Aerosolized Prostacyclins

Mark Siobal RRT

Two prostacyclins (prostaglandin E_1 and prostaglandin I_2) are potent vasodilators. Aerosolized prostacyclins reduce pulmonary artery pressure, improve right heart function, and increase arterial oxygenation by improving ventilation/perfusion matching. This report describes aerosolized prostacyclins and compares them to inhaled nitric oxide. I review the types of inhalable prostacyclins and their indications, evidence of efficacy, delivery, and adverse effects. *Key words: aerosol, prostacyclin, prostaglandin, pulmonary hypertension, ventricular function, acute respiratory distress syndrome, ARDS, inhaled nitric oxide, nebulizer.* [Respir Care 2004;49(6):640–652.

Introduction

Inhaled vasodilators can reduce pulmonary artery pressure and redistribute pulmonary blood flow to ventilated lung regions, with little or no systemic hemodynamic effect.[1] The potential benefits of such targeted pulmonary vasodilation include reduced pulmonary vascular resistance (PVR), reduced right ventricular afterload, improved right-heart function, better ventilation/perfusion ($\dot{V}/\dot{Q}$) matching, and improved arterial oxygenation (Fig. 1).[2]

The utility of inhaled prostacyclins was explored several years before the identification of nitric oxide[3–5] as endothelium-derived relaxing factor.[6] During the 1990s there was extensive research on inhaled nitric oxide (INO) as a vasodilator, in both animals and humans. INO significantly reduces the need for extracorporeal membrane oxygenation among near-term neonates who require mechanical ventilation, and so INO was approved by the Food and Drug Administration (FDA) for treatment of persistent pulmonary hypertension and hypoxemia.

In December 2000 San Francisco General Hospital's pharmacy and therapeutics committee added INO to the

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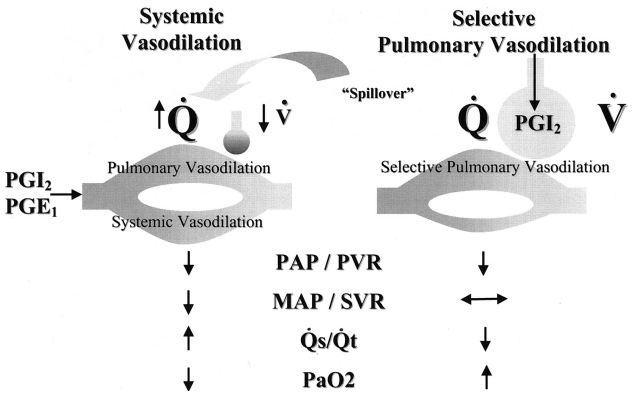

Fig. 1. Effects of systemic vasodilation (from intravenous administration) versus selective pulmonary vasodilation (from inhaled administration) of prostacyclins (prostaglandin E_1 [PGE_1] and prostaglandin I_2 [PGI_2]). Systemic vasodilation affects all vascular beds, thereby decreasing mean arterial blood pressure and worsening oxygenation by increasing blood flow to poorly ventilated alveoli. Inhaled vasodilators selectively dilate pulmonary capillaries in alveoli that are well ventilated, thus reducing pulmonary artery pressure while improving ventilation/perfusion matching and oxygenation. However, "spillover" of inhaled drug to poorly ventilated alveoli and into the systemic circulation worsens shunt fraction and systemic hemodynamics. $\dot{Q}$ = perfusion. $\dot{V}$ = ventilation. MAP = mean arterial pressure. PAP = pulmonary artery pressure. PVR = pulmonary vascular resistance. SVR = systemic vascular resistance. $\dot{Q}s/\dot{Q}t$ = shunt fraction.

hospital's drug formulary for the FDA-approved use in infants. Nonapproved and "off label" use of INO was prohibited because of its high cost and because it does not benefit outcomes in adults.[7] At the request of the departments of anesthesia, pulmonary critical care, and respiratory care services, the pharmacy and therapeutics committee also added aerosolized prostacyclin (prostaglandin I_2 [PGI_2], brand name Flolan) to the hospital's drug formulary, based on evidence that inhaled prostacyclin benefits pulmonary hypertension, right-heart failure, and hypoxemic respiratory failure. We then developed a delivery system for aerosolized prostacyclin that allows easy dose calculation and adjustment,[8] perioperatively, intraoperatively, and in the intensive care unit.

The present review describes the inhalable prostacyclins (PGI_2 and prostaglandin E_1 [PGE_1]) and their potential benefits for pulmonary hypertension, right-heart failure, and hypoxemia from acute respiratory distress syndrome (ARDS). I will also discuss the prostacyclins' potential benefits in decreasing platelet-aggregation and compare PGI_2 and INO with regard to duration of action, adverse effects, toxicology, methods of delivery during mechanical ventilation, problems associated with continuous aerosolization, and efficacy.

Prostacyclins Available for Aerosolization

Prostaglandin I_2

PGI_2 is a naturally occurring prostaglandin, a potent vasodilator, and an effective inhibitor of platelet aggregation, with an in vivo half-life of approximately 3–6 min. PGI_2 is FDA-approved for pulmonary hypertension via continuous intravenous infusion. PGI_2 must be reconstituted with a specific sterile diluent. Once reconstituted it is stable for 8 hours at room temperature, for 48 hours with refrigeration, and must be discarded after those time limits. The reconstituted solution of PGI_2 has a pH of 10.2–10.8 and is increasingly unstable at a lower pH. PGI_2 is photosensitive and must be protected from direct sunlight.[9]

Walmrath et al[10] were first to publish data that directly compared the short-term use of aerosolized PGI_2 to INO in 16 mechanically ventilated ARDS patients. PGI_2 and INO were individually titrated in random order to maximize arterial oxygenation. Both aerosolized PGI_2 (at 7.5 ± 2.5 ng/kg/min, range 1.5–34 ng/kg/min) and INO (at 17.8 ± 2.7 ppm, range 2–40 ppm) improved oxygenation, reduced pulmonary shunt fraction ($\dot{Q}s/\dot{Q}t$), and lowered pulmonary artery pressure and PVR, with similar efficacy profiles (Fig. 2).

Iloprost

Iloprost, a stable analogue of PGI_2, is soluble in saline and has a plasma half-life of 20–30 min.[11] Inhaled iloprost, INO, and inhaled PGI_2 have similar pulmonary and hemodynamic effects in treating pulmonary hypertension.[12–14] Hoeper et al[14] evaluated the short-term use of

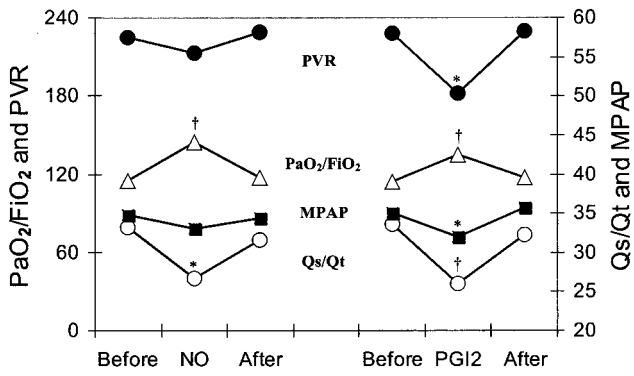

Fig. 2. Comparison of aerosolized prostacyclin (prostaglandin I_2 [PGI_2]) (7.5 ± 2.5 ng/kg/min) and inhaled nitric oxide (NO) (17.8 ± 2.7 ppm) titrated to maximum oxygenation improvement in 16 patients with acute respiratory distress syndrome. PVR = pulmonary vascular resistance. P_{aO_2}/F_{IO_2} = ratio of P_{aO_2} to fraction of inspired oxygen ratio. MPAP = mean pulmonary artery pressure. $\dot{Q}s/\dot{Q}t$ = shunt fraction. * $p < 0.05$. † $p < 0.001$. (Adapted from Reference 10.)

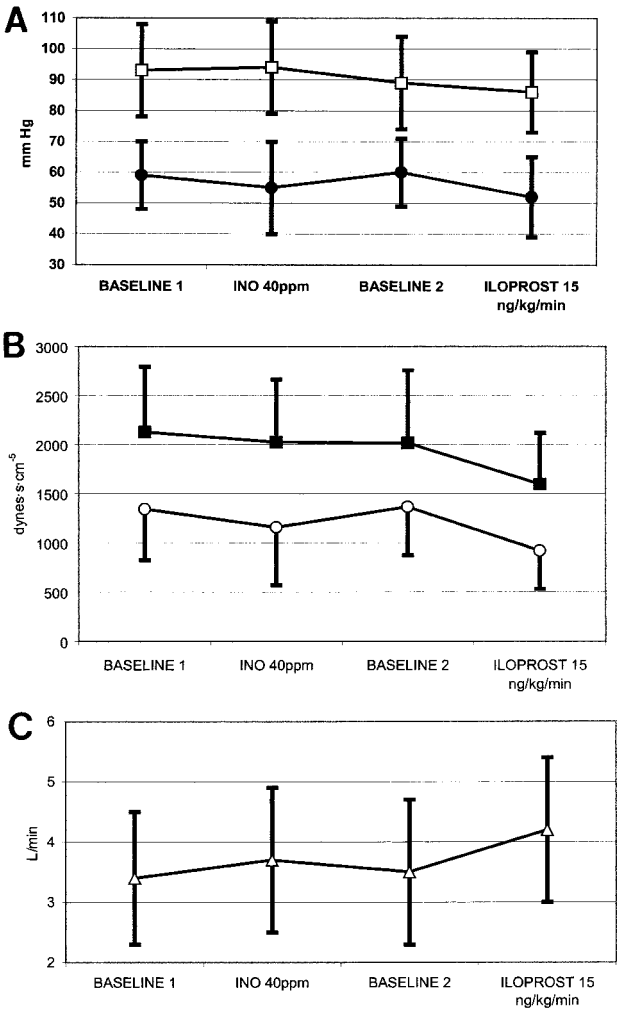

Fig. 3. Comparison of the effects of inhaled nitric oxide (INO at 40 ppm for 15 min) and a single dose of aerosolized iloprost (14–17 μg over 15 min, approximately 15 ng/kg/min) in 35 patients with primary pulmonary hypertension. Values are mean ± SD: A: Mean systemic arterial pressure (open squares) and pulmonary artery pressure (closed circles). B: Systemic vascular resistance (closed squares) and pulmonary vascular resistance (open circles). C: Cardiac output. (Adapted from Reference 14.)

INO (at 40 ppm) versus a single dose of aerosolized iloprost (approximately 15 ng/kg/min for 15 min) in 35 patients with severe pulmonary hypertension (mean pulmonary artery pressure 59–60 ± 11 mm Hg). Inhaled iloprost had a greater effect in decreasing mean pulmonary artery pressure and PVR and increasing cardiac output and P_{aO_2}. However, inhaled iloprost significantly reduced both mean systemic arterial pressure and systemic vascular resistance (SVR) (Fig. 3), whereas INO did not. That effect on systemic vasomotor tone is presumably due to spillover into the systemic circulation, which is directly related to the longer duration of action (up to 2 h),[12–14] which makes intermittent aerosolized iloprost a potential treatment for chronic pulmonary hypertension in ambulatory patients.[15]

In Europe inhaled iloprost has been studied in a large randomized, placebo-controlled trial,[16] 2 small randomized comparisons to INO,[17,18] several other observational studies,[19–21] and case reports.[22–25] Unfortunately, iloprost is not available in the United States.

Prostaglandin E_1

PGE_1 (generic name alprostadil, brand name Prostin VR Pediatric) is another naturally occurring prostaglandin; it causes vasodilation, inhibits platelet aggregation, and stimulates intestinal and uterine smooth muscle. Intravenous PGE_1 is used in neonates with congenital heart defects to maintain the patency of the ductus arteriosus until corrective surgery can be performed.[26] When administered intravenously PGE_1 is rapidly distributed and metabolized, has an estimated half-life of 5–10 min, and 70–80% of it is removed via the pulmonary vascular bed with a single pass through the lungs. Ampules (1 mL) of PGE_1 must be stored refrigerated. Contact of undiluted solution with the plastic sidewalls of volumetric infusion chambers must be avoided. PGE_1 diluted with saline or dextrose must be discarded after 24 hours.[27] Published reports of experience with inhaled PGE_1 is limited. In animals inhaled PGE_1 appeared to be less effective in reducing pulmonary hypertension during pharmacologically induced pulmonary vasoconstriction than was inhaled PGI_2 or INO.[28,29] In 10 adult ARDS patients INO and both intravenous and aerosolized PGE_1 decreased mean pulmonary artery pressure and PVR and increased right-ventricular ejection fraction.[30] With PGE_1 inhalation requires a smaller mean dose than intravenous infusion (10 ± 1 vs 12 ± 2 ng/kg/min) for a similar effect in lowering pulmonary artery pressure. However, in contrast to inhaled PGE_1 and INO, intravenous infusion of PGE_1 causes systemic vasodilation, which lowers mean systemic arterial pressure and SVR and worsens arterial oxygenation and $\dot{Q}s/\dot{Q}t$ (Fig. 4).

Indications and Evidence for Aerosolized Prostacyclin

The indications for use of aerosolized prostacyclins parallel the indications for INO, which include treatment of primary and secondary pulmonary hypertension, cardiac-surgery-associated pulmonary hypertension and right-ventricle failure, lung-transplantation-related reperfusion injury, liver transplantation that results in portopulmonary hypertension, hypoxemia due to single-lung ventilation or ARDS, and sickle cell disease.[31,32] In numerous case reports and observational trials aerosolized prostacyclins have been effective for all of the above indications,[1,12–25,30,33–39] though not for sickle-cell related vaso-occlusive crisis (acute chest syndrome).

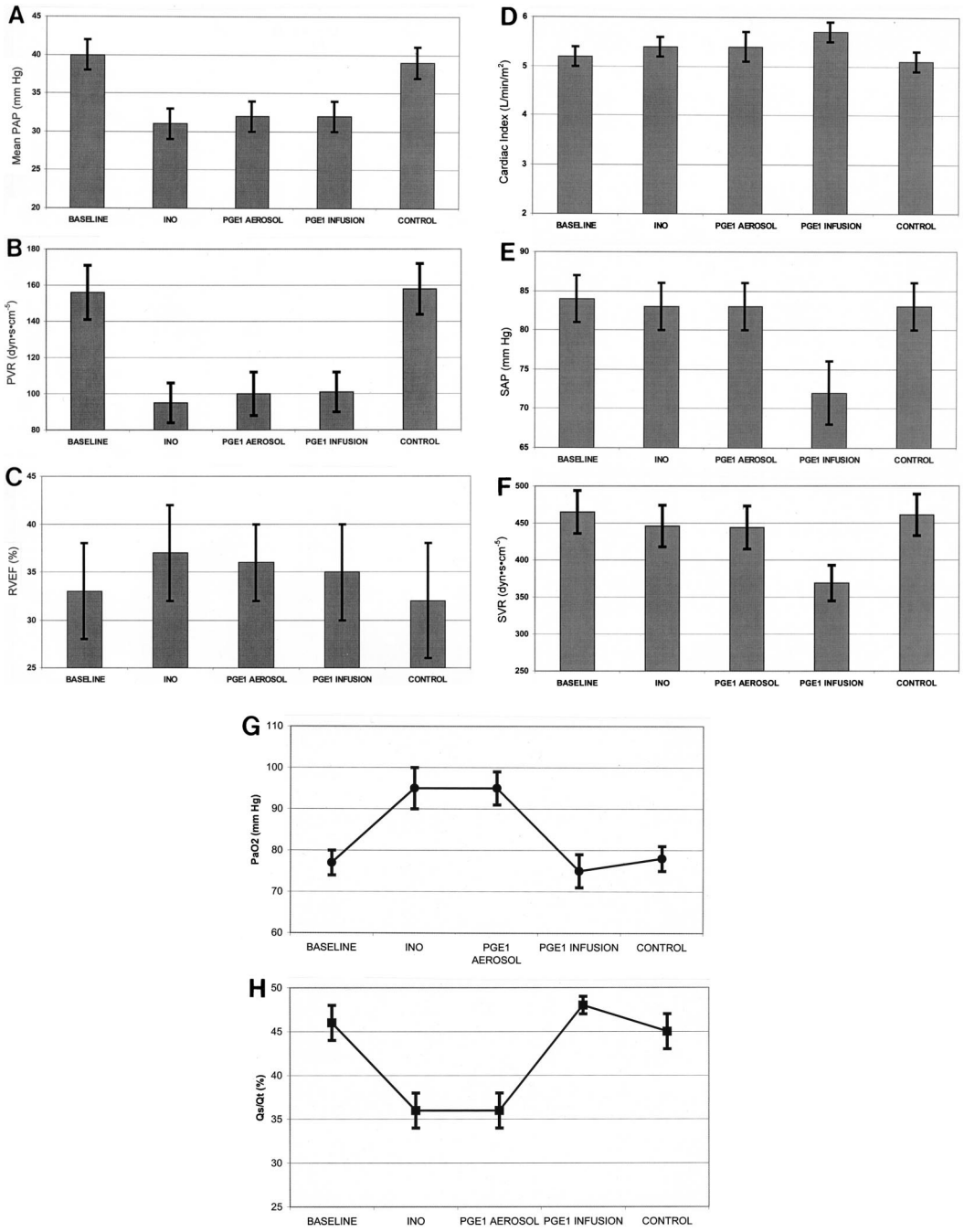

Fig. 4. Hemodynamic and oxygen gas exchange variables during inhalation of aerosolized PGE_1 (10 ± 1 ng/kg/min) and inhaled nitric oxide (INO at 7 ± 1 ppm) in 10 adult patients with acute respiratory distress syndrome. A: Mean pulmonary artery pressure (PAP). B: Pulmonary vascular resistance (PVR). C: Right-ventricular ejection fraction (RVEF). D: Cardiac index. E: Systemic arterial pressure (SAP). F: Systemic vascular resistance (SVR). G: P_{aO_2}. H: Pulmonary shunt fraction (Qs/Qt). Panels E through H show the systemic hemodynamics and oxygenation effects of the nonselective vasodilation caused by intravenous infusion of PGE_1. (Data adapted from Reference 30.)

Pulmonary Hypertension

Inhaled vasodilators benefit acute and chronic pulmonary hypertension.[1,33,40] Hache et al[33] retrospectively reviewed 37 patients who received inhaled PGI_2 over a 1-year period. Twenty-two patients received aerosol boluses, 4 received continuous aerosolization, 9 received a combination of aerosol boluses and continuous aerosolization, 1 received aerosol treatment via face mask prior to intubation, and 1 received direct intratracheal boluses prior to

nebulization. Of the 27 patients who had pulmonary artery pressure monitoring, there was a significant decrease in mean pulmonary artery pressure, from 34.9 ± 11.8 to 32.1 ± 11.8 mm Hg ($p = 0.0017$), and the best response was 27.5 ± 11.1 mm Hg ($p < 0{,}0001$).

Oslchewski et al[12] tested the short-term effects of 15 min of INO (at 10–28 ppm), PGI_2 (53–115 ng/kg/min), and iloprost (9–22 ng/kg/min) based on an estimated average ideal body weight of 65 kg in 6 patients suffering severe pulmonary hypertension. PGI_2 and its long-acting analog, iloprost, had identical efficacy profiles. PGI_2 lowered pulmonary artery pressure 18%, whereas INO lowered pulmonary artery pressure only 10%; PGI_2 lowered PVR 41%, whereas PGI_2 lowered PVR 28%. Ten minutes of aerosolized PGI_2 (10 μg/mL) was also compared to INO (40 ppm) in evaluating heart-transplant patients who were suffering elevated pulmonary artery pressure and PVR.[34] Inhaled PGI_2 and INO both reduced mean pulmonary artery pressure 7%. PGI_2 lowered PVR 49%, whereas INO lowered pulmonary artery pressure 43%. PGI_2 increased cardiac output 11%, whereas INO caused no change in cardiac output.

Aerosolized prostacyclins have been used with pre-term and term infants and with older pediatric patients who had pulmonary hypertension from prematurity, meconium aspiration, and congenital heart disease.[25,41,42] In those case reports inhaled PGI_2 and iloprost used intraoperatively or in the intensive care unit reduced pulmonary artery pressure and improved oxygenation. Kelly et al[43] used inhaled PGI_2 to treat 4 hypoxemic term infants who had persistent pulmonary hypertension refractory to INO and found improvements in both P_{aO_2} (57 ± 6 to 100 ± 27 mm Hg, $p = 0.06$) and oxygenation index (29 ± 5 to 19 ± 7, $p < 0.05$).

The development of pulmonary hypertension in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass predicts higher mortality, perioperative myocardial infarction, and stroke.[44] The benefits of intraoperative and perioperative inhaled vasodilators to treat pulmonary hypertension is well documented in the anesthesia literature.[33,35,40] Five patients treated intraoperatively with aerosolized PGI_2 (calculated average dose 35 ng/kg/min) during surgery had a small but significant decrease in pulmonary artery pressure (7%, $p < 0.03$) and a 35% reduction in PVR ($p < 0.004$).[35] Lowsen et al[36] used a dose of 50 ng/kg/min of inhaled PGI_2 and reported pulmonary artery pressure reductions of 44% and 31% during 2 attempts to wean a patient from cardiopulmonary bypass following mitral and aortic valve replacement. Because of the technical complexity, cost, and potential toxicity of INO, inhaled PGI_2 is an effective alternative inhalable vasodilator for perioperative, intraoperative, and intensive care use.

Right Ventricular Failure

The pulmonary circulation is normally a low-pressure, low-resistance circuit that is highly distensible with recruitable vessels that can accommodate large increases in cardiac output. Acutely or chronically elevated pulmonary artery pressure increases PVR and right-ventricle afterload (the resistance the right ventricle pumps against) and results in a progressive inability of the right ventricle to sustain its flow output (decreased right ventricular stroke volume and right-ventricular ejection fraction). This eventually leads to elevated right-ventricle end-diastolic volume, right-ventricle hypertrophy, right-ventricle failure,[40] and in extreme cases can lead to left-ventricular pump failure in critically ill patients[45,46] and higher mortality.[47–50] Current state-of-the-art pulmonary-artery catheters allow continuous monitoring of right-ventricular ejection fraction, right-ventricle end-diastolic volume, and cardiac output,[51–53] and thus allow close monitoring of the effects of inhaled pulmonary vasodilators on RV function.

Reducing right-ventricle afterload by decreasing PVR and pulmonary artery pressure is an important goal in the management of acute right-heart failure.[32,35,54,55] Case reports by Schroeder et al[35] demonstrate the effectiveness of inhaled PGI_2 for altering right-ventricle function in cardiopulmonary patients. Patients treated with aerosolized PGI_2 (calculated average dose 35 ng/kg/min) for right-ventricle failure during cardiac and abdominal surgery had a 26% increase in cardiac index ($p < 0.003$) and a 35% decrease in PVR ($p < 0.004$). With 9 patients suffering pulmonary hypertension and right-ventricle failure, Haraldsson et al[56] studied the effects of inhaled PGI_2 after cardiac surgery and heart transplantation. Aerosolized PGI_2 (10 μg/mL via continuous nebulization) improved right-ventricle performance and reduced PVR by 29%.

Inhaled PGI_2 is as effective as INO in lowering PVR, pulmonary artery pressure, and right-ventricle afterload. Because PGI_2 has a longer half-life and provides longer vasodilation than INO, it is a more potent inhaled vasodilator for pulmonary hypertension and right-ventricle failure. In dose-comparison trials the pulmonary artery pressure[10,57,58] and PVR[10,34,58] reductions were greater with PGI_2 than with INO (see Figs. 2 and 5).

Acute Respiratory Distress Syndrome

ARDS is characterized by severe hypoxemia from intrapulmonary shunting, areas of low $\dot{V}/\dot{Q}$,[59] and pulmonary hypertension from elevated PVR.[60] Pulmonary hypertension develops early in ARDS,[61] and the primary causes of the pulmonary hypertension are mechanical obstruction of the pulmonary microcirculation by microthromboemboli (composed of platelets and leukocytes) and hypoxic pulmonary vasoconstriction from alveolar and

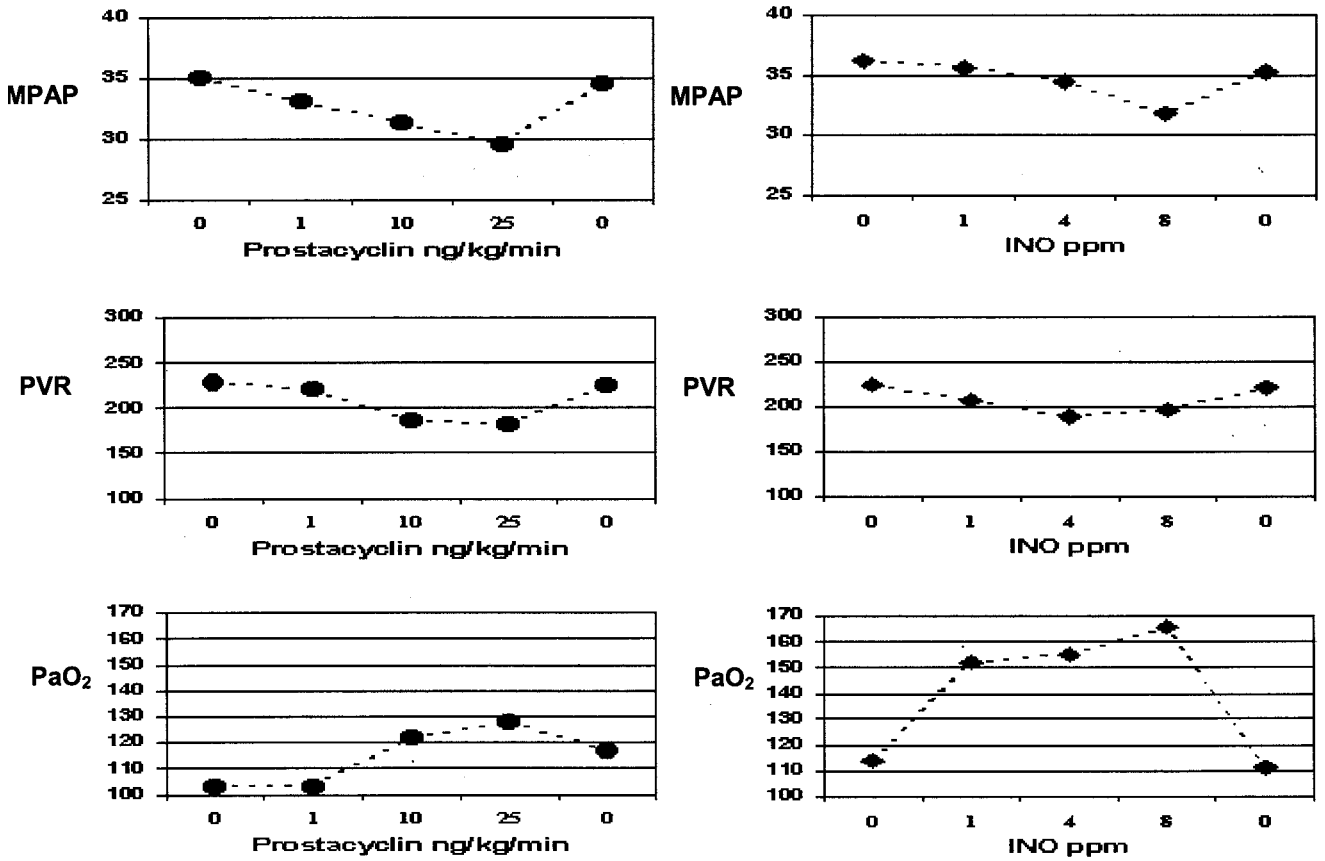

Fig. 5. Dose-response curves comparing the effects of aerosolized prostacyclin (1, 10, and 25 ng/kg/min) and inhaled nitric oxide (INO at 1, 4, and 8 ppm) in 8 patients with acute respiratory distress syndrome. MPAP = mean pulmonary artery pressure. PVR = pulmonary vascular resistance. (Adapted from Reference 58.)

interstitial edema triggered by inflammation mediators.[61–63] Prostacyclin's antithrombotic and platelet-disaggregation effects may help prevent obstruction of pulmonary microcirculation (endarteritis obliterans, inflammation, and fibrous tissue formation of the arterial inner wall) commonly seen postmortem in ARDS patients.[2] Pulmonary hypertension and the consequent right-ventricle dysfunction in ARDS patients predict higher mortality[61–64] and correlate with the severity of lung injury.[61,63–65] Villar et al[64] found that among 225 patients suffering acute respiratory failure, 70 who had hemodynamic or pulmonary instability monitored via pulmonary-artery catheter had higher mortality (79%, 30/38) when pulmonary hypertension was present (mean pulmonary artery pressure 29 ± 6 mm Hg) than those who did not have pulmonary hypertension (44% mortality [14/32], mean pulmonary artery pressure 15 ± 3 mm Hg) ($p < 0.01$). Thirty of the 38 patients who had pulmonary hypertension also met ARDS diagnosis criteria, and their mortality was 70% (21/30). The 21 ARDS patients who died had significantly higher PVR and lower cardiac index than patients who did not die ($p < 0.001$).

Walmrath et al[66] were the first to report the effects of aerosolized PGI_2 for ARDS. In 3 patients with severe ARDS inhaled PGI_2 (at doses between 17 and 50 ng/kg/min) improved the ratio of P_{aO_2} to fraction of inspired oxygen (F_{IO_2}) by 44% (120 ± 19 to 173 ± 18 mm Hg), reduced shunt fraction by improving $\dot{V}/\dot{Q}$ matching, decreased pulmonary artery pressure from 40.3 ± 13.5 to 32.0 ± 3.8 mm Hg, and lowered PVR by 30%.

Van Heerden et al[67] found marked oxygenation improvements and reduced $\dot{Q}s/\dot{Q}t$ in 2 hypoxemic ARDS patients who received aerosolized PGI_2 doses of 50 ng/kg/min. The efficacy of aerosolized PGI_2 versus INO in hypoxemic ARDS patients has been studied in short-term observational trials in pediatric[68] and adult patients.[10,66,67] Both PGI_2 and INO improve oxygenation and reduce $\dot{Q}s/\dot{Q}t$ (see Figs. 2 and 5). Doses as low as 10 ng/kg/min improve oxygenation (Fig. 6).[8,10,68,69] Inhaled prostacyclins cause minimal systemic vasodilation, are anti-inflammatory, and inhibit platelet aggregation,[70,71] so they may be effective against the severe refractory hypoxemia and pulmonary-hypertension-induced right-ventricle dysfunction in severe ARDS.[72,73]

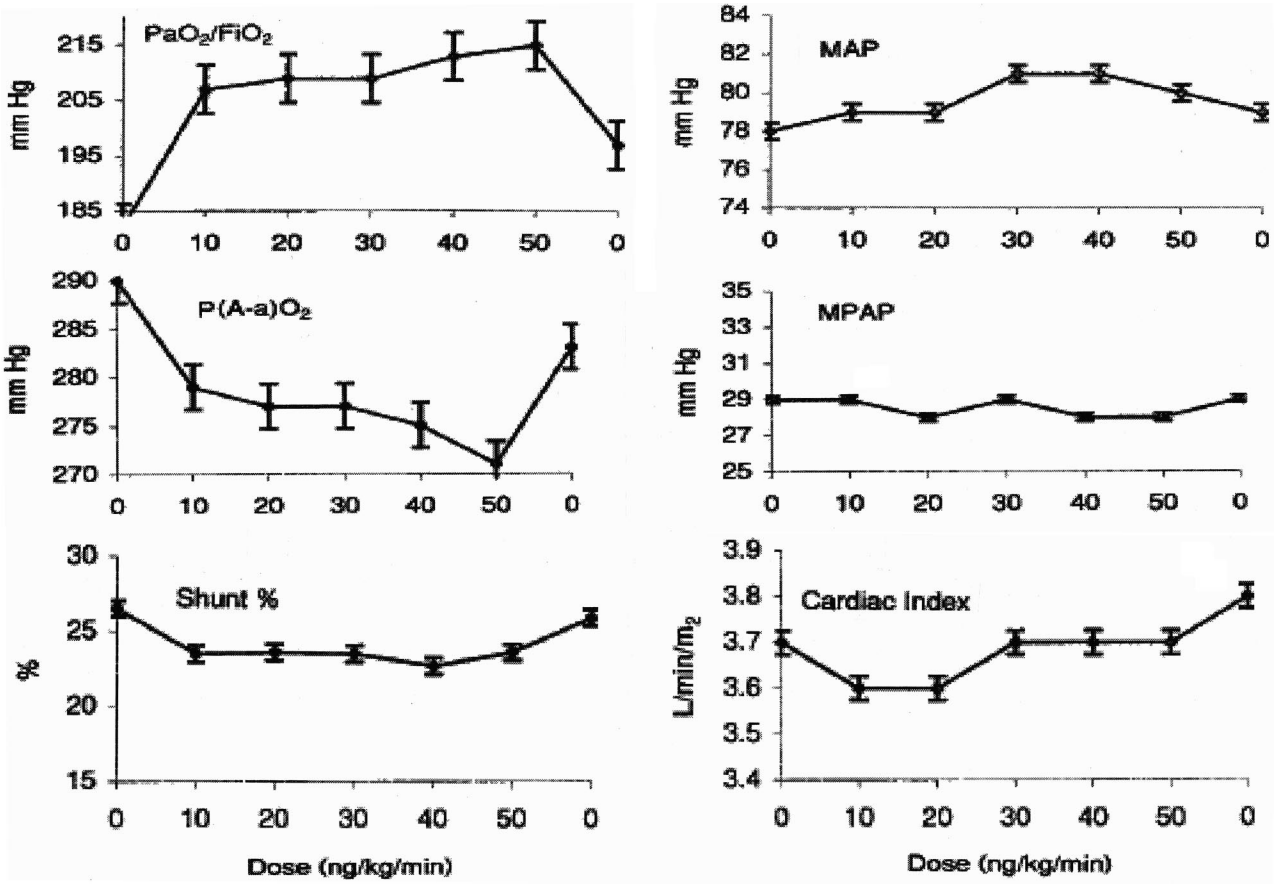

Fig. 6. Dose-response curves showing the effects of aerosolized prostacyclin (at 0, 10, 20, 30, 40, and 50 ng/kg/min) on ratio of P_{aO_2} to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}), mean arterial pressure (MAP), alveolar-arterial oxygen difference ($P_{(A\text{-}a)O_2}$), mean pulmonary artery pressure (MPAP), shunt fraction (shunt %), and cardiac index in 9 patients with hypoxemia due to acute respiratory distress syndrome (ARDS). (From Reference 69, with permission.)

Other Potential Benefits

The longer half-life of PGI_2 and spillover into the systemic circulation were suggested as the cause of the improved splanchnic perfusion observed by Eichelbronner et al.[74] Sixteen patients with pulmonary hypertension and septic shock that required norepinephrine and/or epinephrine to maintain mean arterial pressure $>$ 65 mm Hg were randomized to received INO (19 $\pm$ 10 ppm) or inhaled PGI_2 (18 $\pm$ 9 ng/kg/min) until mean pulmonary artery pressure decreased by 15% (35 $\pm$ 4 to 30 $\pm$ 4, $p < 0.05$, and 34 $\pm$ 4 to 30 $\pm$ 3, $p < 0.05$ respectively). Neither INO nor PGI_2 affected systemic hemodynamics, cardiac index, or right-ventricular function, but PGI_2 nonsignificantly increased the indocyanine-green dye clearance rate (an index of hepatic blood flow) (6.7 to 4.8 min), whereas INO did not. In addition, unlike INO, inhaled PGI_2 significantly increased gastric pH, from 7.26 $\pm$ 0.07 to 7.30 $\pm$ 0.05 ($p < 0.05$) and reduced the arterial-gastric mucosal P_{CO_2} gradient from 19 $\pm$ 6 to 15 $\pm$ 4 ($p < 0.05$), indicating improved splanchnic perfusion. Eichelbronner et al also hypothesized that the PGI_2 platelet-aggregation inhibition, antithrombotic, and anti-inflammatory effects might have contributed to the observed improved splanchnic perfusion.

Prostacyclin also stimulates endothelial release of nitric oxide,[75] which suggests that prostacyclin may have an additive benefit when used in combination with other therapies.[2] This was confirmed in a study by Della Rocca et al,[76] which demonstrated that combined INO and inhaled PGI_2 reduced pulmonary artery pressure and improved P_{aO_2}/F_{IO_2} significantly more than INO alone.

Inhaled prostacyclins have also been administered in combination with both aerosolized and oral phosphodiesterase inhibitors in animal models of pulmonary hypertension[77,78] and in human subjects with severe pulmonary hypertension.[17] Ghofrani et al[17] compared (1) INO (at 20 to 40 ppm), (2) the combination of oral sildenafil (12.5 and 50 mg) and inhaled iloprost, and (3) oral sildenafil alone, in random order, with 30 patients suffering severe pulmo-

nary hypertension (class IV by the classification system of the New York Heart Association). Combining oral sildenafil (both doses) and inhaled iloprost enhanced and prolonged the vasodilatory effect without affecting systemic arterial pressure or oxygenation. Patients who received 50 mg of sildenafil and inhaled iloprost had the greatest reduction in pulmonary vascular resistance, −44.2% compared with −14.1% for INO. The synergistic effect of combining other vasodilators with inhaled prostacyclins may be an effective strategy in treating severe pulmonary hypertension.

Adverse Effects and Toxicity

The potent vasodilation and platelet-aggregation-inhibition effects of PGI_2 make systemic hypotension and bleeding the most important potential adverse effects. The effective dose range established by dose-response trials[10,58,66–69,79–81] is 5–50 ng/kg/min. No systemic hemodynamic effects have been reported with that dose range. Systemic hypotension was reported in one patient when the aerosolized dose exceeded 200 ng/kg/min[37] and in a series of 5 healthy male volunteers who inhaled approximately 700 ng/kg/min.[4] Moreover, hypotension from an overdose of PGI_2 can be rapidly reversed with supportive therapy and discontinuation of PGI_2.[9] Problems with bleeding have not been reported, but it would be reasonable to avoid aerosolized PGI_2 during active pulmonary hemorrhage.

The effect of intrapulmonary and systemic spillover of inhaled PGI_2 may help reduce pulmonary hypertension and improve splanchnic perfusion but simultaneously may adversely effect $\dot{V}/\dot{Q}$ matching, oxygenation, and systemic hemodynamics (see Fig. 1). Among pneumonia patients with and without pulmonary fibrosis, higher doses of aerosolized PGI_2 (33.6 ± 12.0 vs 6.6 ± 3.0 ng/kg/min) were required to reduce mean pulmonary artery pressure in patients who had fibrosis.[81] That higher dose significantly reduced P_{aO_2}/F_{IO_2} (from 73.8 ± 6.6 to 65.5 ± 6.8 mm Hg, $p < 0.05$), increased $\dot{Q}s/\dot{Q}t$ (from 44.7 ± 3.0 to 49.4 ± 5.0%), decreased mean arterial pressure (from 80.3 ± 3.6 to 71.3 ± 4.7 mm Hg, not a significant difference), and reduced SVR (755 ± 120 to 701 ± 115 dyn·s·cm^{-5}, not a significant difference).

In another study, mean arterial pressure and SVR were insignificantly lowered (3.7% and 10.0%, respectively) by aerosolized PGI_2 (compared to INO) in heart transplant patients who had pulmonary hypertension.[34] And in yet another study, intraoperative aerosolized PGI_2 decreased mean arterial pressure by 5.2% and significantly reduced SVR (23.3%).[35] The adverse effects of spillover on $\dot{Q}s/\dot{Q}t$ and systemic vasodilation are probably offset by the improvements in $\dot{V}/\dot{Q}$ matching and right-ventricle function, but clinicians should be aware of this potential effect.

Common adverse effects during initial intravenous administration of PGI_2 are generally related to vasodilation and include (in order of frequency) flushing, headache, nausea, vomiting, hypotension, anxiety, chest pain, and dizziness.[9] The degree and frequency of those adverse effects has not been established and none have been reported from inhaled PGI_2.

As with INO the accidental or intentional abrupt withdrawal of inhaled PGI_2 could cause rebound pulmonary vasoconstriction, acute $\dot{V}/\dot{Q}$ mismatch, hypoxemia, pulmonary hypertension, and right-ventricle failure, though the potential for those adverse effects may be less with aerosolized PGI_2 than with INO, because PGI_2 has a longer half-life and duration of action (20–25 min vs 5 min for INO).[10] The potential for rebound may also be reduced by weaning slowly.

Unlike INO, prostacyclin has no known toxic effects or toxic metabolites. However, reconstituted PGI_2 solution has a very alkaline pH (10.2–10.8)[9] that may act as an irritant when inhaled. Habler et al[82,83] found no evidence of substantial acute pulmonary toxicity, lung tissue damage, or increase in bleeding time in lambs that received doses and volumes of PGI_2 solution equivalent to what would be administered to humans (28 ng/kg/min). Conversely, development of mild acute sterile tracheitis (polymorphonuclear leukocyte infiltration) was observed in piglets that received aerosolized PGI_2 at doses and volumes approximately 9 times the maximum that would be given to an adult human patient.[84] The importance of those findings is unclear, but we have had experience with one patient who received aerosolized PGI_2 via face mask and developed a severe coughing episode during a cardiac catheterization procedure. We have administered aerosolized PGI_2 therapy for as long as 4.8 days to intubated patients[8] and have observed no adverse effects, but we advise caution when administering this extremely alkaline aerosol to patients with reactive airways disease.

Aerosol Delivery Methods

Aerosol administration of drugs is a very inefficient method of delivery in that as little as 3% of the nominal dose deposits in the lungs.[85] Aerosolized PGI_2 therapy requires continuous aerosolization usually during mechanical ventilation over an extended period, from several hours to as long as several days. It is essential to select an appropriate nebulizer and delivery method to promote alveolar deposition and ensure a stable dose administration.

Alveolar deposition is favored when the aerosol particles are in the range of 1–2 μm in diameter.[86] Therefore nebulizers that produce a small median particle size are optimal for aerosolized PGI_2 therapy. Various jet nebulizers, with an average particle size of 3.4 μm (range 2.1–5.2 μm) and an average driving flow of 6 L/min

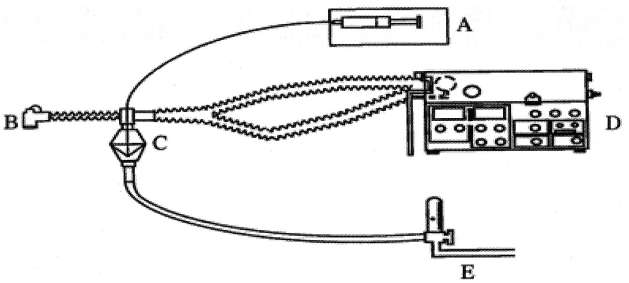

Fig. 7. Syringe pump delivery system for aerosolized prostacyclin. A: Syringe pump with 50-mL syringe of diluted prostacyclin. B: Connector to endotracheal tube. C: Jet nebulizer. D: Ventilator. E: Flow meter for air-oxygen mixture (6 L/min). (From Reference 69, with permission.)

(range 4–12 L/min), can effectively administer aerosolized PGI_2.[10,12,35,38,57,58,66,67,69,81] Delivery via ultrasonic nebulizers with particle sizes of 2.5 μm and 4.0 μm has also been reported.[68,80]

The evaporation of solvent during both jet and ultrasonic nebulization gradually concentrates the drug solution in the nebulizer.[87] Steckel and Eskandar found a greater drug-concentration effect with an ultrasonic nebulizer than with a jet nebulizer (48% vs 13% increase respectively).[88] Ultrasonic nebulization generates heat and the medication may reach 40–55°C,[89–91] which results in higher evaporation and concentration effects. Reconstituted PGI_2 in the specified diluent solution remains stable at room temperature (15–25°C) for 8 hours.[9] It has not been determined whether the heating from ultrasonic nebulization substantially affects the potency of PGI_2. Recent modifications in ultrasonic nebulizer design have reduced aerosol particle size and the evaporative concentration effect,[92,93] and only ultrasonic nebulizers with those operating characteristics should be used for prolonged aerosolized PGI_2 therapy.

Jet nebulizers have several inherent properties that affect dose delivery during prolonged continuous nebulization. Aerosol output and particle size from a jet nebulizer partly depend on the flow rate of the gas powering the nebulizer[94] and the pneumatic pressure during operation.[95,96] Jet nebulizers operating at different flows can have a large range of aerosol volume output and particle size, so there is the potential of large variability in dose delivery.[97] Operating a jet nebulizer from an external flow source alters tidal volume, accuracy of exhaled tidal volume measurement, ventilator circuit pressures, patient-initiated triggering, and F_{IO_2} if an external oxygen blender is not used. Use of a built-in nebulizer-driver function on a ventilator also affects the delivered dose over time,[98] with various ventilation settings, such as respiratory rate and inspiratory time. Variability in the performance of individual nebulizers of the same model and manufacturer can also influence

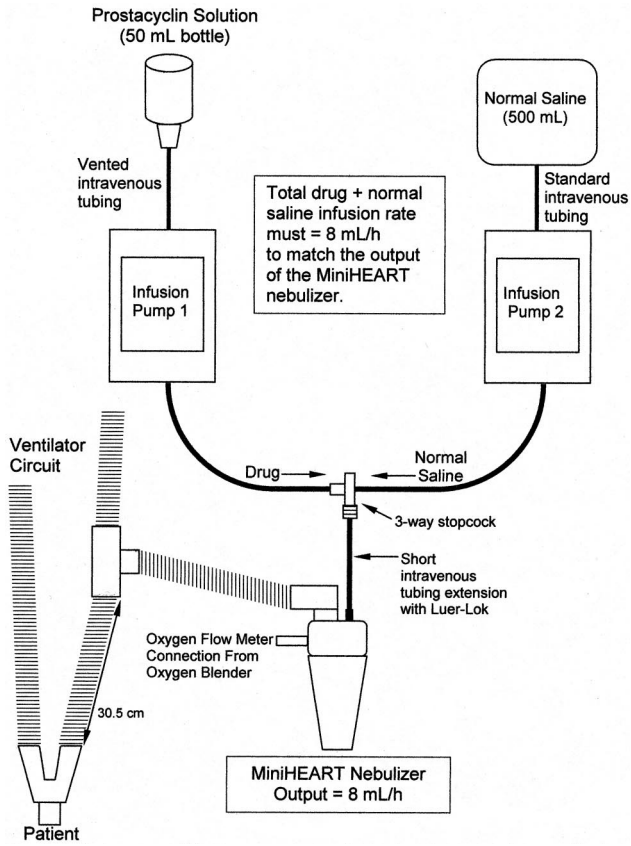

Fig. 8. A delivery system for aerosolized prostacyclin. A drug solution concentration of 30 μg/mL enables administration of dose ranges of 10–50 ng/kg/min to patients with predicted body weights between 40 and 100 kg.

dose delivery.[99,100] Furthermore, during operation the volume loss from a jet nebulizer is the sum of the aerosol produced plus the evaporative loss of solvent. Because water vapor does not carry any drug, the amount of drug emitted from a jet nebulizer does not equal the amount calculated based on the volume loss from the nebulizer.[8,96] Therefore, during continuous jet nebulization the initial aerosolized dose is always lower than the intended dose. Solvent evaporation concentrates drug in the nebulizer solution, which alters the delivered dose over time.[8]

Delivery methods for aerosolized PGI_2 therapy have been described vaguely[58,80] and have had restrictive dose titration capability. The delivery system used by Van Heerden et al[57] incorporates a syringe pump and jet nebulizer with 6 L/min flow (Fig. 7). Setting or adjusting dose delivery with that system requires mixing the appropriate drug concentration in the syringe and adjusting the pump infusion rate to obtain the desired dose, based on the patient's body weight. The delivery method we developed at my institution uses a dual infusion pump system with a low-flow (approximately 2 L/min) jet nebulizer that en-

Table 1. Evidence Ranking of Studies Cited in This Report That Support the Use of Aerosolized Prostacyclin for Treating Pulmonary Hypertension and/or Hypoxemia

Evidence Level*	PGI_2 References	PGE_1 References	Iloprost References
I: Large randomized controlled trials	none	none	16
II: Small randomized controlled trials	none	none	none
III: Non-randomized, concurrent cohort controls	none	none	none
IV: Non-randomized, historical controls	10, 13, 34, 57, 58, 74, 80† 12, 38, 56, 66-69, 76, 79, 81	30†	13, 14, 17, 18† 12, 15, 19, 20
V: Case series reports	8, 33, 35–37, 39, 41–43	none	22–25

* Evidence Level I is highest (strongest evidence). Level V is lowest.
PGI_2 = prostaglandin I_2.
PGE_1 = prostaglandin E_1.
† Comparisons to inhaled nitric oxide.
(Adapted from References 102 and 103.)

Table 2. Grades of Recommendation for Aerosolized Prostacyclin

Grade of Recommendation*	Prostacyclin Type
Grade A: Supported by at least 2 Level I investigations	none
Grade B: Supported by at least 1 Level I investigation	iloprost
Grade C: Supported by at least 2 Level II investigations	none
Grade E: Supported by at least 1 Level III investigation	none
Grade F: Supported by Level IV or Level V investigations	PGI_2, PGE_1

* Grade A is highest (strongest evidence). Grade F is lowest.
PGI_2 = prostaglandin I_2.
PGE_1 = prostaglandin E_1.
(Adapted from Reference 105.)

ables the administration of a wide range of doses and dose titrations over a wide range of patient body weights, using a single drug solution concentration (Fig. 8).[8]

Certain new (and currently available) electronic nebulizers do not generate heat but do produce a constant volume output of small aerosol particles, without an external flow source.[101] That eliminates interference with ventilator function and the problems associated with solvent evaporation and dose variability. Unfortunately, these new nebulizers are designed for intermittent use and are not FDA approved for continuous nebulization.

Efficacy of Aerosolized Prostacyclin

Examination of the hierarchy of evidence in the studies cited in this report, using standard methodology,[102–104] reveals primarily low levels of supporting evidence for aerosolized prostacyclins (Table 1). The efficacy of aerosolized iloprost is supported by one large, randomized, placebo-controlled trial of the treatment of severe pulmonary hypertension.[16] In the established hierarchy of evidence-grading[105] the evidence supporting aerosolized iloprost qualifies for a grade B recommendation (Table 2). In contrast, the results from predominately short-term, uncontrolled studies of aerosolized PGI_2 and PGE_1 merit only a grade F (the lowest) recommendation. A recent Cochrane Review of prostacyclin for pulmonary hypertension[106] recognized the potential benefit of aerosolized iloprost, compared to other treatments, but the efficacy of aerosolized PGI_2 and PGE_1 was not assessed.

The evidence is clear that inhaled prostacyclins have effects similar to INO in improving oxygenation in ARDS and reducing pulmonary hypertension.[10,13,14,17,18,30,34,57,58,74,80] Also, similar to INO, only around 60% of patients respond to aerosolized PGI_2.[8,10,79] Numerous early trials of INO for hypoxemia and pulmonary hypertension in ARDS also looked promising, but 4 level-1 randomized, controlled clinical studies failed to show positive differences in important patient outcomes.[107] However, the similarities of prostacyclins and INO should not disqualify prostacyclin as a treatment option. Randomized, controlled trials are needed to determine the efficacy of inhaled prostacyclin.

Summary

Prostacyclins are potent vasodilators, they inhibit platelet aggregation, and they are anti-inflammatory. Aerosolized prostacyclins reduce pulmonary artery pressure, improve right-heart function, and increase arterial oxygenation by improving $\dot{V}/\dot{Q}$ matching. Their longer duration of action and spillover into the systemic circulation may prove to have additional benefits over other inhaled vasodilators. There are no known serious toxic effects or toxic metabolites associated with aerosolized prostacyclins. Current nebulizers that are designed for continuous aerosol generation suffer variable dose delivery. The efficacy of aerosolized prostacyclin therapy has not been proven in large, randomized, controlled studies.

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