

Inhaled therapy for the management of perioperative pulmonary hypertension

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ABSTRACT

Patients with pulmonary hypertension (PH) are at high risk for complications in the perioperative setting and often receive vasodilators to control elevated pulmonary artery pressure (PAP). Administration of vasodilators via inhalation is an effective strategy for reducing PAP while avoiding systemic side effects, chiefly hypotension. The prototypical inhaled pulmonary-specific vasodilator, nitric oxide (NO), has a proven track record but is expensive and cumbersome to implement. Alternatives to NO, including prostanoids (such as epoprostenol, iloprost, and treprostinil), NO-donating drugs (sodium nitroprusside, nitroglycerin, and nitrite), and phosphodiesterase inhibitors (milrinone, sildenafil) may be given via inhalation for the purpose of treating elevated PAP. This review will focus on the perioperative therapy of PH using inhaled vasodilators.

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INTRODUCTION

The pathology of pulmonary hypertension (PH) involves vascular remodeling due to endothelial cell dysfunction and smooth muscle cell proliferation^[1] that restricts the cross-sectional area of the pulmonary vascular bed, resulting in elevated pulmonary artery pressure (PAP), increased pulmonary vascular resistance (PVR), and hypoxia. Although the right ventricle (RV) has a remarkable ability to compensate for markedly elevated PAP and PVR, RV failure is the ultimate consequence of severe PH.^[2-4]

The arsenal of drugs for the treatment of PH in the perioperative and intensive care settings has traditionally depended on intravenous vasodilators that lack specificity for the pulmonary circulation and may cause systemic vasodilation, which is undesirable. While inhaled nitric oxide (iNO) is the “gold standard” for pulmonary-specific PH treatment in many localities, there has been interest among clinicians in developing less expensive alternatives. Prostacyclin, milrinone, and nitroglycerin (NTG) are examples of intravenous vasodilators that

become pulmonary-specific when given via inhalation. This review will discuss the pharmacologic targets and perioperative use of inhaled vasodilators, with an emphasis on intravenous vasodilators given via the inhaled route.

TARGETS OF DRUG THERAPY RELEVANT TO PULMONARY HYPERTENSION

Although numerous cellular mediators associated with PH and RV failure have been targeted for drug development, perioperative drug therapy primarily relies on three pathways of vasodilation: Nitric oxide (NO)

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donors, adenylate cyclase (AC) stimulators, and phosphodiesterase (PDE) inhibitors.

Nitric oxide donors

NO, first described as the endothelium-derived relaxing factor, is produced by three variants of NO synthase. The endothelial variant (endothelial nitric oxide synthase [eNOS]) is important in the regulation of systemic and pulmonary vascular tone. In the body, eNOS uses the amino acid L-arginine as a substrate to produce NO, which freely diffuses from the endothelial cell into the blood stream and nearby smooth muscle cells. In the blood, NO oxidizes the iron of hemoglobin and is quickly inactivated. In smooth muscle cells, NO interacts with the heme moiety of soluble guanylate cyclase (sGC) to stimulate the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). cGMP, in turn, interacts with protein kinases to produce relaxation of myofilaments. The gold standard therapy for PH is iNO, which readily crosses from the alveolus to smooth muscle cell to directly stimulate sGC. Sodium nitroprusside (SNP) and NTG stimulate sGC after undergoing chemical reactions that release NO.

Adenylate cyclase stimulators

AC is a key enzyme in signal transduction pathways throughout the body. In vascular smooth muscle, AC is under regulatory control by stimulatory and inhibitory transmembrane G protein-coupled receptors (Gs and Gi, respectively). Prostacyclin, an endogenous prostaglandin, binds to prostanoid receptor type IP and activates Gs, which in turn stimulates AC to convert adenosine triphosphate to cyclic adenosine monophosphate (cAMP). cAMP interacts with protein kinases to promote smooth muscle relaxation. Therapeutic stimulation of AC can be achieved with administration of prostacyclin and its synthetic analogs (epoprostenol, treprostinil, and beraprost).

Phosphodiesterase inhibitors

PDEs are a family of enzymes that regulate vascular tone by hydrolyzing cGMP and cAMP to guanosine monophosphate (GMP) and adenosine monophosphate (AMP), respectively. By reducing the amount of cGMP and cAMP, PDEs tend to increase vascular tone. Phosphodiesterase type 3 (PDE3) hydrolyzes primarily cAMP and is inhibited by milrinone, while PDE5 primarily hydrolyzes cGMP and is inhibited by sildenafil. Both PDE3 and PDE5 are present in vascular smooth muscle and are targets for PH therapy.

INHALED NITRIC OXIDE DONORS

Inhaled Nitric Oxide

iNO easily crosses the alveolar-capillary barrier and stimulates sGC in the vascular smooth muscle near the alveoli. Due to rapid inactivation by circulating hemoglobin, iNO has no effect on vascular beds beyond the lungs.^[5] iNO produces pulmonary vasodilation at concentrations from 5 to 40 parts per million (ppm), resulting in a reduction in PVR, PAP, and RV afterload, while avoiding systemic hypotension. Those changes, along with maintenance of coronary perfusion pressure, tend to improve RV performance. iNO can improve oxygenation by increasing blood flow to pulmonary units that are well-ventilated (ventilation-perfusion matching).

iNO is used for management of PH and/or hypoxemia in many perioperative situations where lowering PAP and improving RV function is paramount. In mitral valve surgery in adults with severe PH, iNO significantly reduces PVR, increases cardiac index (CI), reduces the use of systemic vasoactive medications, and reduces Intensive Care Unit stay.^[6] Heart transplant recipients who receive iNO demonstrate improved RV function and a trend toward lower 30-day mortality.^[7] RV failure is a well-known complication that occurs at variable rates following left ventricular assist device (LVAD) implantation^[8] and is associated with higher morbidity and mortality.^[9-12] iNO reduces PAP and improves LVAD flow in LVAD recipients.^[13] In critically ill patients with circulatory shock due to RV failure, iNO significantly improves CO and mixed venous oxygen saturation (SVO₂).^[14]

Use of iNO is limited by the potential for toxicity and high cost. NO forms methemoglobin and nitrate upon exposure to oxyhemoglobin in the pulmonary circulation.^[15] In humans without methemoglobin reductase deficiency, doses <40 ppm do not cause methemoglobinemia,^[16] and animal data suggests that long-term administration at comparable doses are nontoxic.^[17] In addition to methemoglobinemia, lung injury may occur if excessive amounts of NO are oxidized to nitrogen dioxide (NO₂), a pulmonary irritant that can cause bronchospasm and pulmonary edema. Modern iNO delivery systems include monitoring for NO and NO₂ levels.^[18] Yahagi *et al.*^[19] followed 65 pediatric recipients of iNO for a mean of 3.1 years and found no occurrence of chronic inflammation or malignancy of the respiratory tract. The daily cost for of iNO using the Food and Drug Administration (FDA)-approved apparatus was \$3000 in 1999.^[20,21]

Sodium nitroprusside

SNP is an iron-containing inorganic compound that releases NO and cyanide (CN) after undergoing a redox reaction with hemoglobin in red blood cells. Intravenously administered SNP causes systemic and pulmonary vasodilation. Use of intravenous SNP to lower PAP typically requires a vasoconstrictor to compensate for reduced mean arterial pressure (MAP).

When administered through a nebulizer connected to the inspiratory limb of the breathing circuit, SNP has been shown to be a selective pulmonary vasodilator.^[22,23] In a porcine model of PH,^[24] nebulized SNP (total dose of 25 mg) caused a rapid reduction in PAP that was equivalent to iNO at 20 ppm, without decreasing MAP. In a sheep model of PH,^[25] low-dose inhaled SNP (concentration ≤ 0.02 M) decreased PAP by 42% and systemic vascular resistance (SVR) by 5%. However, high-dose inhaled SNP (concentration > 0.02 M) caused pulmonary and systemic vasodilation.^[25] Thus, it appears there is a dose ceiling beyond which inhaled SNP becomes a nonselective vasodilator.

Experience with inhaled SNP in human subjects is extremely limited. Several investigators^[26,27] have found that inhaled SNP significantly increased oxygenation in mechanically ventilated newborns with hypoxia. In the study by Mestan *et al.*,^[26] newborns with hypoxic respiratory failure receiving nebulized SNP (in doses of 5 mg and 25 mg) had dose-dependent increases in oxygenation that were comparable to iNO. MAP and heart rate (HR) did not change significantly during SNP treatment, and no attempt to record PAP was made.

Toxicity from SNP, which manifests as CN toxicity, thiocyanate toxicity, or methemoglobinemia, is a concern when the drug is administered at high doses for prolonged periods. Multiday intravenous infusions of SNP at doses of 0.5 mcg/kg/min are generally safe, while infusions exceeding 2 mcg/kg/min increase the risk of CN toxicity.^[28] It is difficult to extrapolate these numbers to inhalational SNP therapy as a significant portion of the nebulized drug may not reach the alveolus, where absorption occurs.^[29] In the study of newborns with hypoxia,^[26] the dose of nebulized SNP exceeded 6 mg/kg over 20 min yet was not associated with overt CN toxicity. Patients receiving multiple doses or continuous treatments of nebulized SNP should be monitored for CN toxicity.

In addition to the concern for CN toxicity, there are several caveats to using inhaled SNP clinically.

Because the effect of a single dose of nebulized SNP is short,^[26] sustained pulmonary vasodilation requires giving multiple doses or continuous nebulization. As a practical matter, it is probably best to use inhaled SNP as a bridge to starting a conventional pulmonary vasodilator with established safety profile and delivery method.

Nitroglycerin

NTG is a well-known venous-and arterial vasodilator that stimulates sGC through a NO-donating mechanism catalyzed by aldehyde dehydrogenase-2.^[30]

As is the case with inhaled SNP, preliminary experience with inhaled NTG in animal models of PH^[31,32] was followed by human investigations.^[33,34] Mandal *et al.*^[35] compared nebulized and intravenous NTG, both at a dose of 2.5 mcg/kg/min for 10 min, in 40 adults after mitral and aortic valve surgery, and found that inhaled and intravenous NTG produced equivalent reductions in mean PAP (mPAP) (approximately 20% decrease) and pulmonary vascular resistance index (PVRI) (approximately 25% decrease), but only intravenous NTG caused significant changes in central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), MAP, and systemic vascular resistance index. The duration of hemodynamic effect from inhaled NTG lasted about 20 min.^[35]

Yurtseven *et al.*^[36] recorded hemodynamic and gas exchange data in 20 intubated, mechanically ventilated adults recovering from mitral valve replacement surgery. During the nebulized NTG treatments (2.5 mcg/kg/min over 5 h), there were significant decreases in mPAP and PVR and increases in oxygenation parameters, without significant change CVP, PCWP, MAP, or CI. mPAP and PVR returned to baseline values within 1 h after ending the NTG treatment.

Nebulized NTG (20 mcg/kg) was compared to nebulized iloprost (2.5 mcg/kg) in a study of 100 patients with elevated PAP after mitral valve surgery.^[37] Both drugs produced significant decreases in mPAP and PVR, but the effect was larger with iloprost. In addition, the inhaled iloprost increased cardiac output (CO) and stroke volume, which did not occur with nebulized NTG.

Singh *et al.*^[38] performed a three-way comparison of nebulized NTG (50 mcg/kg), nebulized milrinone (50 mcg/kg), and 100% inspired oxygen in 40 children with left-to-right intracardiac shunt and

elevated mPAP (>30 mmHg) undergoing right heart catheterization. Both nebulized NTG and nebulized milrinone lowered mPAP (–15%) and PVRI (–70%) while keeping other hemodynamic variables stable. Interestingly, the efficacy of nebulized NTG (given with a gas mixture that was 50% oxygen) was not superior to inhalation of 100% oxygen, while inhaled milrinone was slightly better than 100% oxygen.^[38]

In total, while there is more clinical experience with inhaled NTG than with inhaled SNP, both drugs have similar limitations. Given the short duration of action of inhaled NTG, sustained pulmonary vasodilation would require multiple administrations or continuous nebulization. Methemoglobinemia is a theoretical concern with prolonged exposure to NTG. Inhaled NTG might be useful as temporizing agent until a conventional drug can be started.

Nitrite

The inorganic anions nitrate (NO_3^-) and nitrite (NO_2^-) are end-products of endogenous NO metabolism. Although previously thought to be inert, nitrate and nitrite undergo “recycling” to form NO through a route that is distinct from the classic arginine-NO synthase-NO pathway, occurs predominantly in hypoxic states, and is catalyzed by deoxyhemoglobin, deoxymyoglobin, and xanthine oxidoreductase.^[39-41] Therapeutic use of nitrite anion for PH has been investigated in dietary,^[42] intravenous,^[43,44] and inhaled^[45-47] preparations. Although inhaled nitrite anion for the management of PH in humans has not yet been reported, studies involving induced PH in animal models suggest that inhaled nitrite anion is a selective pulmonary vasodilator.^[46]

Distinct from the inorganic anion nitrite, the alkyl nitrites are gaseous organic compounds that release NO through an aldehyde dehydrogenase-dependent pathway. Historically, inhalation of amyl nitrite was employed during bedside examination to augment the murmur of mitral stenosis and diminish the murmur of mitral regurgitation.^[48] In a swine model of severe PH induced by a thromboxane analog,^[49] inhalation of amyl nitrate produced substantial decreases in mPAP (–50%) and PVR (–92%) while improving CO and MAP. A small study of newborns with PH^[50] showed that pulmonary gas exchange (oxygenation and ventilation) and blood pressure improved during 4 h of ethyl nitrite inhalation.

INHALED PROSTANOIDS

Prostacyclin, a naturally occurring prostaglandin derived from arachidonic acid, increases intracellular cAMP, leading to vascular smooth muscle relaxation. It also has antiplatelet effects and suppresses proliferation of smooth muscle cells.^[51] There are three prostacyclin analogs approved by the FDA for treatment of PAH: Epoprostenol, iloprost, and treprostinil.^[52] In addition, beraprost had been approved in Japan. Epoprostenol, the first prostanoid developed, is unstable and has a half-life of 3–6 min, whereas the newer analogs have increasingly longer half-lives (iloprost 20–30 min, treprostinil 4 h).^[52] Although prostacyclin has *in vitro* antiplatelet effects, it has been shown that inhaled prostanoids can be used safely without increased bleeding risk.^[53]

Although high-quality controlled trials of inhaled prostanoids are lacking, many clinicians have utilized inhaled prostanoids as an iNO alternative. Compared to iNO, the inhaled prostanoids produce similar reductions in PAP, are relatively free of toxicity, require no special monitoring, and may be less expensive to administer.^[54,55] Inhaled prostanoids have been used in patients with acute lung injury and acute respiratory distress syndrome to improve gas exchange and increase blood flow to well-ventilated lung regions.^[56]

A prospective, randomized, crossover study comparing iNO (20 ppm) and inhaled epoprostenol in heart and lung transplant recipients ($n = 25$) showed that both drugs similarly reduced PAP and CVP and improved CI and SVO₂ without lowering MAP or other complications.^[54] Due to the short half-life of epoprostenol, a syringe pump was utilized to deliver the drug to a jet nebulizer, which in turn was attached to the inspiratory limb of the breathing circuit. Approximately 8 mL of epoprostenol (diluted in a glycine buffer to 20,000 ng/mL) was administered per hour. The authors noted several caveats of epoprostenol administration, including: (1) Uncertainty regarding the amount of epoprostenol reaching the alveoli, (2) the potential for accidental bolus if the nebulization chamber is tipped over, and (3) the potential for ventilator valves to become stuck due to the glycine buffering agent.^[54]

A systematic review of inhaled iloprost in pediatric patients^[57] showed that inhaled iloprost was well-tolerated and apparently safe, although indications, delivery methods, and doses varied greatly. The authors

concluded that inhaled iloprost may have a role in countries where iNO is not available or as a “rescue” option, and that well-designed prospective clinical trials are needed.^[57] A recent retrospective study of pediatric patients undergoing congenital heart surgery who were receiving stable doses of iNO were successfully transitioned to inhaled iloprost without adverse hemodynamic effects, thrombocytopenia, or bleeding complications.^[58] Unlike epoprostenol, iloprost does not require continuous nebulization because its half-life is longer, but the frequency of administration must be 6–9 times during waking hours.

Treprostinil and beraprost, the most recently developed prostanoids, have limited history of use in the perioperative setting. Inhaled treprostinil, which is typically administered via ultrasonic nebulizer 4 times daily during waking hours, would be a convenient inhaled therapy for PH. Beraprost, which is available in Japan, has an oral formulation only.

INHALED PHOSPHODIESTERASE INHIBITORS

Milrinone

Intravenous milrinone is a selective PDE3 inhibitor that is commonly given during cardiac surgery to treat left and RV failure, often with a concomitant decrease in systemic blood pressure.^[59] Over the past 15 years, much attention has been directed to inhaled milrinone as a selective pulmonary vasodilator^[60-63] and to prevent lung injury during warm ischemia^[64,65] and cardiopulmonary bypass.^[66]

In 2001, Haraldsson *et al.*^[67] reported the hemodynamic effects of inhaled milrinone in nine patients with PH (mPAP >25 mmHg and PVR >200 dynes/s/cm⁵) after cardiac surgery. When given by jet nebulizer via the inspiratory limb of a breathing circuit, nebulized milrinone at a concentration of 1 mg/mL was shown to decrease mPAP (–9%), PVR (–20%), transpulmonary gradient (TPG; –15%), and PVR/SVR ratio (–17%) without any effect on HR, MAP, CVP, PAOP, or CO. In a different group of postcardiac surgery patients ($n = 11$), the same investigators compared nebulized epoprostenol to the combination of nebulized epoprostenol and milrinone. Nebulized epoprostenol, given alone at a concentration of 10 mcg/mL, decreased mPAP by 6%, PVR by 20%, TPG by 21%, and PVR/SVR ratio by 21%. When nebulized milrinone was added, there was an additional 8% decrease in PVR over epoprostenol alone.

Sablotzki *et al.*^[68] found that nebulized milrinone (2 mg over 10 min) significantly reduced mPAP (–13%), PVR (–25%), and TPG (–29%) in a small study ($n = 18$) of heart transplant candidates with PH undergoing right heart catheterization. Maximum hemodynamic effect was seen at 10 min after inhalation, and the hemodynamic parameters returned to baseline within 30 min.

In a retrospective review of 70 patients having cardiac surgery, Lamarch *et al.*^[66] analyzed the effect of nebulized milrinone given either at initiation or termination of CPB. In both groups, there was a similar decrease in mPAP before and after CPB. However, the group receiving nebulized milrinone before CPB had no change in the MAP: mPAP ratio, while the group receiving the drug at the end of CPB had a decrease in the MAP: mPAP ratio, indicating development of PH. In a univariate analysis of predictors for difficult separation from CPB, nebulized milrinone before CPB was a protective factor (odds ratio [OR] = 0.2, confidence interval [CI]: 0.05–0.8; $P = 0.02$), but the multivariate analysis showed that only CPB duration was a risk factor (OR = 1.02, CI: 1.007–1.03; $P = 0.002$) for difficult separation from CPB.

As discussed earlier, Singh *et al.*^[38] performed a three-way comparison of nebulized milrinone, nebulized NTG, and inspiration of 100% oxygen in 35 children with acyanotic congenital heart disease with left-to-right shunt. The group receiving nebulized milrinone had a 15% decrease in mPAP and PVRI decreased from approximately 9 WU/m² to 2.9 WU/m². The investigators concluded that the three treatments had comparable effects on PAP.

Sildenafil

Sildenafil, a selective PDE5i that slows the degradation of cGMP to GMP, is used to treat erectile dysfunction by enhancing vasodilation in the corpora cavernosa. Oral sildenafil is a selective, well-tolerated PAP-lowering agent for patients with PAH.^[69-72] Oral sildenafil has been used to manage PH in cardiac surgical patients, in particular as an adjunct to reduce rebound PH during weaning of other pulmonary vasodilators.^[73-78] Intravenous sildenafil is comparable to intravenous milrinone in terms of hemodynamic and right heart inotropic effects.^[79,80]

Inhaled sildenafil should theoretically be a potent, selective pulmonary vasodilator. Unfortunately, to

Table 1: Comparison of iNO and its alternatives

	iNO	iNO alternatives
Regulatory status	Approved by many regulatory bodies	Except for iloprost and treprostinil, regulatory approval for most iNO alternatives is lacking
Cost	Expensive drug and equipment Delivery device requires calibration and maintenance	Drugs are typically inexpensive Cost of nebulizer is low (jet nebulizer) to moderate (ultrasonic nebulizer)
Delivery	Easy continuous delivery	Requires frequent bolus administration or continuous nebulization with IV pump
Safety	Rebound PH with abrupt discontinuation To avoid NO ₂ buildup, high fresh gas flow (≥6 L/min) and lowest FiO ₂ possible required Methemoglobinemia	Rebound PH likely to occur with short-acting drugs Accidental administration into IV could be lethal Drug may contain residue-forming additive that leads to sticking of ventilator valves NO-donor drugs (NTG, SNP) can cause methemoglobinemia
Pitfalls	Administration during patient transport is cumbersome Anesthetic gases (N ₂ O, isoflurane) may alter measured NO value	Tipping of nebulizer may give excessive dose and must be avoided during patient care and transport Continuous nebulization during patient transport may not be feasible Jet nebulizers require high-flow oxygen Gas analyzers for CO ₂ and volatile anesthetics may not be compatible with nebulization

NO: Nitric oxide, iNO: Inhaled nitric oxide, IV: Intravenous, PH: Pulmonary hypertension, NO₂: Nitrogen dioxide, NTG: Nitroglycerin, SNP: Sodium nitroprusside, N₂O: Nitrous oxide, CO₂: Carbon dioxide

date there is little published experience with inhaled sildenafil. A lamb model of PH found that 10 mg and 30 mg aerosols of sildenafil decreased PAP by 21% and 26%, respectively, and that 10 mg of aerosolized sildenafil combined with low-dose iNO (2 and 5 ppm) resulted in even greater PAP-lowering effect (–35% and –43%, respectively).^[81] Inhaled sildenafil was found to prevent postcardiopulmonary bypass PH, improve oxygenation, and reduce endothelial dysfunction in pigs.^[82]

CONCLUSION

Physicians who treat PH in the perioperative setting should be aware of the caveats of iNO and the iNO alternatives [Table 1]. The ideal pulmonary vasodilator for perioperative use which should be highly specific for the pulmonary circulation, free of side effects, inexpensive, and convenient to implement, has yet to be designed. iNO has the advantage of being recognized as a highly reliable pulmonary vasodilator that is approved by regulating authorities. The main disadvantages of iNO are its expense and cumbersome equipment. The inhaled forms of the prostanoids, PDE inhibitors, and NO donors (NTG, SNP) achieve reductions in PAP and PVR that are comparable to iNO and appear to be safe and well-tolerated. In addition, the iNO alternatives are typically inexpensive and rely on nebulization devices that many hospitals have on hand. Unfortunately, the cumulative experience with the iNO alternatives is substantially less than iNO. Routine use of a

pulmonary-specific vasodilator must take into account how the drug will fit into a hospital's perioperative environment. Given that perioperative therapy for PH typically occurs in patients who are medically complex and unforgiving of misadventure, the choice of therapy should emphasize safety and reliability.

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