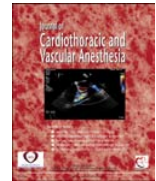




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Review Article

Inhaled Nitric Oxide (iNO) and Inhaled Epoprostenol (iPGI₂) Use in Cardiothoracic Surgical Patients: Is there Sufficient Evidence for Evidence-Based Recommendations?

Vidya Rao, MD^{*}, Kamrouz Ghadimi, MD[†],
Worasak Keeyapaj, MD^{*}, Cody A. Parsons, PharmD[‡],
Albert T. Cheung, MD^{*,1}

^{*}Department of Anesthesiology, Stanford University, Stanford, CA

[†]Department of Anesthesiology, Duke University Medical Center, Durham, NC

[‡]Stanford Health Care, Stanford, CA

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INHALED NITRIC OXIDE (iNO) and inhaled epoprostenol or prostacyclin I₂ (iPGI₂) are used widely to treat pulmonary hypertension, right ventricular failure, and hypoxemia in cardiac surgical patients.¹⁻⁵ The widespread use of inhaled pulmonary vasodilators in this patient population can be justified by the well-established and often immediately observable physiologic actions of these agents, the high-stakes nature of the operations that these agents are being used for, the seriousness of the conditions they are used to treat, and the lack of therapeutic alternatives with proven efficacy. These factors have contributed to institution- and physician-specific practice patterns on the use and choice of iNO or iPGI₂ that have become well established over time. However, economic pressures to contain increasing pharmacy costs are forcing hospitals and physicians to scrutinize the routine administration of iNO and iPGI₂, because these agents are expensive and the published evidence supporting the clinical efficacy of these agents on patient outcomes remains controversial. Furthermore, the cost differential between using iNO and different formulations of

iPGI₂ can be substantial (Table 1). In the cost-benefit analysis, it is important to determine if these agents provide clinical efficacy, whether iNO offers advantages to justify its added cost, whether these 2 agents are interchangeable, or whether less expensive substitutes are clinically equivalent. Finally, there are potential adverse effects associated with the use of these selective pulmonary vasodilators that include precipitating pulmonary edema, contributing to surgical bleeding, contributing to systemic hypotension, causing methemoglobinemia, as well as delivery system malfunction causing acute hypoxemia or right heart failure.

The purpose of this review is to address the cost-benefit and risk-benefit considerations on the clinical use of iNO and iPGI₂ in cardiac surgical patients based on the available evidence in the medical literature. Establishing and implementing clinical guidelines on the appropriate clinical indications for iNO and iPGI₂, contraindications to the administration of iNO or iPGI₂, the comparative advantages of iNO versus iPGI₂, and the use of less expensive formulations of iPGI₂ have already demonstrated that they can have a marked impact on clinical practices and pharmacy expenses. Identifying the knowledge gaps that exist in the medical literature on the clinical efficacy of iNO and iPGI₂ in cardiac surgical patients also may serve to guide future clinical investigations.

¹Address reprint requests to Albert T. Cheung, MD, Professor, Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, 300 Pasteur Dr., H3578, Stanford, CA 94305.

E-mail address: ATCheung@stanford.edu (A.T. Cheung).

Clinical Actions of Inhaled Pulmonary Vasodilator Therapy

The pharmacologic actions of iNO and iPGI₂ as selective pulmonary artery vasodilators to decrease pulmonary artery pressure, decrease pulmonary vascular resistance, and increase the arterial partial pressure of oxygen are well established.^{3,5} Major pathways that affect pulmonary vascular tone include nitric oxide-induced vasodilation, prostaglandin-induced vasodilation, and endothelin-induced vasoconstriction. Nitric oxide dilates the pulmonary vasculature by augmenting intracellular cyclic guanosine monophosphate, while epoprostenol exerts its effect by increasing cyclic adenosine monophosphate levels. These inhaled medications function selectively on the pulmonary vasculature, thereby avoiding adverse systemic hemodynamic effects and offering a distinct advantage over intravenously administered vasodilators, such as nitroglycerin, sodium nitroprusside, or the calcium channel antagonists. The pharmacologic actions of selective inhaled pulmonary vasodilators provide compelling reasons for the treatment of hypoxemia, right ventricular dysfunction, pulmonary hypertension, and primary graft dysfunction in cardiothoracic surgery patients. During cardiothoracic operations, in particular, heart transplantation, lung transplantation, or left ventricular assist device (LVAD) implantation, temporary alterations in pulmonary vasomotor tone may contribute to right ventricular dysfunction or hypoxemia. In these clinical situations, the administration of iNO or iPGI₂ improves right ventricular function and cardiac output by promoting pulmonary vasodilation while simultaneously improving ventilation-to-perfusion matching. iNO is delivered as a gas and iPGI₂ is delivered as an aerosolized solution. Both agents are administered into the inhalation limb of the breathing circuit in mechanically ventilated patients or in combination with supplemental oxygen in spontaneously breathing patients. This mode of administration results in a fast onset of action on the order of 5 to 10 seconds for iNO and 30 to 60 seconds for iPGI₂. Administration by the inhaled route also results in a short half-life upon discontinuation on the order of 10 to 20 seconds for iNO and 1 to 2 minutes for iPGI₂ that permits rapid titration of these drugs. Although endothelin antagonists, such as bosentan, are used routinely for the treatment of pulmonary hypertension, these agents are not normally considered appropriate for acute therapy in the perioperative period because

they require oral administration. The gastrointestinal absorption of orally administered drugs may be unpredictable in surgical patients on high-dose inotropic support. The delay in bioavailability of orally administered agents also may make it difficult to titrate drugs to achieve a desired physiologic effect.

The clinical experience with the use of selective inhaled pulmonary vasodilator therapy is consistent with its pharmacologic actions, and immediate improvements in physiologic parameters such as the cardiac output, pulmonary artery pressure, and arterial oxygenation are typically observed. Despite these immediately observable actions, the medical evidence to support the efficacy of inhaled pulmonary vasodilators based on outcomes from published clinical trials and meta-analysis has not been substantiated.³⁻⁵ The majority of clinical trial data focused on testing the efficacy of iNO and less clinical outcome data is available for iPGI₂. For example, a meta-analysis from the Cochrane Collaborative failed to show a reduction in mortality for iNO used to treat adult and pediatric acute respiratory distress syndrome or for the management of postoperative pulmonary hypertension in infants and children with congenital heart disease.^{1-3,6,7} Randomized controlled studies have failed to demonstrate a benefit of iNO treatment for the prevention of right ventricular failure in patients undergoing left ventricular assist device implantation and the prevention of graft dysfunction by early administration of iNO during lung transplantation.^{8,9}

Clinical Efficacy of iNO Versus iPGI₂ in Cardiac Surgical Patients

There are 2 prospective randomized-controlled trials comparing iNO and iPGI₂¹⁰⁻¹¹; 1 retrospective observational cohort trial comparing iNO and iPGI₂¹¹ and 1 randomized trial comparing iPGI₂ to placebo in cardiac surgical patients.¹³ Other published small-scale single-center investigations, case series, and case reports, indicate that both iNO and iPGI₂ decrease the pulmonary artery pressure, improve right ventricular function in the presence of elevated pulmonary artery pressures, and increase the cardiac output in cardiac surgical patients without affecting the systemic arterial pressure (Table 2).^{1,14,15} Several small comparative investigations, retrospective studies, and randomized controlled studies also have shown clinical equivalence in the ability of iNO and

Table 1
Cost Comparison of Inhaled Pulmonary Vasodilators

Brand	Generic	Dosing (IBW)	Cost per hour (70 kg IBW)	pH
Flolan (GSK)	Glycine-based epoprostenol sodium	0.01-0.05 µg/kg/min	\$2.01-\$10.05*	10.2-10.8
Epoprostenol sodium (TEVA)	Glycine-based epoprostenol sodium	0.01-0.05 µg/kg/min	\$1.71-\$8.55*	10.2-10.8
Veletri (Actelion)	Arginine-based epoprostenol sodium	0.01-0.05 µg/kg/min	\$1.30-\$6.52*	11-13
INOMax (Mallinckrodt)	Nitric oxide	10-80 ppm	\$220.46†	NA

Abbreviations: cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; IBW, ideal body weight; NA, not-applicable; ppm, parts per million.

*Based off October 2017 average wholesale drug price for 1.5 mg vial (reconstituted).

†Based off January 2017 non-contracted price.

Table 2
Studies Comparing iNO to iPGI₂ in Cardiac Surgical Patients with Pulmonary Hypertension

Study	Group	n	ΔPAP	ΔPVR	ΔCI	ΔCO	ΔRVEF	ΔCVP	ΔSVO ₂
Fattouch	iNO	19	-13	-150	+1.3	-	+10	-	-
2006 ^a	iPGI ₂	21	-11	-180	+1.2	-	+11	-	-
Winterhalter	iNO	23	-10	-195	-	+1.0	-	0	+3
2008 ^b	iPGI ₂	23	-8	-247	-	+2.7	-	-1	+2
Khan	iNO	14	-6	-	+0.5	-	-	-3	+8
2009 ^c	iPGI ₂	11	-9	-	+0.4	-	-	-3	+5

*Fattouch K, et al. J Cardiovasc Med 2006;7:119. Values are differences compared with control group (n = 18) 1 hour prior to arrival to the intensive care unit after mitral valve operations for mitral stenosis.

†Winterhalter M, et al. J Cardiothorac Vasc Anesth 2008;22:406. Values are change from preoperative baseline before treatment in cardiac surgical patients with pulmonary hypertension upon arrival in the intensive care unit after operation.

‡Khan TA, et al. J Thorac Cardiovasc Surg 2009;138:1417. Values are change in response to treatment after cardiopulmonary bypass in a crossover study of patients undergoing heart (n = 6) or lung (n = 19) transplantation.

Abbreviations: ΔCI, change in cardiac index in L/min/m² body surface area; ΔCO, change in cardiac output in L/min; ΔCVP, change in central venous pressure in mmHg; ΔPAP, change in mean pulmonary artery pressure in mmHg; ΔPVR = change in pulmonary vascular resistance in dynes•sec•cm⁻⁵; ΔRVEF, change in right ventricular area ejection fraction in %; ΔSVO₂, change in mixed venous oxygen saturation in %.

iPGI₂ to decrease pulmonary artery pressures when administered to cardiac surgical patients (Table 2).^{2,10-12}

The decrease in pulmonary artery pressures caused by iNO and iPGI₂ has been demonstrated to be associated with improvements in right ventricular function and cardiac output. In a randomized controlled trial, both iNO and iPGI₂ produced statistically significant improvements in right ventricular ejection fraction measured by transesophageal echocardiography and the improvement in right ventricular function was associated with increases in cardiac output.¹⁰ In a placebo-controlled trial, iPGI₂ improved right ventricular stroke work index along with right ventricular fractional area change measured by transesophageal echocardiography.¹³ The combination of iPGI₂ with inhaled milrinone also has been demonstrated to normalize the transduced right ventricular pressure waveform among cardiac surgical patients with pulmonary hypertension prior to the initiation of cardiopulmonary bypass (CPB).¹⁶ The improvement in cardiac output in response to inhaled vasodilators have been demonstrated in studies of iNO alone,^{15,17} and in 2 studies comparing iNO and iPGI₂ in patients with pulmonary hypertension undergoing mitral valve surgery.^{10,18} Only 1 published study failed to detect an increase in cardiac index in response to iPGI₂.¹³

Despite the hemodynamic improvements produced by iNO and iPGI₂ in cardiac surgical patients, the existing evidence fails to provide long-term morbidity or mortality data to support a benefit of these agents on clinical outcomes. While isolated reports also have suggested that the administration of inhaled pulmonary vasodilators improved the ability to separate from cardiopulmonary bypass during cardiac operations, decreased the need for inotropic or vasopressor support, decreased the duration of postoperative mechanical ventilation, and decreased intensive care unit (ICU) length of stay,^{10,16-18} these observed benefits have not been reproduced in other studies.¹²

In summary, existing studies support the effectiveness of both iNO and iPGI₂ to decrease pulmonary artery pressures, decrease pulmonary vascular resistance, improve right ventricular performance, increase the cardiac index, or improve the

mixed venous oxygen saturation, but fail to demonstrate any clinically important differences between iNO or iPGI₂ among cardiac surgical patients (Table 2). Furthermore, in comparisons between iNO and iPGI₂, there was no difference in the duration of therapy, duration of mechanical ventilator support, ICU length of stay, hospital length of stay, or in-hospital mortality when these endpoints were examined. The existing studies in cardiac surgical patients demonstrate consistently that both iNO and iPGI₂ act selectively on the pulmonary vasculature without associated effects on the systemic arterial pressure. Despite the potential of iPGI₂ to inhibit platelet function if it is systemically absorbed, there is insufficient evidence to indicate that iPGI₂ increased the risk of hemorrhage or increased blood loss in cardiac surgical patients. Although the sample sizes of the published studies were limited, the existing medical literature indicates that the pharmacologic actions and therapeutic effects of iNO and iPGI₂ in a mixed population of cardiac surgical patients were equivalent. It remains to be proven whether the physiologic actions of iNO or iPGI₂ improves mortality or clinical outcomes when administered as a therapeutic agent to a mixed population of cardiac surgical patients.

Heart Transplantation and Lung Transplantation

The pharmacologic actions of iNO and iPGI₂ predict that they could be effective for managing perioperative pulmonary hypertension, right ventricular dysfunction, and hypoxemia in patients undergoing heart or lung transplantation. Experimental and small-scale clinical trials also have suggested that iNO may attenuate ischemia-reperfusion injury in lung transplantation.¹⁹⁻²²

In clinical trials, there is little evidence to support a long-term benefit of iNO in patients undergoing lung transplantation. Randomized, double-blinded studies have failed to show benefits of iNO for preventing or treating ischemia-reperfusion injury in lung transplantation, regardless of the timing of initiating iNO treatment in the perioperative period. iNO

administration failed to reduce extravascular lung water, affect neutrophil sequestration, improve hemodynamics, improve the PaO₂/FiO₂ ratio, decrease the incidence of graft dysfunction, improve renal function, decrease ICU length of stay, or modify operative mortality.^{9,23,24}

Studies on the use of iPGI₂ in lung transplantation patients are limited to isolated case reports, small case series, and investigations of cardiothoracic surgical patients in which lung transplantation was a subset.^{14,25,26} Based on these reports, iPGI₂ was effective for decreasing the mean pulmonary artery pressure, improving the PaO₂/FiO₂ ratio, and improving right ventricular function in lung transplant recipients.

A single prospective, randomized crossover trial has been performed to compare iNO with iPGI₂ in heart and lung transplant patients.¹¹ In this trial, 17 patients undergoing single-lung transplantation, 2 patients undergoing double-lung transplantation, and 6 patients undergoing heart transplantation were randomized to receive either iNO or iPGI₂. After 6 hours of administration, the pulmonary vasodilator was discontinued and permitted to “wash out” before switching to the crossover agent. Both iNO and iPGI₂ produced significant reductions in the pulmonary artery and central venous pressures. The decrease in pulmonary artery and central venous pressures was associated with improvements in the cardiac index and mixed venous oxygen saturation, but surprisingly had little effect on the PaO₂/FiO₂ ratio. There were no significant differences observed between the crossover periods and no effects of either agent on systemic arterial pressure, suggesting that the pharmacologic actions of iNO and iPGI₂ were equivalent.

In heart transplantation, inhaled pulmonary vasodilators also have been used clinically to assess the reversibility of pulmonary hypertension for evaluating transplant eligibility. A prospective comparative study of iNO and iPGI₂ in 20 heart transplant candidates found that both medications reduced mean pulmonary artery pressure and pulmonary vascular resistance to a similar degree, but only iPGI₂ increased the cardiac output.²⁷ Another study of 6 patients undergoing evaluation for heart transplantation demonstrated that iPGI₂ was superior to intravenous sodium nitroprusside for reducing the pulmonary artery pressure.²⁸

Studies performed on the perioperative use of iNO in heart transplant recipients have shown that it reduces pulmonary artery pressures and improves hemodynamic parameters, but did not affect long-term survival.²⁹ In a study comparing iNO to intravenous prostacyclin and sodium nitroprusside, intravenous prostacyclin produced the greatest improvements in cardiac output, pulmonary vascular resistance, right ventricular end diastolic volume, stroke volume, and central venous pressure, but also caused the greatest decrease in systemic vascular resistance.³⁰ In contrast, iNO produced similar hemodynamic improvements, and decreased pulmonary vascular resistance without significant effects on arterial pressure. In a prospective study of 16 heart transplant patients started on iNO therapy before separation from cardiopulmonary bypass, planned interruption of iNO therapy at 6 and 12 hours later resulted in increases in the mean pulmonary artery pressure, pulmonary vascular resistance, and right ventricular stroke

work index without changes in systemic hemodynamics.³¹ When the iNO treatment group was compared with matched historical controls, no statistically significant 30-day survival benefit could be detected.

There is limited published data comparing iPGI₂ with iNO in heart transplant recipients. In a small, prospective, randomized crossover trial involving a mixed group of lung and heart transplant recipients, the relative efficacies of iNO and iPGI₂ for ameliorating pulmonary hypertension was equivalent.¹¹ In trials that included heart transplant recipients as part of a larger study population, both iPGI₂ and iNO had similar actions on pulmonary artery pressure without significant adverse effects.^{12,14} Evidence to support a long-term benefit of iNO or iPGI₂ on survival in heart transplantation is lacking and remains an area for further investigation.

Left Ventricular Assist Device Implantation

Right ventricular failure is a problematic complication of left ventricular assist device (LVAD) implantation for patients with end-stage heart failure. Advanced heart failure is often associated with pulmonary hypertension and increased pulmonary vascular resistance that increases right ventricular afterload and impairs left ventricular filling after LVAD implantation. The pharmacologic and hemodynamic actions of iNO and iPGI₂ suggest that these agents have the potential to decrease the incidence of right ventricular failure and avoid the need for biventricular mechanical assist in patients undergoing LVAD implantation. Initial studies demonstrated that both iNO and iPGI₂ decreased pulmonary artery pressures, improved right ventricular function, and increased LVAD flows in patients undergoing LVAD implantation.³²⁻³⁴ Based on this early experience, a randomized, double-blind, multicenter, placebo-controlled trial involving 150 patients undergoing LVAD implantation was conducted to investigate the effectiveness of iNO for the treatment of right ventricular dysfunction in this setting.⁸ In the study, iNO or placebo was administered for 48 hours after separation from cardiopulmonary bypass. Although the incidence of the primary endpoint, right ventricular dysfunction, was less in the group that received iNO, the difference was not statistically significant (9.6% v 15.6%, $p = 0.330$). Secondary endpoints demonstrated favorable trends, but also did not achieve statistical significance (Table 3). Fewer patients in the group that received iNO required right ventricular assist devices (5.6% v 10.0%, $p = 0.468$) and the duration of mechanical ventilator support was less in the group that received iNO (2 days versus 3 days, $p = 0.077$). Hospital length of stay, intensive care length of stay, and 28-day mortality was not different between groups.

Cost-Benefit Considerations

Proprietary pricing contract agreements prohibit disclosure of the precise cost for a day of therapy for iNO or iPGI₂ for a specific hospital and both the relative and absolute costs of therapy may vary among different institutions. In general, the

Table 3
Randomized Controlled-Trial of iNO Versus Placebo for 48 hours after Left Ventricular Device Implantation: Outcomes in the Intent-to-Treat Population*

Outcome measure	iNO	Placebo	p Value [†]
Sample size	73	77	
Right ventricular dysfunction (%) [‡]	7/73 (9.6)	12/77 (15.6)	0.330
Requirement for RVAD support	4/71 (5.6)	7/70 (10.0)	0.468
28-Day mortality	8/71 (11.3)	8/70 (11.4)	0.924

Abbreviations: iNO, inhaled nitric oxide; RVAD, right ventricular assist device.

*From Potapov E, et al. *J Heart Lung Transplant* 2011;30:870–88.

[†]p Values from the per-protocol analysis yielded similar, nonsignificant differences.

[‡]Right ventricular dysfunction defined as death, inability to wean from cardiopulmonary bypass, or any 2 of the following: 1) LVAD flow per body surface area ≤ 2.0 L/min/m²; 2) high inotropic and vasopressor requirements (see Ref 8); 3) MAP ≤ 55 mmHg; and 4) CVP ≥ 16 mmHg, or SVO₂ $\leq 55\%$.

costs associated with the administration of Flolan, a brand-specific glycine-based epoprostenol, consists of the price of a 1.5 mg vial of the drug together with its diluent. The dosing of Flolan is weight-based and once prepared, the drug expires within 8 hours. Veletri, another brand-specific epoprostenol that is arginine-based, is approximately 35% less expensive than Flolan, largely because it can be diluted with sterile water for administration and does not have to be reformulated every 8 hours. The commercial delivery system (INOMax) for administering iNO generates costs based on per hour of use (Table 1). At the Stanford University Medical Center and Duke University Medical Center, which have active heart transplant, lung transplant, and mechanical circulatory support programs, both iNO and iPGI₂ are available for use in cardiac surgical patients. The annual estimated pharmacy expenditure for iPGI₂ ranges from \$200,000 to \$1,000,000 per year and the annual estimated expense for iNO is in the range of 3 million to 8 million dollars per year, making both of these agents important line items in the hospital budget.

Risk-Benefit Considerations

The decrease in pulmonary vascular resistance in response to iNO and iPGI₂ administration to patients with left ventricular dysfunction is associated with an increase in the pulmonary artery wedge pressure.³⁵ This increased left ventricular filling pressures in response to iNO administration in patients with severe heart failure may cause pulmonary edema in susceptible patients.³⁶ Severe pulmonary edema and even death have been reported in response to both iNO and prostacyclin infusion in patients with pulmonary veno-occlusive diseases, CREST syndrome, scimitar syndrome, and scleroderma.^{37–41} The known physiologic action of inhaled pulmonary vasodilators combined with these reports suggest that they should be administered with caution in patients with pulmonary arterial hypertension caused by veno-occlusive diseases or left heart failure, but it has not been determined if this potential adverse action affects outcomes during routine use in cardiac surgical patients. Other reported adverse effects include the potential of iNO to cause methemoglobinemia,^{42,43} the association

between iNO and renal failure,^{6,44} the potential of iPGI₂ to increase surgical blood loss due to its platelet inhibitory action,³² but the clinical importance of these potential side effects have not been established definitively. Another important consideration in the clinical use of iNO and iPGI₂ is the risk of acute hypoxemia, acute increase in pulmonary artery pressure, and acute right ventricular failure if these agents are abruptly discontinued.

Conclusion

Existing studies support the potentially beneficial pharmacologic actions and physiologic effects of both iNO and iPGI₂ on pulmonary artery pressure, right ventricular function, cardiac output, and pulmonary gas exchange in cardiac surgical patients. A recently published meta-analysis also supported these physiologic actions of iPGI₂.⁴⁵ There were limited studies that directly compared iNO with iPGI₂, but the existing evidence indicates that the physiologic actions of these 2 agents were equivalent. Existing evidence also supports the overall safety of iNO and PGI₂ with the exception of use in patients with pulmonary hypertension as a consequence of left heart failure or pulmonary venous obstruction. The promising therapeutic potential of inhaled pulmonary vasodilators together with a record of safety provides a compelling reason to justify the continued use of iNO and iPGI₂ in high risk procedures despite the absence of definitive evidence to support a benefit on long-term outcomes or survival among cardiac surgical patients, heart transplant patients, lung transplant patients, and patients undergoing LVAD implantation while clinical investigations continue. Presently, a prospective, randomized, double-blinded clinical trial is in progress to determine if iNO (INOMAX) or iPGI₂ (Veletri) will have similar efficacy in adult patients undergoing heart transplantation, lung transplantation, or LVAD implantation (Inhaled Pulmonary Vasodilator Therapy in LVAD Implantation, Heart Transplantation, and Lung Transplantation, NCT03081052, ClinicalTrials.gov). The primary outcomes being examined in the trial are the incidence of primary graft dysfunction after lung transplantation, the incidence of moderate or severe right ventricular dysfunction after LVAD implantation, and the incidence of severe right ventricular dysfunction after heart transplantation. At present, a major cost differential exists between iNO and different formulations of iPGI₂. Further clinical investigation is warranted to justify the routine use of iNO as a first-line agent in cardiothoracic surgical patients. The major gaps in the present evidence base regarding the use of iNO and iPGI₂ that need to be determined are whether iNO and iPGI₂ are clinically equivalent and whether the routine use of iNO or iPGI₂ has the potential to improve outcomes and decrease the incidence of complications in patients undergoing cardiac operations, lung transplantation, heart transplantation, or LVAD implantation.

References

- 1 Kim JS, McSweeney J, Lee J, et al. Pediatric Cardiac Intensive Care Society 2014 consensus statement: Pharmacotherapies in cardiac critical care pulmonary hypertension. *Pediatr Crit Care Med* 2016;17:S89–100.
- 2 Claesson J, Freundlich M, Gunnarsson I, et al. Scandinavian clinical practice guideline on fluid and drug therapy in adults with acute respiratory distress syndrome. *Acta Anaesthesiol Scand* 2016;60:697–709.

- 3 Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society. *Circulation* 2015;132:2037–99.
- 4 Benedetto M, Roman R, Baca G, et al. Inhaled nitric oxide in cardiac surgery: Evidence or tradition? *Nitric Oxide* 2015;49:67–79.
- 5 Augoustides JG, Ochroch EA. Pro: Inhaled prostaglandin as a pulmonary vasodilator instead of nitric oxide. *J Cardiothorac Vasc Anesth* 2005;19:400–2.
- 6 Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults (Review). *Cochrane Database of Systematic Reviews* 2016;6:CD002787.
- 7 Bizzarro M, Gross I, Barbosa FT. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease (Review). *Cochrane Database of Systematic Reviews* 2014;7:CD005055.
- 8 Potapov E, Meyer D, Swaminathan M, et al. Inhaled nitric oxide after left ventricular assist device implantation: A prospective, randomized, double-blind, multicenter, placebo-controlled trial. *J Heart Lung Transplant* 2011;30:870–8.
- 9 Meade MO, Granton JT, Matte-Martyn, et al. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. *Am J Respir Crit Care Med* 2003;167:1483–9.
- 10 Fattouch K, Sbraga F, Sampognaro R, et al. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: A randomized, prospective, double-blind study. *J Cardiovasc Med* 2006;7:119–23.
- 11 Khan TA, Schnickel G, Ross D, et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg* 2009;138:1417–24.
- 12 McGinn K, Reichert M. A comparison of inhaled nitric oxide versus inhaled epoprostenol for acute pulmonary hypertension following cardiac surgery. *Ann Pharmacother* 2016;50:22–6.
- 13 Hache M, Denault A, Belisle S, et al. Inhaled epoprostenol (prostacyclin) and pulmonary hypertension before cardiac surgery. *J Thorac Cardiovasc Surg* 2003;125:642–9.
- 14 De Wet CJ, Affleck DG, Jacobsohn E, et al. 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* 2004;127:1058–67.
- 15 Winterhalter M, Simon A, Fischer S, et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: A prospective randomized trial. *J Cardiothorac Vasc Anesth* 2008;22:406–13.
- 16 Laflamme M, Perrault LP, Carrier M, et al. Preliminary experience with combined inhaled milrinone and prostacyclin in cardiac surgical patients with pulmonary hypertension. *J Cardiothorac Vasc Anesth* 2015;29:38–45.
- 17 Fernandes JL, Sampaio RO, Brandao CM, et al. Comparison of inhaled nitric oxide versus oxygen on hemodynamics in patients with mitral stenosis and severe pulmonary hypertension after mitral valve surgery. *Am J Cardiol* 2011;107:1040–5.
- 18 Fattouch K, Sbraga F, Bianco G, et al. Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. *J Card Surg* 2005;20:171–6.
- 19 Adatia I, Perry S, Landzberg M, et al. Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation. *J Am Coll Cardiol* 1995;25:1656–64.
- 20 Date H, Triantafyllou AN, Trulock EP, et al. Inhaled nitric oxide reduces human lung allograft dysfunction. *J Thorac Cardiovasc Surg* 1996;111:913–9.
- 21 Moreno I, Vicente R, Mir A, et al. Effects of inhaled nitric oxide on primary graft dysfunction in lung transplantation. *Transplant Proc* 2009;41:2210–2.
- 22 Thabut G, Brugiere O, Leseche G, et al. Preventive effect of inhaled nitric oxide and pentoxifylline on ischemia/reperfusion injury after lung transplantation. *Transplantation* 2001;71:1295–300.
- 23 Perrin G, Roch A, Michelet P, et al. Inhaled nitric oxide does not prevent pulmonary edema after lung transplantation measured by lung water content: A randomized clinical study. *Chest* 2006;129:1024–30.
- 24 Botha P, Jeyakanthan M, Rao JN, et al. Inhaled nitric oxide for modulation of ischemia-reperfusion injury in lung transplantation. *J Heart Lung Transplant* 2007;26:1199–205.
- 25 Fiser SM, Cope JT, Kron IL, et al. Aerosolized prostacyclin (epoprostenol) as an alternative to inhaled nitric oxide for patients with reperfusion injury after lung transplantation. *J Thorac Cardiovasc Surg* 2001;121:981–2.
- 26 Della Rocca G, Coccia C, Costa MG, et al. Inhaled aerosolized prostacyclin and pulmonary hypertension during anesthesia for lung transplantation. *Transplant Proc* 2001;33:1634–6.
- 27 Haraldsson A, Kieler-Jensen N, Nathorst-Westfelt U, et al. Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. *Chest* 1998;114:780–6.
- 28 Weston MW, Isaac BF, Crain C. The use of inhaled prostacyclin in nitroprusside-resistant pulmonary artery hypertension. *J Heart Lung Transplant* 2001;20:1340–4.
- 29 Auler Junior JO, Carmona MJ, Bocchi EA, et al. Low doses of inhaled nitric oxide in heart transplant recipients. *J Heart Lung Transplant* 1996;15:443–50.
- 30 Kieler-Jensen N, Lundin S, Ricksten SE. Vasodilator therapy after heart transplantation: Effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. *J Heart Lung Transplant* 1995;14:436–43.
- 31 Ardehali A, Hughes K, Sadeghi A, et al. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. *Transplantation* 2001;72:638–41.
- 32 Groves DS, Blum FE, Huffmyer JL, et al. Effects of inhaled epoprostenol therapy on pulmonary artery pressure and blood loss during LVAD placement. *J Cardiothorac Vasc Anesth* 2014;28:652–60.
- 33 Antoniu T, Prokakis C, Athanasopoulos G, et al. Inhaled nitric oxide plus iloprost in the setting of post-left assist device right heart dysfunction. *Ann Thorac Surg* 2012;94:792–9.
- 34 Argenziano M, Choudhri AF, Moazami N, et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. *Ann Thorac Surg* 1998;65:340–5.
- 35 Loh E, Stamler JS, Hare J, et al. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. *Circulation* 1994;90:2780–5.
- 36 Bocchi EA, Bacal F, Auler Jr JOC, et al. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. *Am J Cardiol* 1994;74:70–2.
- 37 Baird SJ, Havalad V, Aponte-Patel L, et al. Nitric oxide-associated pulmonary edema in children with pulmonary venous hypertension. *Pediatr Cardiol* 2013;34:817–25.
- 38 Palmer SM, Robinson LJ, Wang A, et al. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. *Chest* 1998;113:237–40.
- 39 Preston IR, Klinger JR, Houtchens J, et al. Pulmonary edema caused by inhaled nitric oxide therapy in two patients with pulmonary hypertension associated with CREST syndrome. *Chest* 2002;121:656–9.
- 40 von Schakenburg C, Peuster M, Norozi K, et al. Acute pulmonary edema caused by epoprostenol infusion in a child with scimitar syndrome and pulmonary hypertension. *Pediatr Crit Care Med* 2003;4:111–4.
- 41 Gugnani MK, Pierson C, Vanderheide R, et al. Pulmonary edema complicating prostacyclin therapy in pulmonary hypertension associated with scleroderma. *Arthritis Rheum* 2000;43:699–703.
- 42 Syed AU, Jelly AEA, Algebaly AA, et al. Methemoglobinemia due to nitric oxide therapy in a child after cardiac surgery. *Asian Cardiovasc Thorac Ann* 2012;21:345–7.
- 43 Dotsch J, Demirkaya S, Hamm R, et al. Extracorporeal circulation increases nitric oxide-induced methemoglobinemia in vivo and in vitro. *Crit Care Med* 1997;25:1153–8.
- 44 Afshari A, Bork J, Moller AM, et al. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: A systematic review with meta-analysis and trial sequential analysis. *Anesth Analg* 2011;112:1411–21.
- 45 Elmi-Sarabi M, Deshamps A, Delise S, et al. Aerosolized vasodilators for the treatment of pulmonary hypertension in cardiac surgical patients: A systematic review and meta-analysis. *Anesth Analg* 2017;125:393–402.