1999]. The results showed that iNO was beneficial in significantly reducing mPAP and increasing the cardiac index and systemic blood pressure. In 5 cases, patients could not be separated from cardiopulmonary bypass until iNO was administered. Significantly, iNO substantially reduced the number of patients who required RVAD placement following LVAD placement for biventricular heart failure with increased PVR [Beck 1999]. In such patients, PAH often limits device filling, subsequently causing RV failure in up to 40% of patients [Beck 1999]. At our institution, iNO use in this setting was correlated in a retrospective analysis with a 72% decline in RVAD placement, with only 3 of 60 LVAD recipients requiring an RVAD.

The role of iNO as an RVAD-sparing strategy in LVAD recipients was further investigated by our group in a blinded randomized trial that enrolled 11 patients with end-stage heart failure who were hemodynamically compromised with significant elevations in PVR and signs of pharmacologically refractory RV failure on weaning from cardiopulmonary bypass [Argenziano 1998]. These patients, who were at high risk for RV failure–related mortality, were randomly assigned to receive iNO or nitrogen. Although the patients who received iNO experienced significant reductions in mPAP and increases in LVAD flow, none of the nitrogen recipients showed any hemodynamic improvement. However, when the nitrogen-treated group subsequently crossed over to receive iNO, their hemodynamic variables improved dramatically. Of these 11 high-risk patients, only 1 required RVAD insertion, and this 1 case was attributable to the abrupt discontinuation of iNO treatment.

In summary, these results demonstrate that iNO is a potent, selective, and possibly RVAD-sparing pulmonary vasodilator useful as an intraoperative adjunct in the management of adult cardiac surgery patients. Prior to having their therapy escalated to RVAD placement, patients with persistent postoperative PAH should receive a trial treatment of iNO. Further controlled studies are needed to investigate the perioperative applications of iNO in adult high-risk surgery patients.

CARDIOTHORACIC TRANSPLANTATION

Clinical trials and experience suggest a role for iNO in the treatment of established ischemic reperfusion (IR) injury subsequent to lung transplantation and of persistent PAH subsequent to lung or heart transplantation. Prompt intervention with iNO therapy may ameliorate early allograft failure [Date 1996].

Pulmonary Transplantation

Acute IR injury, a potentially fatal complication associated with early allograft failure, is characterized by severe PAH, hypoxemia, systemic hypotension, and lung edema and occurs within 24 to 48 hours posttransplantation [Adatia 1994, Macdonald 1995, Date 1996]. Data from several small retrospective studies have shown that iNO improves hemodynamic parameters and oxygenation in patients with established IR injury [Adatia 1994, Macdonald 1995, Date 1996].

Date and colleagues showed that the initiation of iNO therapy (20-60 ppm) in a group of 15 patients immediately after diagnosis of allograft failure and continued for an average of 84 hours resulted in sustained improvement in oxygenation and decreased PAP [Date 1996]. Significantly, iNO therapy appeared to shorten the duration of mechanical ventilation and to reduce the incidence of airway complications.

Similarly, results from a study of 5 patients by Adatia and colleagues showed that iNO treatment lowered PAP and PVR and improved intrapulmonary shunt fraction after lung transplantation [Adatia 1994]. Observing that the therapeutic dosage level "remains controversial," the investigators commented, "Lower doses may optimize ventilation/perfusion relationships whereas higher doses gain maximal pulmonary vasodilation." However, because prolonged high-dose (80 ppm) iNO treatment may cause methemoglobinemia, weaning to the lowest possible therapeutic dose as soon as possible is advisable. Doses as low as 10 ppm and 20 ppm were sufficient to reverse respiratory failure and shock in 2 patients with severe acute IR injury following lung transplantation, as described in the case report [Macdonald 1995].

Although iNO is effective in treating established IR injury, the reports of 3 studies indicated that it does not appear to prevent IR injury when administered at doses of 20 ppm within 10 minutes posttransplantation or during organ perfusion [Ardehali 2001b, Cornfield 2003, Meade 2003].

In summary, the use of iNO to manage IR injury posttransplantation is intriguing and warrants further study in controlled trials.

Cardiac Transplantation

Data suggest that iNO therapy is a useful adjunct in the management of patients with RV dysfunction following heart

Table 2. Agents for the Treatment of Pulmonary Vasoconstriction*

	Pulmonary Vasodilator	Systemic Vasodilator
Oxygen	+	∅
Inhaled nitric oxide	+++	∅
Nitroprusside	+++	+++
Nitroglycerin	++	++
Amrinone/milrinone (PDE-3 inhibitors)	++	++
Prostaglandin E_1	++	+
Adenosine	++	+
Sildenafil (PDE-5 inhibitor)	+++	+++
Aerosolized prostacyclin (iloprost)	+++	∅

*PDE indicates phosphodiesterase.

transplantation. Three studies documented the efficacy of iNO at various doses in the posttransplantation management of patients with PAH [Kieler-Jensen 1995, Auler 1996, Ardehali 2001a].

In a nonrandomized study by Ardehali et al, iNO treatment (20 ppm) reduced PAP, PVR, and RVSWI without affecting systemic hemodynamics in 16 consecutive heart transplant recipients [Ardehali 2001a]. Notably, the 30-day survival rate in the iNO-treated group was 100%, in contrast with 81% in the historical cohort group ($P > .05$).

In summary, although the results of initial clinical studies appear promising, further investigation is needed. Currently, institutional and provider protocols mandate the point at which iNO should enter the treatment course. Typically, trials of other vasodilating agents, including nitroprusside, are required prior to iNO initiation.

COMPARATIVE EFFICACY OF THE PULMONARY VASODILATORS

The major options for the treatment of pulmonary vasoconstriction are listed in Table 2. The intravenous vasodilators (ie, nitroprusside, amrinone/milrinone, adenosine, prostacyclin), although effective, are associated with hypotension, particularly with continuous infusion. For example, the side effects of intravenous prostacyclin therapy may include systemic hypotension and worsened gas exchange [Hoeper 2000]. Oxygen remains a mainstay in the treatment of PAH, particularly when it is augmented with pulmonary vasodilators.

Only 2 inhaled pulmonary vasodilating agents, NO and iloprost, have been used clinically in adults, and of these only iNO has been approved in the United States. A potent and selective pulmonary vasodilator, iNO exerts no systemic side effects, although continuous administration is required because of iNO's short half-life. Aerosolized prostacyclin (iloprost) induces selective and prolonged (1-2 hours) vasodilation but requires up to 12 doses daily for long-term therapy, and its side effects include syncope [Ghofrani 2002, Olschewski 2002a, 2002b].

Interestingly, sildenafil, a phosphodiesterase-5 inhibitor, appears to potentiate the activity of the inhaled pulmonary vasodilators iNO and iloprost in a dose-dependent fashion by slowing the breakdown of cyclic guanosine monophosphate [Ghofrani 2002, Olschewski 2002b]. As was observed in more than 25% of patients in 1 study, discontinuation of iNO has been associated with rebound PAH and/or worsened gas exchange that promptly resolved after reinstitution of iNO treatment [Christenson 2000]. Sildenafil appears to facilitate weaning from iNO treatment by preventing rebound PAH [Lepore 2002].

Preliminary data from comparative studies suggest that the 2 inhaled pulmonary vasodilators, iNO and aerosolized prostacyclin, are roughly equivalent in efficacy. In a crossover study of 8 patients with adult respiratory distress syndrome, iNO and aerosolized prostacyclin demonstrated equivalence in inducing selective pulmonary vasodilation (decreasing PAP) and improving gas exchange (increasing PaO_2) [Zwissler 1996]. Aerosolized prostacyclin also appears to be a potential alternative to iNO for the treatment of IR injury following lung transplantation, as described in an initial case report showing that aerosolized prostacyclin lowered PAP [Fiser 2001]. However, in a crossover study of 35 patients with primary PAH who underwent acute drug testing in the cardiac catheterization laboratory, aerosolized iloprost (14-17 μg) decreased PAP and PVR to a greater degree than iNO (40 ppm), at least in the doses used in this study and with iNO administered first [Hoeper 2000]. Aerosolized prostacyclin was also equivalent to iNO in reducing mPAP, PVR, and the transpulmonary pressure gradient in a comparative study of 10 patients who underwent vasodilator challenge to test their eligibility for heart transplantation [Haraldsson 1998]. In a study of 20 patients, iloprost showed greater efficacy than iNO in lowering PAP, although iNO was administered in relatively low doses in this study [Sablotzki 2003].

Finally, a study of 126 cardiothoracic surgical patients with PAH, refractory hypoxemia, or right heart dysfunction found that aerosolized prostacyclin significantly decreased mPAP without altering mean arterial pressure [De Wet 2004]. The authors calculated the average price of inhaled prostacyclin to be $150 US per day and compared this cost with the potential price of iNO over the same period. They then calculated a savings with the use of inhaled prostacyclin.

An alternative way of describing the costs of a treatment is a cost-effectiveness ratio, which is the difference between the cost of treatment and the cost of placebo divided by the difference in effect between treatment and placebo. As many costs as possible are taken into consideration, including length-of-stay costs, postdischarge costs, and the costs of other interventions that may become unnecessary with an effective treatment. However, any cost-effectiveness analysis will necessarily be heavily influenced by the underlying assumptions, such as the place of administration and the cost of treatment. For instance, a cost-effectiveness analysis of iNO in the treatment of near term newborns with hypoxic respiratory failure found that the relative benefits of iNO changed, depending on whether treatment was assumed to be administered at a tertiary care extracorporeal membrane oxygenation center or at a local hospital [Angus 2003].

Cost of treatment is another assumption that affects cost-effectiveness ratios. For instance, the pricing model of INOmax (NO for inhalation; INO Therapeutics, Clinton, NJ, USA) has changed recently such that hospitals are charged a

usage fee at a rate of $125 per hour for up to 4 days. Use beyond 4 days and up to 30 days is credited back to the institution. This cost has averaged out across institutions to $69.74 per hour in 2004 (INO Therapeutics, personal communication). This type of information will have a direct effect on the utility of iNO compared with its cost in a given situation.

In summary, further studies are needed to clarify the comparative efficacy of these 2 inhaled agents, iNO and iloprost, in pretransplantation screening and posttransplantation treatment of IR injury and PAH. Clinical trials and pharmacoeconomic analyses will both be necessary to directly resolve issues relating to the efficacy and cost-effectiveness of INO in comparison with other agents.

Other promising investigational agents for the treatment of pulmonary vasoconstriction include endothelin receptor antagonists, L-arginine, antiplatelet agents, serotonin inhibitors, statins, and down-regulators of potassium channels.

In summary, compared with other inhaled and intravenous pulmonary vasodilators, iNO is the only agent shown to improve hemodynamics, intrapulmonary shunt pressure, and oxygenation without having an effect on systemic blood pressure. However, clinical studies with other agents, particularly aerosolized prostacyclin, sildenafil, and endothelial receptor antagonists, may define a place for these agents in the near future in the management of adult perioperative patients.

CONCLUSION

Selective for the pulmonary vasculature, iNO therapy provides a safe and effective alternative to intravenous vasodilators for the perioperative management of adult cardiothoracic surgery patients.

Diagnostically, iNO is used routinely to assess vasoreactivity in patients with acute or chronic PAH who seek to qualify for various cardiothoracic procedures, including transplantation, or medical therapy with calcium channel antagonists. In fact, vasoreactivity challenge with iNO is indicated in clinical situations characterized by RV dysfunction, PAH, and hypoxemia.

In the postoperative setting, iNO may improve PAH to the extent that RVAD placement may be averted in some cases. Therefore, iNO treatment should be initiated in patients with persistent RV dysfunction refractory to other agents before therapy is stepped up to RVAD placement. The use of iNO to treat IR injury in the setting of lung transplantation and in heart transplant patients with RV dysfunction appears promising and warrants further evaluation in clinical trials. Finally, issues relating to the efficacy and cost-effectiveness of iNO in comparison with other agents await resolution in clinical trials.

In conclusion, iNO is a useful and possibly RVAD-sparing intraoperative adjunct that has expanded our options for the management of critically ill adult cardiac surgery patients.

REFERENCES

Adatia I, Lillehei C, Arnold JH, et al. 1994. Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. Ann Thorac Surg 57:1311-8.

Addonizio LJ, Gersony WM, Robbins RC, et al. 1987. Elevated pulmonary vascular resistance and cardiac transplantation. Circulation 76:V-52-5.

Angus DC, Clermont G, Watson RS, Linde-Zwirble WT, Clark RH, Roberts MS. 2003. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States. Pediatrics 112:1351-60.

Ardehali A, Hughes K, Sadeghi A, et al. 2001. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. Transplantation 72:638-41.

Ardehali A, Laks H, Levine M, et al. 2001. A prospective trial of inhaled nitric oxide in clinical lung transplantation. Transplantation 72:112-5.

Argenziano M, Choudhri AF, Moazami N, et al. 1998. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg 65:340-5.

Atz AM, Adatia I, Lock JE, Wessel DL. 1999. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. J Am Coll Cardiol 33:813-9.

Auler JO Jr, Carmona MJC, Bocchi EA, et al. 1996. Low doses of inhaled nitric oxide in heart transplant recipients. J Heart Lung Transplant 15:443-50.

Beck JR, Mongero LB, Kroslowitz RM, et al. 1999. Inhaled nitric oxide improves hemodynamics in patients with acute pulmonary hypertension after high-risk cardiac surgery. Perfusion 14:37-42.

Bender KA, Alexander JA, Enos JM, Skimming JW. 1997. Effects of inhaled nitric oxide in patients with hypoxemia and pulmonary hypertension after cardiac surgery. Am J Crit Care 6:127-31.

Bhatia SJ, Kirshenbaum JM, Shemin RJ, et al. 1987. Time course of resolution of pulmonary hypertension and right ventricular remodeling after orthotopic cardiac transplantation. Circulation 76:819-26.

Christenson J, Lavoie A, O'Connor M, Bhorade S, Pohlman A, Hall JB. 2000. The incidence and pathogenesis of cardiopulmonary deterioration after abrupt withdrawal of inhaled nitric oxide. Am J Respir Crit Care Med 161:1443-9.

Cockrill BA, Kacmarek RM, Fifer MA, et al. 2001. Comparison of the effects of nitric oxide, nitroprusside, and nifedipine on hemodynamics and right ventricular contractility in patients with chronic pulmonary hypertension. Chest 119:128-36.

Cornfield DN, Milla CE, Haddad IY, Barbato JE, Park SJ. 2003. Safety of inhaled nitric oxide after lung transplantation. J Heart Lung Transplant 22:903-7.

Costard-Jackle A, Fowler MB. 1992. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol 19:48-54.

Date H, Triantafillou AN, Trulock EP, Pohl MS, Cooper JD, Patterson GA. 1996. Inhaled nitric oxide reduces human lung allograft dysfunction. J Thorac Cardiovasc Surg 111:913-9.

De Wet CJ, Affleck DG, Jacobsohn E, et al. 2004. Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. J Thorac Cardiovasc Surg 127:1058-67.

Dellinger RP, Zimmerman JL, Taylor RW, et al. 1998. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 26:15-23.

Dweik RA, Laskowski D, Abu-Soud HM, et al. 1998. Nitric oxide

synthesis in the lung: regulation by oxygen through a kinetic mechanism. J Clin Invest 101:660-6.

Fiser SM, Cope JT, Kron IL, et al. 2001. Aerosolized prostacyclin (epoprostenol) as an alternative to inhaled nitric oxide for patients with reperfusion injury after lung transplantation. J Thorac Cardiovasc Surg 121:981-2.

Fullerton DA, Jones SD, Jaggers J, Piedalue F, Grover FL, McIntyre RC Jr. 1996. Effective control of pulmonary vascular resistance with inhaled nitric oxide after cardiac operation. J Thorac Cardiovasc Surg 111:753-63.

Gerlach H, Rossaint R, Pappert D, Knorr M, Falke KJ. 1994. Autoinhalation of nitric oxide after endogenous synthesis in nasopharynx. Lancet 343:518-9.

Ghofrani HA, Wiedemann R, Rose F, et al. 2002. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. Ann Intern Med 136:515-22.

Girard C, Lehot J-J, Pannetier J-C, Filley S, Ffrench P, Estanove S. 1992. Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. Anesthesiology 77:880-3.

Haraldsson A, Kieler-Jensen N, Nathorst-Westfelt U, Bergh CH, Ricksten SE. 1998. Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. Chest 114:780-6.

Hart CM. 1999. Nitric oxide in adult lung disease. Chest 115:1407-17.

Hoeper MM, Olschewski H, Ghofrani HA, et al. 2000. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension: German PPH Study Group. J Am Coll Cardiol 35:176-82.

Kieler-Jensen N, Lundin S, Ricksten S-E. 1995. Vasodilator therapy after heart transplantation: effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E_1, and sodium nitroprusside. J Heart Lung Transplant 14:436-43.

Lepore JJ, Maroo A, Pereira NL, et al. 2002. Effect of sildenafil on the acute pulmonary vasodilator response to inhaled nitric oxide in adults with primary pulmonary hypertension. Am J Cardiol 90:677-80.

Loh E, Stamler JS, Hare JM, Loscalzo J, Colucci WS. 1994. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. Circulation 90:2780-5.

Macdonald P, Mundy J, Rogers P, et al. 1995. Successful treatment of life-threatening acute reperfusion injury after lung transplantation with inhaled nitric oxide. J Thorac Cardiovasc Surg 110:861-3.

Maxey TS, Smith CD, Kern JA, et al. 2002. Beneficial effects of inhaled nitric oxide in adult cardiac surgical patients. Ann Thorac Surg 73:529-33.

Meade MO, Granton JT, Matte-Martyn A, et al. 2003. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med 167:1483-9.

Olschewski H. 2002. Inhaled iloprost for treatment of pulmonary arterial hypertension. Adv Pulm Hypertens 1:16-21.

Olschewski H, Simonneau G, Galie N, et al. 2002. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 347:322-9.

Ricciardi MJ, Knight BP, Martinez FJ, Rubenfire M. 1998. Inhaled nitric oxide in primary pulmonary hypertension: a safe and effective agent for predicting response to nifedipine. J Am Coll Cardiol 32:1068-73.

Rich S, Kaufmann E, Levy PS. 1992. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 327:76-81.

Roberts JD Jr, Fineman JR, Morin FC 3rd, et al. 1997. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. N Engl J Med 336:605-10.

Rossaint R, Gerlach H, Schmidt-Ruhnke H, et al. 1995. Efficacy of inhaled nitric oxide in patients with severe ARDS. Chest 107:1107-15.

Sablotzki A, Czeslick E, Gruenig E, et al. 2003. First experiences with the stable prostacyclin analog iloprost in the evaluation of heart transplant candidates with increased pulmonary vascular resistance. J Thorac Cardiovasc Surg 125:960-2.

Schmid ER, Burki C, Engel MHC, Schmidlin D, Tornic M, Seifert B. 1999. Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. Anesth Analg 89:1108-15.

Semigran MJ, Cockrill BA, Kacmarek R, et al. 1994. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 24:982-8.

Zapol WM, Rimar S, Gillis N, Marletta M, Bosken CH. 1994. Nitric oxide and the lung. Am J Respir Crit Care Med 149:1375-80.

Zwissler B, Kemming G, Habler O, et al. 1996. Inhaled prostacyclin (PGI_2) versus inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med 154:1671-7.