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Inhaled Alternatives to Nitric Oxide

Stuart M. Lowson, M.D.

THE considerable interest shown in inhaled nitric oxide (INO) over the last decade, and the number of publications describing the clinical applications of this agent, testify to the perceived clinical need for a drug that acts selectively on the pulmonary vasculature.¹ Such an agent should decrease pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), without affecting systemic arterial pressure (SAP), and potentially improve oxygenation by redistributing pulmonary blood flow to ventilated areas of lung. INO (INO Therapeutics Inc., Clinton NJ) possesses these properties and has gained approval from the Food and Drug Administration (FDA) for the care of neonates with acute lung injury and pulmonary hypertension (PH), and widespread clinical acceptance (but not FDA approval) for adults with PH with or without lung injury. Delivered as a gas, INO is preferentially distributed to the ventilated areas of the lung, where it produces relaxation of pulmonary vascular smooth muscle *via* activation of guanylate cyclase and the conversion of guanosine-5-triphosphate to cyclic guanosine monophosphate.¹ Absorbed INO is rapidly inactivated by hemoglobin, thereby preventing systemic effects and confining its vasodilator properties to the pulmonary circulation.¹

The search for inhaled selective pulmonary vasodilators was an active area of research, particularly in Europe and Australia, before the widespread publicity and testing of INO in the early 1990s. However, research on this subject appears to have declined inversely with the growing acceptance and use of INO. Until FDA approval had been granted, INO had been supplied free of charge in the United States on an investigational-drug basis.

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However, after FDA approval, the cost of treatment with INO became very expensive. This prompted a search at our institution for alternative agents to INO. The purpose of this article is to review the published experience concerning alternative inhaled vasodilators and, when possible, compare their reported efficacy with that of INO.

Nitric Oxide Donor Drugs

A number of synthetic agents release nitric oxide (NO) either spontaneously or after enzymatic cleavage and thereby provide a means of delivering NO to its site of action in a form other than as a gas. The following sections describe those NO donors that have been examined as possible pulmonary vasodilators.

Nitric Oxide-Nucleophile Adducts

Compounds formed by reacting NO with various nucleophiles release NO spontaneously in physiologic solutions, are stable as solids, are highly soluble in aqueous media, and have the potential to function as an aqueous slow-release form of NO. Jacobs *et al.*² demonstrated that an inhaled NONOate [2-(dimethylamino) ethylputreanine-NO] improved oxygenation and reduced PVR, without affecting systemic hemodynamics, in a porcine model of oleic-acid-induced acute lung injury and PH. Similarly, Brill *et al.*³ demonstrated that two investigational inhaled NONOates produced selective pulmonary vasodilation lasting 30-50 min in a porcine model of PH. Adrie *et al.*⁴ compared the pulmonary effects of the NONOate, sodium 1-(*N,N*-diethylamino) diazen-1-ium-1,2-diolate, with INO and inhaled sodium nitroprusside (SNP) in an ovine model of PH. Although SNP caused dose-dependent selective pulmonary vasodilation, the NONOate decreased both pulmonary and systemic vascular resistances, implying a nonselective action. The pulmonary vasodilation produced by either inhaled SNP or the NONOate was of longer duration than that produced by INO.

There are currently no clinical investigations describing the use of these novel NO donor drugs. However, animal studies suggest that their properties in terms of pulmonary selectivity and duration of effect may be highly dependent on their specific chemical structure.

Sodium Nitroprusside

Inhaled SNP has been evaluated in animal models of PH. It has been shown to produce dose-dependent pulmonary vasodilation in isolated perfused rabbit lungs with thromboxane-induced PH.⁵ In an ovine model of PH, inhaled SNP produced selective pulmonary vasodilation at concentrations less than 10^{-2} M but nonselective vasodilation at concentrations greater than 10^{-2} M.⁴

Yu and Saugstad⁶ compared the effects of a 30-min nebulization of either saline or SNP in a lavaged-induced lung injury model in newborn piglets. Inhaled SNP produced a significant decrease in mean PAP (from 32 to 17 mmHg) and PVR, which was sustained for the 30-min treatment period. There was no effect on SAP. The arterial oxygen tension (P_{aO_2}) increased from 71 to 130 mmHg and was associated with a significant decrease in arterial carbon dioxide tension. The dose of SNP used in the study was based on the results of pilot studies in which the investigators found that higher doses produced systemic hypotension. Meadow *et al.*,⁷ investigated the short-term effects of inhaled SNP (50 mg in 5 ml saline) in a porcine model of PH, induced by either hypoxia or group B streptococci. Inhaled SNP selectively decreased PAP in hypoxia-induced PH, which was sustained with continuous treatment for longer than 60 min. A reduced response was observed in streptococci-induced PH, and there was no associated improvement in oxygenation.

There is one report of the clinical use of inhaled SNP. Ten cyanotic newborns were treated with aerosolized SNP, at a concentration of 0.25 mg/ml in distilled water, for a duration of 97–157 h.⁸ Nine of the newborns responded with a significant, often dramatic, increase in their ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{iO_2}) after 1 h of therapy (mean increase from 32 to 94 mmHg). The effect on SAP was variable, decreasing in some patients and increasing in others, but overall producing no significant change.

The animal studies suggest that the dose of inhaled SNP to produce selective pulmonary vasodilation is critical, which would not allow SNP to be an ideal inhaled pulmonary vasodilator. However, the results of the one clinical study were sufficiently impressive to justify further studies with inhaled SNP.

Nitroglycerin

There is little reported on the use of inhaled nitroglycerin. In a canine model of thromboxane-induced PH, Gong *et al.*,⁹ demonstrated that aerosolized nitroglycerin caused a 31% decrease in PVR with no effect on SAP. Schutte *et al.*⁵ studied several NO donors, including nitroglycerin, in the isolated rabbit lung. Nitroglycerin produced dose-dependent pulmonary vasodilation, which was noted to be significantly less efficacious than the other agents tested, including SNP.

Phosphodiesterase Inhibitors

Nitric oxide exerts its biologic properties by increasing intracellular concentrations of cyclic guanosine monophosphate. Cyclic guanosine monophosphate is rapidly metabolized by phosphodiesterases, thereby terminating the effect of NO. Ichinose *et al.*^{10,11} investigated the pulmonary vascular effect of inhalation of phosphodiesterase inhibitors of the type 5 class (zaprinast, sildenafil), which block the hydrolysis of cyclic guanosine monophosphate with minimal effects on the metabolism of adenosine-3,5-cyclic monophosphate, in an ovine model of PH. They demonstrated that these phosphodiesterase inhibitors not only augmented the effect of combined INO administration but produced selective pulmonary vasodilation when given alone. The selectivity of the pulmonary vasodilation was dose-dependent for zaprinast, with systemic hypotension occurring at the highest doses tested.

Haraldsson *et al.*¹² recently demonstrated that inhaled milrinone, a type 3 phosphodiesterase inhibitor that increases vascular smooth muscle adenosine-3,5-cyclic monophosphate concentrations, caused selective pulmonary vasodilation in cardiac surgical patients with postoperative PH.

Prostaglandin E₁ (Alprostadi, Prostin VR Pediatric)

In contrast to the aforementioned agents that mediate their effects *via* release of NO and activation of soluble guanylate cyclase, vasodilator prostaglandins bind to cell surface prostaglandin receptors, which are part of the G-protein superfamily, causing activation of adenylate cyclase.¹³ Prostaglandin E₁ (PGE₁) is normally present within the lung, where it produces smooth muscle relaxation. PGE₁ is a stable compound at neutral pH but is rapidly degraded *in vivo* by the enzyme 15-hydroxyprostaglandin dehydrogenase to 15-keto-PGE₁,¹⁴ which is then further transformed into 13,14-dihydro-15-keto-PGE₁. There is some evidence that 15-keto-PGE₁, which is inactive, may also be reduced to 13,14-dihydro-PGE₁, which possesses vasodilator properties.¹⁵

Intravenous PGE₁ has an established place for maintaining the patency of the ductus arteriosus in infants with congenital heart disease until a formal shunt procedure can be performed. It has also been used in the treatment of PH in patients with mitral valve disease,¹⁶ acute respiratory distress syndrome (ARDS),¹⁷ and after heart transplantation.^{18,19} Because the lung removes more than 70% of an intravenously administered dose of PGE₁ during one passage,^{20,21} it has been suggested that intravenous PGE₁ may act as a selective pulmonary vasodilator. However, other investigators have not been able to confirm this pulmonary selectivity.¹⁷

There have been very few studies examining the hemodynamic effects of inhaled PGE₁. Animal models of

thromboxane-induced PH suggest that inhaled PGE₁ is a less effective pulmonary vasodilator than either INO or inhaled prostacyclin (prostaglandin I₂ [PGI₂]).^{22,23} Putensen *et al.*²⁴ compared the effects of INO and nebulized PGE₁ in 10 adult patients with ARDS. The dose of both INO and PGE₁ was individually titrated to obtain the maximum improvement in PaO₂. This was achieved with a dose of 2–10 ppm of INO and 6–15 ng · kg⁻¹ · min⁻¹ of PGE₁. INO and PGE₁ produced comparable decreases in mean PAP and PVR and increases in right ventricle ejection fraction and PaO₂. Neither drug had any effect on SAP. To produce a comparable decrease in mean PAP, the investigators had to intravenously administer 8–16 ng · kg⁻¹ · min⁻¹ of PGE₁. This study demonstrated that, for short-term exposure in patients with ARDS, inhaled PGE₁ produced identical responses to INO at doses comparable to those used intravenously. As well as inducing relaxation of vascular smooth muscle, inhaled PGE₁ also produces bronchodilation.²⁵

Prostaglandin E₁ is readily available in many hospitals caring for neonates and, based on the preliminary data, deserves further examination, particularly comparing its clinical efficacy with INO and inhaled PGI₂.

Iloprost

Iloprost is the stable carbacyclin derivative of PGI₂. Studies examining the actions of inhaled iloprost have shown that it has comparable pulmonary hemodynamic effects to INO and PGI₂.^{26,27} Its advantages over PGI₂ include its solubility in saline, obviating the need for an alkaline buffer, a lower viscosity, which aids nebulization, and a significantly longer duration of action, permitting effective intermittent rather than continuous nebulizations. The plasma half-life of iloprost is 20–30 min,²⁸ and the hemodynamic effects of a single inhaled dose lasts approximately 1 h.²⁷ Hoepfer *et al.*²⁷ compared the short-term effects of INO (40 ppm) *versus* a single treatment of inhaled iloprost (14–17 μg) in 35 patients with primary PH. The effects of iloprost on PVR were evident within 2–5 min, caused a maximum decrease of 30% from the baseline PVR, and dissipated by 75 min. Iloprost produced a greater decrease in PVR and increase in cardiac output than INO.

In one of the first descriptions of the long-term use of inhaled iloprost, Olschewski *et al.*²⁹ described the use of repeated daily nebulizations of iloprost (150 μg/day) in the management of a patient with severe primary PH and right heart failure. Iloprost decreased PAP and PVR, increased cardiac output, and improved gas exchange. The beneficial responses were sustained during long-term inhalational therapy. Furthermore, no evidence of tolerance with long-term therapy or rebound PH between doses was detected. Studies examining larger series of patients with primary PH have confirmed that

inhaled iloprost produces a sustained long-term (up to 12 months) improvement in exercise capacity and pulmonary hemodynamics.^{30–32} Inhaled therapy overcomes one of the major disadvantages of continuous intravenous therapy, namely, the need for a permanent central venous catheter. There is one report of patients with severe PH developing right ventricular (RV) failure when the investigators attempted to substitute intermittent inhaled iloprost for continuous therapy with intravenous PGI₂.³³ Conversely, Olschewski *et al.*³² were unable to substitute intravenous PGI₂ for inhaled iloprost in three of their patients because of worsening arterial hypotension.

Inhaled iloprost appears to have comparable hemodynamic effects to INO and has been administered for both short- and long-term use with just the one report of adverse effects. Unfortunately, iloprost is not available in the United States.

Prostaglandin I₂ (Epoprostenol, Prostacyclin, Flolan, Prostaglandin I₂)

Prostacyclin (PGI₂) is a member of the prostaglandin family of lipid mediators derived from arachadonic acid and is synthesized predominantly by endothelial cells, including the pulmonary vascular endothelium.³⁴ PGI₂ is a vasodilator and is the most potent known inhibitor of platelet aggregation. These properties suggest that it has a role in preventing clot formation in uninjured vessels and producing vasodilation in low resistance vascular beds such as the pulmonary circulation.³⁵ PGI₂ has also been shown to stimulate endothelial release of NO,³⁶ and, in turn, NO has been shown to enhance the production of PGI₂ in human pulmonary artery smooth muscle cells.³⁷

Prostaglandin I₂ is spontaneously hydrolyzed at neutral pH in plasma to its inactive metabolite, 6-keto-prostaglandin-F_{1α}. The *in vitro* half-life of prostacyclin in human blood at 37°C and pH of 7.4 is approximately 6 min.³⁸ Animal studies demonstrate that intravenous PGI₂ has a high clearance (93 ml · min⁻¹ · kg⁻¹), small volume of distribution (357 ml/kg), and a short half-life (2.7 min).³⁵

Most of our knowledge concerning the pharmacologic effects of PGI₂ is derived from the clinical experience using intravenous PGI₂. Intravenous PGI₂ has been used in the management of primary PH for nearly 20 yr. Other indications have included ARDS,³⁹ peripheral vascular disease, and congestive cardiac failure. The reported adverse reactions to intravenous PGI₂ include flushing, headache, jaw pain, nausea and vomiting, anxiety, chest pain, flu-like symptoms, dizziness, abdominal pain, bradycardia, and tachycardia. In contrast to INO,⁴⁰ PGI₂ has no known toxic effects or metabolites.

Inhaled PGI₂ is not metabolized within the lung to any significant extent. Systemic absorption of PGI₂ can be

determined by measuring the serum concentration of its major metabolite, 6-keto-PGF_{1α}. Concentrations of 6-keto-PGF_{1α} were undetectable after 8 h of inhaled PGI₂ in healthy lambs⁴¹; however, increased serum concentrations have been noted in patients with ARDS.⁴²

Prostacyclin is supplied as a powder that must be dissolved in the glycine buffer supplied by the manufacturer before use. After reconstitution, PGI₂ has satisfactory stability for up to 12 h at room temperature and for 48 h if refrigerated. The solution must be protected from light after reconstitution to avoid photodegradation.

The administration of inhaled PGI₂ to humans was first reported in 1978.⁴³ A number of trials have since been published examining its effects in animal models and a number of clinical settings. The studies described have a number of limitations. These include the small number of enrolled patients and the fact that most examine only the short-term response to inhaled PGI₂ rather than the response to sustained treatment. The latter is a more relevant model of the clinical situation where prolonged (hours to days) selective pulmonary vasodilation is required.

Animal Studies

Inhaled PGI₂ and INO have been compared in a number of animal models of PH. In canine,^{44,45} porcine,⁴⁶ and ovine⁴⁷ models of hypoxia-induced PH, both agents selectively decreased PAP without affecting SAP, with INO appearing to possess greater efficacy at the doses tested. In a porcine model of acute lung injury and PH, induced by repeated lung lavage and a continuous infusion of a thromboxane analog,⁴⁸ INO and inhaled PGI₂ were equally effective at selectively decreasing PAP, whereas INO was more effective at decreasing intrapulmonary shunt and improving Pao₂. A similar finding was observed by Walmrath *et al.*⁴⁹ in a rabbit model of PH. The majority of these studies suggest that INO is the more efficacious of the two agents; however, with one exception,⁴⁹ fixed doses were compared rather than titrating either agent to maximum effect.

Inhaled NO and PGI₂ exert their effects by different cellular mechanisms: NO *via* activation of guanylate cyclase producing cyclic guanosine monophosphate, and PGI₂ *via* adenylate cyclase producing adenosine-3,5-cyclic monophosphate. The net effect of activation of either of these pathways is relaxation of vascular smooth muscle, raising the possibility of an additive effect if the two agents were combined. This has been confirmed in a rodent model of chronic PH.⁵⁰ Furthermore, the pulmonary vasodilatory response to inhaled PGI₂ can be enhanced by concomitant therapy with phosphodiesterase inhibitors, thereby further increasing cellular concentrations of adenosine-3,5-cyclic monophosphate.⁵¹ All of the phosphodiesterase inhibitors studied amplified the response to inhaled PGI₂; however, the combined type 3 and 4 inhibitors proved the most potent, prolong-

ing the posttreatment response duration of a single treatment of inhaled PGI₂ from less than 10 to more than 30 min.⁵¹

Human Studies of Pulmonary Hypertension

Although intravenous PGI₂ has an established role in the long-term management of primary PH,⁵² a number of studies have examined the response to inhaled therapy. Mikhail *et al.*,⁵³ compared increasing doses of inhaled PGI₂ (15–50 ng · kg⁻¹ · min⁻¹) to INO (10–100 ppm) in 12 patients with PH (7 with primary PH and 5 with PH secondary to such causes as thromboembolism and ischemic cardiomyopathy). Both agents produced selective pulmonary vasodilation, with inhaled PGI₂ producing the greater decrease in mean PVR (38 *vs.* 12%). There was no detectable dose-response during the 15–50-ng · kg⁻¹ · min⁻¹ dose range, suggesting that a maximum response had been attained at the lowest dose tested. Olschewski *et al.*²⁶ compared INO, inhaled PGI₂, and inhaled iloprost in four patients with primary PH and two patients with severe PH secondary to connective tissue disease. All drugs produced comparable selective pulmonary vasodilation and improved Pao₂. Webb *et al.*⁵⁴ described the emergency use of inhaled PGI₂ in the management of a cyanotic, hypotensive patient with severe PH caused by an acute on chronic pulmonary thromboembolism. A dose of 200 ng · kg⁻¹ · min⁻¹ decreased the mean PAP from 59 to 53 mmHg with no effect on SAP, and increased the Pao₂/Fio₂ ratio from 66 to 225 mmHg.

Haraldsson *et al.*⁵⁵ compared the short-term response to INO (40 ppm) and inhaled PGI₂ (20–30-μg bolus dose) in 10 patients with PH (PVR > 200 dyne · s⁻¹ · cm⁻⁵) awaiting heart transplantation. Both INO and inhaled PGI₂ selectively decreased mean PAP (–7% *vs.* –7%) and PVR (–43% *vs.* –49%) to a similar degree. An 11% increase in cardiac output was observed with inhaled PGI₂ but not INO. Both drugs increased pulmonary artery occlusion pressures, which was associated in some cases with the development of overt pulmonary edema. The proposed mechanism for this finding is that pulmonary vasodilation produces increased RV ejection and pulmonary blood flow, increasing blood return to a left ventricle that cannot increase its stroke volume to compensate for the increased preload.⁵⁶ This phenomena has previously been described for INO^{57,58} and cautions against the use of selective pulmonary vasodilators in patients with severe left ventricular dysfunction.

Eichelbronner *et al.*⁵⁹ investigated the effects of inhaled PGI₂ and INO in 16 patients with septic shock (requiring pressors to maintain mean arterial pressures) and PH. Both agents were equally effective in reducing PAP and improving Pao₂ without affecting systemic hemodynamics. Interestingly, therapy with inhaled PGI₂, but not INO, was associated with an improvement in splanchnic perfusion and oxygenation.

Inhaled PGI₂ has also been successfully used in the management of portopulmonary hypertension.⁶⁰ In common with INO, inhaled PGI₂ has no effect on PAP in patients with normal pulmonary vasculature.⁶¹

Postcardiac Surgery

Inhaled NO has proved to be a valuable agent in the treatment of patients with PH and acute RV failure after cardiac surgery.^{1,56} The selective pulmonary vasodilation reduces RV afterload, thereby improving RV ejection fraction and cardiac output, without decreasing SAP and jeopardizing blood flow to major organs. There are as yet only limited studies of the effects of inhaled PGI₂ for this indication. Haraldsson *et al.*⁶² examined the short-term effects of inhaled PGI₂ at three different doses (2.5, 5.0, and 10 μg) in nine postoperative patients with PH, two after heart transplantation and seven after coronary artery bypass grafting. A significant decrease in mean PAP and PVR was observed in response to the 5- and 10-μg doses, with no decrease in SAP. Schroeder *et al.*⁶³ recently reported on the intraoperative use of inhaled PGI₂ in four cardiac surgical patients with increased PAP and impaired RV function. A dose of 36 ng · kg⁻¹ · min⁻¹ decreased PVR by 35% with no effect on SAP, improved RV function, and increased cardiac index by 26%.

Inhaled PGI₂ has also been administered to patients after lung transplantation. In one study, 10 ng · kg⁻¹ · min⁻¹ of inhaled PGI₂ produced an 11% decrease in mean PAP and a 25% decrease in intrapulmonary shunt.⁶⁴ The same investigators also demonstrated that combined therapy with inhaled PGI₂ and INO after lung transplantation produced a greater decrease in PAP and intrapulmonary shunt than INO alone,⁶⁵ thereby validating the animal studies.⁵⁰

Impaired platelet function is a potential undesirable effect of PGI₂ therapy in patients after cardiac surgery. Haraldsson *et al.*⁶⁶ studied platelet aggregation and thromboelastographic responses in patients scheduled for elective cardiac surgery receiving an aerosol of saline or 30 or 62 ng · kg⁻¹ · min⁻¹ of inhaled PGI₂ for 6 h postoperatively. Impaired *in vitro* platelet aggregation, beyond that expected after cardiopulmonary bypass, was noted after 2 h of PGI₂ therapy, with a suggestion of further impairment at 6 h, the maximum duration of therapy. Despite *in vitro* evidence of platelet dysfunction, there was no difference between groups with respect to bleeding time, chest tube drainage, or transfusion requirements. Interestingly, there was no difference in 6-keto-PGF_{1α} concentrations between the control and the two PGI₂ groups after 6 h of therapy, suggesting minimal absorption of PGI₂ from the lungs into the systemic circulation.

Haraldsson *et al.*¹² recently demonstrated that the pulmonary vasodilation caused by inhaled PGI₂ can be augmented by concomitant treatment with inhaled milrinone, thereby supporting the results of animal studies.⁵¹

Acute Respiratory Distress Syndrome

A number of studies have shown that the use of intravenous PGI₂ in ARDS is limited by its propensity to cause systemic hypotension and increase pulmonary venous admixture.^{39,67} In contrast, inhaled PGI₂ has been found to produce selective pulmonary vasodilation comparable to that caused by INO.⁶⁸ In 1993, Walmrath *et al.*⁶⁸ administered inhaled PGI₂ (17–50 ng · kg⁻¹ · min⁻¹) to three patients with ARDS. Mean PAP decreased in all patients (from 40 to 32 mmHg) associated with an increase in the PaO₂/Fio₂ ratio from 120 to 173 mmHg. Van Heerden *et al.*⁴² studied the response to 10–50 ng · kg⁻¹ · min⁻¹ of inhaled PGI₂ in nine patients with ARDS. Oxygenation improved in response to 10 ng · kg⁻¹ · min⁻¹, with no further significant improvement at higher doses. Although there was no apparent effect on PAP, none of the patients studied had significant PH (see Human Studies of Pulmonary Hypertension). There was also no demonstrable effect on *in vitro* platelet aggregation studies. In one of the larger reported studies, Walmrath *et al.*⁶⁹ compared the effects of the lowest dose of either INO or inhaled PGI₂ that produced the maximum increase in PaO₂ in 16 patients with ARDS. The dose of INO that produced the maximum increase in PaO₂ ranged from 2 to 40 ppm, whereas the comparable dose range for inhaled PGI₂ was 1.5–34 ng · kg⁻¹ · min⁻¹ (mean, 7.5 ng · kg⁻¹ · min⁻¹). Both agents produced a 7% decrease in measured intrapulmonary shunt and a comparable increase in the PaO₂, whereas inhaled PGI₂ produced a greater decrease in PVR than INO. Neither drug decreased SAP. Some patients were given either drug for 48 h or longer, demonstrating that the beneficial effects of inhaled PGI₂ on PaO₂ and selective pulmonary vasodilation were sustained. Zwissler *et al.*⁷⁰ compared three doses of INO (1, 4, and 8 ppm) and inhaled PGI₂ (1, 10, and 25 ng · kg⁻¹ · min⁻¹) in eight patients with ARDS (PaO₂/Fio₂ ratio < 155 mmHg). PVR was decreased by 10 and 25 ng · kg⁻¹ · min⁻¹ of inhaled PGI₂ but not by INO. Oxygenation improved with the 10- and 25-ng · kg⁻¹ · min⁻¹ doses of inhaled PGI₂ and all doses of INO, with 8 ppm of INO producing a greater increase in PaO₂ (+ 45%) than 25 ng · kg⁻¹ · min⁻¹ of PGI₂ (+ 25%) (fig. 1).

One study suggested that the response to inhaled PGI₂ in patients with ARDS may differ according to the cause of the lung injury.⁷¹ Overall, 53% of patients responded to inhaled PGI₂ (≥ 10% increase in PaO₂/Fio₂ ratio) which is comparable to the percentage of patients with ARDS that respond to INO.⁷² However, the majority of the responders to inhaled PGI₂ consisted of patients whose ARDS was caused by extrapulmonary disease (sepsis, major trauma). Few patients whose ARDS was caused by primary pulmonary injury (pneumonia, aspiration) responded. A significant decrease in PAP in response to inhaled PGI₂ was also only observed in the former patient group. In contrast, Walmrath *et al.*,⁷³

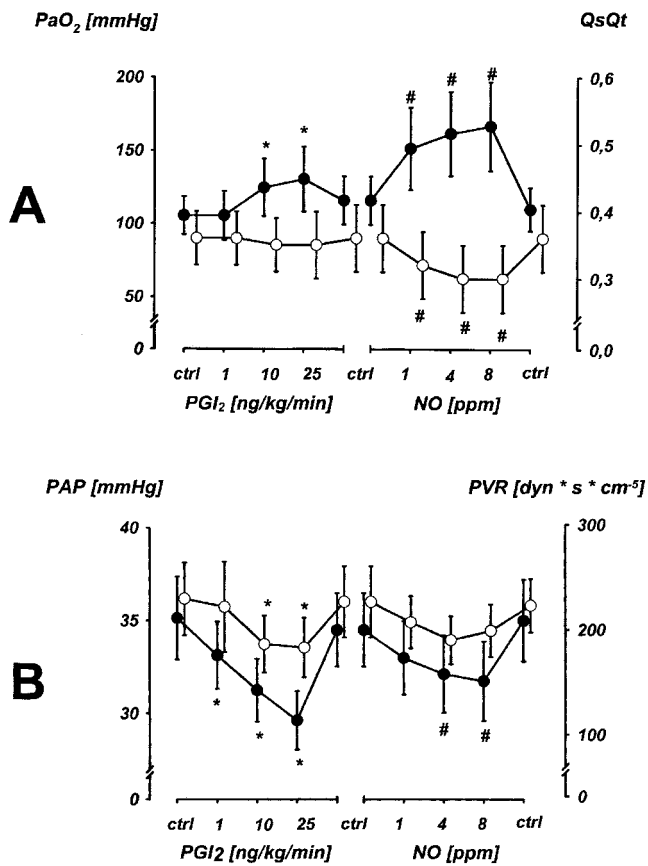


Fig. 1. (A) The effects of three doses of inhaled prostaglandin I₂ (PGI₂; 1, 10, and 25 ng · kg⁻¹ · min⁻¹) and inhaled nitric oxide (INO; 1, 4, and 8 ppm) on mean pulmonary artery pressure (PAP; closed circles) and pulmonary vascular resistance (PVR; open circles). All data are mean ± SEM. *P < 0.05 versus control value before administration of inhaled PGI₂. #P < 0.05 versus control value before administration of INO. (B) The effect of three doses of inhaled PGI₂ (1, 10, and 25 ng · kg⁻¹ · min⁻¹) and INO (1, 4, and 8 ppm) on PaO₂ (closed circles) and intrapulmonary shunt (QsQt) (open circles). All data are mean ± SEM. *P < 0.05 versus control value before administration of inhaled PGI₂. #P < 0.05 versus control value before administration of INO. (Reprinted with permission from Zwissler *et al.*⁷⁰)

demonstrated that patients with severe community-acquired pneumonia had a good response to inhaled PGI₂ provided that preexisting interstitial lung disease was absent.

From the few clinical studies to date, inhaled PGI₂ may be more effective at treating PH and less effective at improving PaO₂ as compared with INO. Despite decreasing PVR and improving oxygenation in approximately 60% of patients with ARDS, INO therapy has not been shown to improve outcome.^{72,74} Whether inhaled PGI₂ is capable of altering outcome of ARDS is not known. Furthermore, the results obtained for one pulmonary vasodilator may not be applicable to all such agents, particularly those acting *via* different cellular mechanisms.

Pediatric Patients

Inhaled NO is approved by the FDA for the treatment of term and near-term (> 34 weeks) neonates with

hypoxic respiratory failure associated with PH. There have been very few studies examining inhaled PGI₂ in this patient population. Bindl *et al.*,⁷⁵ reported the effects of inhaled PGI₂ in two neonates with PH. Inhaled PGI₂ (20–28 ng · kg⁻¹ · min⁻¹) produced a significant decrease in the alveolar-arterial oxygen difference, associated with a modest decrease in PAP but no decrease in SAP. Pappert *et al.*⁷⁶ compared the effects of INO (range, 0.1–10 ppm) and inhaled PGI₂ (range, 2–20 ng · kg⁻¹ · min⁻¹) in three children with ARDS. Both agents produced a decrease in intrapulmonary shunt and PAP in response to at least one of the doses tested.

Zwissler *et al.*⁷⁷ described a 4-kg infant with total anomalous pulmonary venous drainage who developed severe postoperative PH and acute RV failure, despite the administration of enoximone and intravenous PGI₂. Inhaled PGI₂ (50 ng · kg⁻¹ · min⁻¹) decreased the systolic PAP from 60 to 50 mmHg, which was associated with an increase in SAP. This was administered for a total of 13 h. Attempts to terminate treatment were associated with a rapid increase in PAP and decrease in PaO₂ (from 259 to 65 mmHg).

De Jaegere *et al.*⁷⁸ studied the effects of a 50-ng/kg bolus dose of inhaled PGI₂ to four hypoxic preterm neonates with PH. PGI₂ increased the PaO₂/FIO₂ ratio from a mean of 47 to 218 mmHg, with no change in SAP. In one infant, inhaled PGI₂ was continuously nebulized at a rate of 50 ng · kg⁻¹ · min⁻¹ for 12 h with no evidence of tolerance or systemic effects. Soditt *et al.*⁷⁹ showed that inhaled PGI₂ significantly improved PaO₂ without affecting SAP in a preterm infant (28 weeks' gestational age) with persistent PH of the newborn.

These studies and others⁸⁰ suggest that inhaled PGI₂ can selectively decrease PAP and improve PaO₂ in the pediatric patient with acute lung injury or PH. The one comparative study of INO and inhaled PGI₂ to date⁷⁶ does not permit any conclusion to be reached concerning the relative efficacy of either agent.

Summary of Inhaled Prostaglandin I₂

There has been no investigation directly comparing equal doses of inhaled *versus* intravenous PGI₂, but both animal⁴⁸ and clinical studies in adult^{39,53,67} and pediatric populations^{79,80} clearly demonstrate that intravenous PGI₂ has a significant disadvantage in that it is not a selective pulmonary vasodilator, producing parallel decreases in SVR and PVR and increasing intrapulmonary shunt. In contrast, the overall conclusion from the published studies is that inhaled PGI₂ and INO are comparable in terms of their ability to selectively decrease PAP and improve oxygenation.

The ideal dose for inhaled PGI₂ has yet to be determined. Reports^{41,52} suggest that it is in the 5–50-ng · kg⁻¹ · min⁻¹ range, but it may be lower. Zwissler *et al.*⁴⁵ found that a

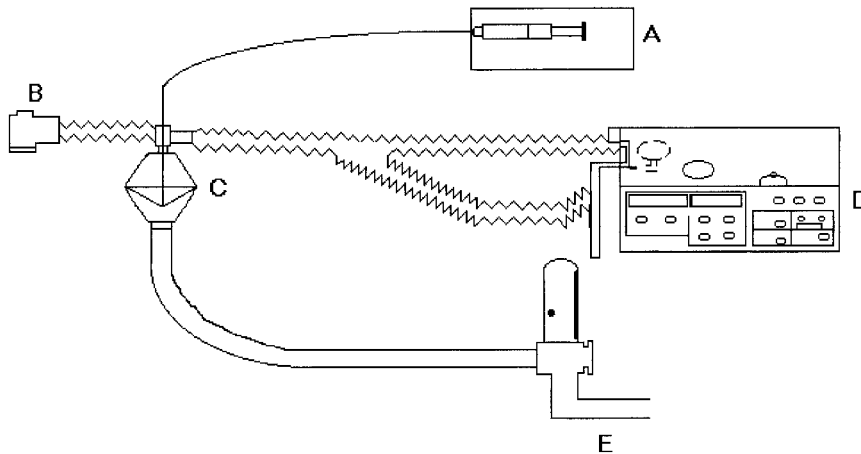


Fig. 2. Delivery system for inhaled prostaglandin I₂. A = syringe pump delivering prostaglandin I₂ solution; B = patient end of ventilator tubing; C = jet nebulizer; D = mechanical ventilator; E = driving gas flowmeter to nebulizer. (Reprinted with permission from Van Heerden *et al.*⁴¹.)

dose of inhaled PGI₂ as low as 0.9 ng · kg⁻¹ · min⁻¹ produced a significant reduction in PAP in dogs. The actual dose reaching the pulmonary vasculature is, of course, unknown since only approximately 10% of the dose of a nebulized agent reportedly reaches the alveolus.⁸¹ Systemic absorption of inhaled PGI₂ can occur as shown by the detection of its metabolites in the systemic circulation in some⁴² but not all⁶⁶ clinical studies. However, the typical side effects attributed to intravenous PGI₂ (facial flushing, headache, jaw pain, diarrhea) are not observed with inhaled therapy, suggesting that systemic absorption is minimal.⁸² The vast majority of studies have demonstrated that inhaled PGI₂ has little to no effect on SAP. One report noted a significant decrease in diastolic arterial pressures in female (but not male) patients; however, a 250–500-μg bolus dose of inhaled PGI₂ was administered.⁸³ This dose is more than 20 times greater than that used in other published reports. Selective pulmonary vasodilation is almost certainly dose related, and further studies are needed to determine the optimum dose-response of inhaled PGI₂, which may differ between individuals, in different disease states, and whether pulmonary vasodilation or improved oxygenation is the primary goal of therapy. However, the available literature suggests that the usual dose used by us and other investigators (≤ 50 ng · kg⁻¹ · min⁻¹) is well below the upper limit that may cause systemic hypotension.

Abrupt withdrawal of intravenous PGI₂,⁸⁴ including interruptions in drug delivery and sudden large reductions in dosage, may result in severe rebound PH, as described for INO.⁸⁵ There are as yet no reports of this phenomenon with inhaled PGI₂, but this should be regarded as a potential side effect until proven otherwise. There are conflicting reports concerning the effect of PGI₂ on bronchial tone, with some studies showing bronchoconstriction and others bronchodilation.^{43,81,86–88} However, no case of bronchospasm has been reported in the numerous clinical trials cited above. The effect of long-term therapy with inhaled PGI₂ on pulmonary function is not known. There is one report of PGI₂ causing a mild trache-

itis when given intratracheally to piglets, which may be related to the alkalinity (pH 10.5) of the glycine buffer in which it is dissolved.⁸⁹ However, in this study the investigators gave nine times the normal dose of diluent that would be administered to an adult human. A separate study was unable to detect any evidence of pulmonary toxicity, as measured by changes in lavaged cell counts, protein concentrations, concentrations of lactate dehydrogenase and alkaline phosphatase (nonspecific markers of cell injury), and fibronectin after 8 h of inhaled PGI₂ in healthy lambs.⁴¹ *In vitro* evidence of inhibition of platelet aggregation has been reported in some clinical studies of inhaled PGI₂^{43,66} but not in others.⁴² No studies have reported bleeding to be a problem even in patients after cardiac surgery.⁶⁶ In this respect, the studies examining the antiplatelet effects of INO^{90,91} and inhaled PGI₂ have produced identical results.

Inhaled PGI₂ has some potential advantages over INO. The lack of toxicity of PGI₂ or its metabolites implies that accurate measurement of the concentration of delivered drug and its metabolites in inspiratory and expiratory gases is not critical, unlike with INO. In contrast to INO, the apparatus for the delivery of inhaled PGI₂ is inexpensive and readily available in any medical center. At a minimum, all that is required is a continuous nebulizer driven by an external gas source inserted into the inspiratory limb of the ventilator circuit adjacent to the Y-piece. A number of investigators have described their delivery technique to ventilated (fig. 2)⁴² and nonventilated⁵⁶ patients. At our institution we use the MiniHeart nebulizer (Westmed Inc., Tucson, AZ), which delivers 8 ml/h of the PGI₂ solution at a low driving gas flow rate of 2 l/min. The particle size delivered at this gas flow rate is 2 μm (information provided by Westmed Inc.). This is connected to a T-piece placed in the inspiratory limb of the ventilator circuit approximately 10 inches from the Y-piece (according to manufacturer instructions). The PGI₂ solution is reconstituted in the hospital pharmacy and diluted to a concentration that will deliver a dose of 50 ng · kg⁻¹ · min⁻¹, based on 8 ml of the solution being nebulized per hour. The solution is contained in a 60-ml

syringe that is placed in a syringe pump and set to deliver 8 ml/h to the nebulizer. The 60-ml syringe and nebulizer are foil wrapped to provide protection from light. Prostacyclin is continued at $50 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ until the patient's condition has stabilized, at which time the dose is decreased to achieve the minimal effective concentration.

Conclusion

Although inhaled PGI₂ is an obvious alternative to INO, some of the other drugs described here deserve further attention. PGE₁ is more readily available than PGI₂ in hospitals that care for pediatric patients, but it has been the subject of only one clinical study.²³ The lack of published data related to PGE₁, as opposed to PGI₂, was clearly influential in our own decision to investigate PGI₂ as an alternative to INO. The few studies to date suggest that both SNP and nitroglycerin also have the potential to be inexpensive alternatives to INO. The elaboration of NO donor drugs is an active area of research and may produce useful agents for clinical applications.

An important concern for physicians in the United States is that, with the exception of the use of INO in neonates, none of the agents mentioned here have FDA approval for delivery *via* the inhaled route. If these agents are administered as part of a research investigation, the investigators must obtain local institutional review board approval for the study and informed consent, and may require an FDA-approved investigational new drug license (verbal communication, Norman Stockbridge, M.D., Ph.D., Division of Cardio-renal Drug Products, FDA, March 1, 2002). The FDA does not require an investigational new drug license for a drug administered for a non-FDA-approved use or by a non-FDA-approved route, providing it is given for purely clinical purposes, so called "off-label" use.[†] However, it is advised that all physicians in the United States wishing to administer an inhaled vasodilator should consult their local institutional review board regarding the need for an approved protocol, informed consent, and an FDA investigational new drug license.

The daily cost of PGI₂ is only a small fraction of that of INO. The cost of INO has forced many clinicians in the United States to reconsider their indications for this therapy and may have had the unexpected effect of rekindling interest and promoting research into alternative inhaled pulmonary vasodilators. Based on the evidence to date, it would appear that other selective pulmonary vasodilators may be as effective as INO with less potential for toxicity, significantly lower costs, and greater ease of administration. Further research is required to determine whether these agents have any advantage over INO in terms of altering pulmonary pathology and patient outcome.

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