Pulmonary Vasodilators

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Summary

Pulmonary vasodilators are an important treatment for pulmonary arterial hypertension. They reduce pulmonary artery pressure; improve hemodynamic function; alter ventilation/perfusion matching in the lungs; and improve functional quality of life, exercise tolerance, and survival in patients with severe pulmonary arterial hypertension. This paper reviews the currently available pulmonary vasodilators and those under development, many of which can be administered via inhalation. I will also give an overview of the clinical pharmacology of, the indications for, and the evidence supporting pulmonary vasodilators, their delivery via inhalation, and potential toxic and adverse effects. *Key words: pulmonary vasodilators, oxygen, calcium channel blockers, nitric oxide, nitric oxide donors, prostacyclins, phosphodiesterase inhibitors, endothelin receptor antagonists*. [Respir Care 2007;52(7):885–899. © 2007 Daedalus Enterprises]

Introduction

Pulmonary arterial hypertension (PAH) can be characterized histopathologically by vasoconstriction, vascular proliferation, and remodeling and narrowing or thrombosis of small pulmonary arteries.[1] If left untreated, these pathological changes result in a progressive rise in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), which eventually leads to right-ventricular failure and early death (Fig. 1). PAH is associated with multiple risks factors and conditions (Table 1). One of the 5 major classifications of PAH is PAH associated with diseases of the respiratory system. Conditions that result in obliteration of the pulmonary vascular bed and/or hypoxemia, alveolar hypoventilation, and

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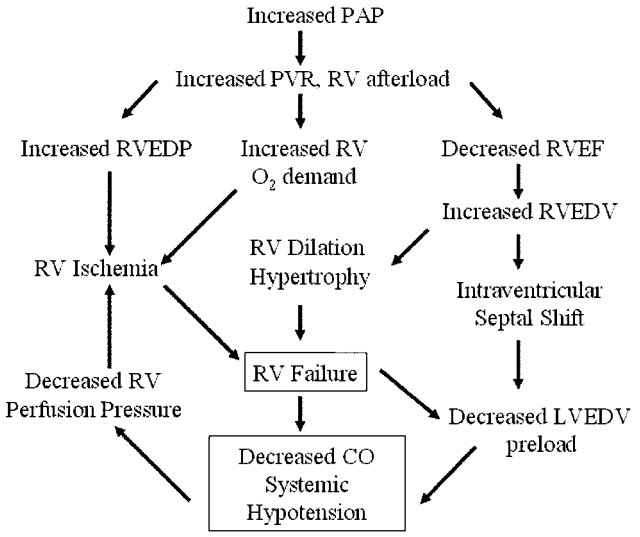

Fig. 1. Pulmonary hypertension results in a "vicious circle" of right-ventricular failure. Acutely or chronically elevated pulmonary arterial pressure (PAP) increases pulmonary vascular resistance (PVR) and right-ventricular (RV) afterload (the resistance the right ventricle pumps against), and results in a progressive inability of the right ventricle to sustain its flow output (decreased RV stroke volume and ejection fraction [RVEF]). This eventually leads to elevated RV end-diastolic volume, hypertrophy, ischemia, and failure. RV hypertrophy and failure decreases left-ventricular preload (the end-diastolic volume prior to left-ventricle contraction), displaces the intraventricular septum, and decreases cardiac output. RVEDP = right-ventricular end-diastolic pressure. RVEDV = right-ventricular end-diastolic volume. LVEDV = left-ventricular end-diastolic pressure. CO = cardiac output. (Adapted from Reference 2.)

Table 1. Pulmonary Hypertension Classification System From the 2003 World Symposium on Pulmonary Hypertension

1. Pulmonary Arterial Hypertension
   - 1.1. Idiopathic pulmonary arterial hypertension
   - 1.2. Familial pulmonary arterial hypertension
   - 1.3. Associated with pulmonary arterial hypertension
     - 1.3.1. Collagen vascular disease
     - 1.3.2. Congenital systemic to pulmonary shunts
     - 1.3.3. Portal hypertension
     - 1.3.4. Human immunodeficiency virus
     - 1.3.5. Drugs and toxins
     - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hemoglobinopathies, hereditary hemorrhagic telangiectasia, myeloproliferative disease, splenectomy)
   - 1.4. Associated with venous or capillary involvement
     - 1.4.1. Pulmonary veno-occlusive disease
     - 1.4.2. Pulmonary capillary hemangiomatosis
   - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary Hypertension With Left Heart Disease
   - 2.1. Left-sided atrial or ventricular heart disease
   - 2.2. Left-sided valvular heart disease
3. Pulmonary Hypertension Associated With Lung Disease and/or Hypoxemia
   - 3.1. Chronic obstructive pulmonary disease
   - 3.2. Interstitial lung disease
   - 3.3. Sleep-disordered breathing
   - 3.4. Alveolar hypoventilation disorders
   - 3.5. Long-term exposure to high altitude
   - 3.6. Developmental abnormalities
4. Pulmonary Hypertension Due to Chronic Thrombotic/Embolic Disease
   - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2. Thromboembolic obstruction of distal pulmonary arteries
   - 4.3. Nonthrombotic pulmonary embolism
5. Miscellaneous; sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

From Reference 1.

hypoxic pulmonary vasoconstriction, such as chronic obstructive pulmonary disease (COPD) and sleep-disordered breathing, are common causes of PAH.

Persistent pulmonary hypertension of the neonate can be associated with a primary developmental defect or as a condition secondary to other diseases such as hyaline membrane disease, meconium aspiration syndrome, pneumonia, sepsis, pulmonary hypoplasia, and congenital diaphragmatic hernia. In these states, PVR is elevated to the point that results in right-to-left shunting of venous blood through patent fetal circulatory channels. This diversion of flow through the ductus arteriosus and foramen ovale into the systemic circulation bypasses the lungs and results in systemic arterial hypoxemia.[3]

Vasodilators that target the pulmonary circulation are administered to neonatal, pediatric, and adult patients in the acute care setting. In the out-patient setting, various agents and delivery routes are used to treat the debilitating functional effects of severe chronic PAH and associated right heart failure. Improved methods of inhaled delivery to selectively target the pulmonary circulation are under development. Treatments for pulmonary hypertension under investigation include therapies based on combined mechanisms of action[1] that can be administered via inhalation. These new treatments are being examined because the definitive treatment for severe PAH, after failure of aggressive medical therapy, is lung transplantation.[1,4,5] If left untreated, the median survival following diagnosis of PAH is 2.8 years.[6]

Systemic Versus Selective Pulmonary Vasodilation

Vasodilators administered systemically are effective in treating PAH, but their clinical usefulness can be limited by their nonselectivity and effects on blood pressure and oxygenation. Systemic vasodilation affects vasomotor tone in all vascular beds, causing both pulmonary and systemic vasodilation. Systemic vasodilation decreases mean arterial blood pressure, and can result in dose-related hypotension. Nonspe-

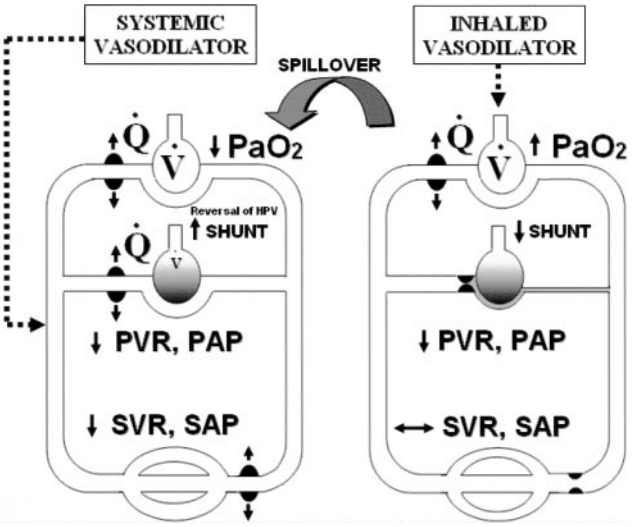

Fig. 2. Effects of systemic vasodilation (from intravenous, subcutaneous, or oral administration) versus selective pulmonary vasodilation (from inhaled administration). Systemic vasodilation affects all vascular beds, thereby decreasing mean arterial blood pressure and worsening oxygenation by increasing blood flow to poorly ventilated alveoli, secondary to reversal of hypoxic pulmonary vasoconstriction. Inhaled vasodilators selectively dilate pulmonary capillaries in alveoli that are well ventilated, thus reducing pulmonary artery pressure (PAP) while improving ventilation/perfusion matching and oxygenation. However, "spillover" of long-acting inhaled drug into poorly ventilated alveoli and into the systemic circulation can worsen shunt fraction and systemic blood pressure. $\dot{Q}$ = perfusion. $\dot{V}$ = ventilation. HPV = hypoxic pulmonary vasoconstriction. PVR = pulmonary vascular resistance. SVR = systemic vascular resistance. SAP = systemic arterial pressure.

cific vasodilation in the lungs can also redistribute pulmonary blood flow to poorly ventilated lung regions, worsening ventilation/perfusion matching and hypoxemia. Administration of vasodilators via inhalation selectively dilates pulmonary capillaries in alveoli that are well-ventilated, thus reducing PAP while improving oxygenation (Fig. 2). Current and developing PAH therapies include inhaled vasodilators for selective pulmonary vasodilation.[1,4,5]

Pulmonary Vasodilators Currently Available or Under Development

Pulmonary vasodilation can be achieved with various agents and routes of administration, through different vasodilator pathways and mechanisms of action in the vascular epithelial and smooth-muscle cells. Conventional PAH therapy includes supplemental oxygen and calcium antagonists. Developing therapies on the horizon include additional long-acting prostacyclin analogues, nitric oxide (NO) donors, phosphodiesterase type 3 and 4 inhibitors, and type-A-specific endothelin receptor antagonists.

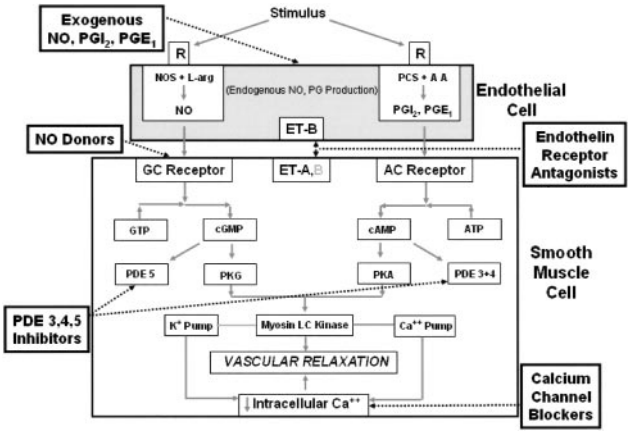

Fig. 3. Pulmonary vasodilator site of action in the endothelial and smooth-muscle cell. NO = nitric oxide. PGI_2 = prostaglandin I-2. PGE_1 = prostaglandin E-1. R = receptor. NOS = nitric oxide synthase. L-arg = L-arginine. PCS = prostacyclin synthase. AA = arachidonic acid. ET-A = endothelin type A receptor. ET-B = endothelin type B receptor. GC = guanylate cyclase. AC = adenylate cyclase. GTP = guanosine triphosphate. cGMP = cyclic guanosine monophosphate. ATP = adenosine triphosphate. cAMP = cyclic adenosine monophosphate. PDE = phosphodiesterase. PKG = protein kinase G. PKA = protein kinase A. LC = light-chain. (Adapted from Reference 2.)

Oxygen

Hypoxemia causes vasoconstriction of the pulmonary vasculature by an important autoregulatory reflex known as hypoxic pulmonary vasoconstriction. Hypoxic pulmonary vasoconstriction is intrinsic to the lung and is modulated by the endothelial and smooth-muscle cells, but the exact mechanism of this effect is unknown.[7] The regulation of pulmonary blood flow by hypoxic pulmonary vasoconstriction contributes to both the efficiency of gas exchange and pulmonary hemodynamics.[8,9] Chronic hypoxia ($P_{aO_2} < 60$ mm Hg or oxyhemoglobin saturation below 90%) may worsen PAH.[10,11] Mean PAP > 20 mm Hg and age > 60 years are prognostic for higher mortality in patients with COPD.[12] Several studies have found a survival benefit from early use of long-term oxygen in COPD patients with PAH.[13,14] In a small uncontrolled trial, the vasodilator effect of oxygen therapy appeared to reverse the progression of PAH in COPD patients.[15] Supplemental oxygen is a recommended core component of conventional therapy for patients with PAH and COPD.[1,4,5,10,16]

Calcium Channel Blockers

Calcium channel blockers inhibit the influx of calcium ions into smooth-muscle cells and therefore cause relaxation and vasodilation (Fig. 3). Calcium channel blockers are a first-line treatment for patients with mild functional impairment from PAH.[1,4,5,10] In patients with an acute response to

a short-acting vasodilator, oral calcium channel blockers can sustain vasodilation over long periods.[17,18] In uncontrolled clinical trials, long-term use of calcium channel blockers (diltiazem and nifedipine) reduced PAP, decreased right-ventricular hypertrophy,[19] and improved survival over a 5-year period, with improvement in symptoms.[17,20] The use of oral calcium channel blockers is limited by their dose-related systemic vasodilator effects, which can cause hypotension, worsening right-ventricular functioning, increased intrapulmonary shunt, and hypoxemia.[21,22]

Aerosolized calcium channel blockers have been studied for their protective properties against bronchial reactivity,[23,24] and they did not cause systemic vasodilation. The possible benefit of selective pulmonary vasodilation from inhaled calcium channel blockers in PAH has not been evaluated.

Nitric Oxide Gas

Endogenous NO is released by endothelial cells when stimulated by acetylcholine.[25–27] Endogenously produced NO is synthesized by the enzyme NO synthase, which combines oxygen with the amino acid L-arginine.[28] NO is synthesized in the lung by the vascular endothelium, epithelial cells, smooth-muscle cells, nerve cells, and in inflammatory cells such as macrophages.[25]

In vascular smooth-muscle cells, NO stimulates soluble guanylate cyclase and converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP). In turn, protein kinases mediate a cGMP-induced decrease in intracellular calcium and produce relaxation and vasodilation (see Fig. 3).[25]

Other important pulmonary and systemic effects of NO include pulmonary vasoconstriction in nonventilated alveoli, bronchodilation, up-regulation of airway ciliary beat frequency, inhibition and stimulation of mucus secretion, inhibition of surfactant activity, antimicrobial actions, inhibition of platelet aggregation, modulation and distribution of systemic blood flow, increased renal output, anticellular proliferation, and complex effects on both pro-inflammatory and anti-inflammatory processes.[25,29,30]

The vasodilator effects of endogenous NO are recognized as an important contributor to the maintenance of normal vascular function and structure.[31–33] Dysfunction of endogenous NO regulation may be an important factor in the pathogenesis of many cardiovascular disorders.[4] Impaired NO production may be particularly important in the normal adaptation of circulation at birth and may contribute to the development of pulmonary hypertension in neonates.[34,35]

NO is also generated by cells of the upper airway, especially in the nose and paranasal sinuses,[36,37] and is inhaled in large enough quantities that oxygenation is affected when the air is inspired through the nose.[38] It has been suggested that bypassing the upper airway with endotracheal intubation eliminates the effect of nasal endogenous NO on regulation of biological functions, including pulmonary circulation, oxygen uptake, and bronchomotor tone.[39–41] Replacing nasal-derived gases into the inspiratory limb of the ventilator circuit affects oxygenation and PVR.[39] The physiological implications of eliminating nasal endogenous NO inhalation in disease states remain to be determined.

Inhaled NO (INO) gas diffuses rapidly across the alveolar-capillary membrane into the vascular smooth muscle and mediates relaxation. The vasodilator effect of INO can decrease PAP and reduce right-ventricular afterload. Improvement in ventilation/perfusion matching and oxygenation occurs in approximately 60% of patients who receive supplemental INO.[42,43] Once in the bloodstream, NO is metabolized within seconds and its duration of effect is only a few minutes.[44] Because of this short duration of action, INO is useful as a screening agent to safely identify responders to oral calcium-channel blockers in primary pulmonary hypertension, by acute vasoreactivity testing during cardiac catheterization.[45]

NO is an environmental pollutant created by the combustion of fossil fuels. NO is also present in tobacco smoke and is produced by lightning. The atmospheric NO concentration is generally 10–500 ppb, but can reach 1.5 ppm in traffic-congested areas.[46] The NO concentration can reach 1,000 ppm in cigarette smoke, from a single 40-mL puff.[47]

The contamination of hospital compressed air with NO is well documented.[48–52] Hospitals that use a compressor reservoir system draw air from the local environment into the compressor for immediate delivery to patients. NO contamination in hospital compressed air was found to vary directly with increases and decreases of the environmental NO level, the time of day, and day of the week.[49,51] Variable NO concentrations in hospital compressed air are unwittingly administered to patients on mechanical ventilation and can reach a level that can cause important physiologic effects on oxygenation,[48,52] PAP, and PVR.[49] It has been suggested that this inadvertent replacement of endogenous NO may interfere with its therapeutic use,[52] may impose a potential confounding variable in the clinical management of patients, and could have influenced the results of past randomized controlled clinical trials.[48] Unintentional NO inhalation may also affect endogenous NO production and may have unknown long-term clinical importance.[48,52]

The delivery system for INO approved by the U.S. Food and Drug Administration (FDA) is well-designed and easy to use, but somewhat complicated. Using the INO delivery system in-line in the circuit during mechanical ventilation requires extensive user training, and a high level of technical support and service is required. INO has also been administered to ambulatory adult and pediatric patients via transtracheal catheter[53] and nasal cannula[54–56] for up to 30 months.[57] Long-term delivery of INO reduces PAP and

PVR,[54–57] improves exercise tolerance and oxygenation,[57] and is effective as a bridge to heart/lung transplantation.[53,57]

INO therapy has several potential toxicities and toxic metabolites. NO is unstable in the presence of oxygen; it undergoes spontaneous oxidation to nitrogen dioxide (NO_2), which is toxic when inhaled.[58] The formation of NO_2 during INO treatment depends on the dose administered, the fraction of inspired oxygen, and the residence time in the delivery system and ventilator circuit.[59] NO_2 exposure as low as 1.5 ppm can increase airway reactivity.[60] High levels of exposure can cause pulmonary edema and death.[61] Following inhalation, NO rapidly diffuses into the bloodstream and reacts with hemoglobin to form methemoglobin. Although uncommon, a significant rise in methemoglobin has been reported in adults and children who received high doses of INO. The enzyme methemoglobin reductase converts methemoglobin back to hemoglobin. Infants and children are more prone to inactivity of methemoglobin reductase and are at greater risk than adults for developing methemoglobinemia during INO therapy. NO toxicity is also caused by its reaction with oxygen species, such as superoxide, which forms peroxynitrite. Peroxynitrite is a potent cytotoxic oxidant and pro-inflammatory mediator that can alter surfactant function.[30] Other reported adverse effects include dose errors associated with misuse of the delivery system, health care worker headaches from environmental NO exposure, hypotension and hypoxemia associated with acute withdrawal of INO, and pulmonary edema in patients with poor left-ventricular function.[62]

INO was the first selective pulmonary vasodilator approved by the FDA. INO is approved for the treatment of term and near-term neonates ($>$ 34 weeks gestation) who require mechanical ventilation and have hypoxic respiratory failure associated with clinical or echocardiographic evidence of persistent pulmonary hypertension of the neonate. In those patients, analysis of several randomized controlled trials found systematically reviewed evidence that INO improves oxygenation and reduces the need for extracorporeal membrane oxygenation but does not reduce mortality.[63]

Studies on the effect of INO to reduce intrapulmonary shunting and improve oxygenation in pre-term infants with hypoxic respiratory failure and patients with acute respiratory distress syndrome (ARDS) had mixed results. A meta-analysis and systematic review of 7 randomized controlled trials in pre-term infants did not reveal a significant effect of INO on mortality, prevention of bronchopulmonary dysplasia, or the risk of intraventricular hemorrhage.[64] This analysis, however, did not include data from 2 more recent studies, which found reduced chronic lung disease and better survival in pre-term infants in the birth-weight range 750–1,250 g.[65,66] The application of INO therapy in hypoxic respiratory failure secondary to ARDS in children[67] and adults[42,43,68–70] demonstrated a transient effect on improving oxygenation but no significant effect on mortality.[71,72]

INO has also gained widespread clinical acceptance as supportive therapy for treating hypoxemia, PAH, and right heart failure in the perioperative, intraoperative, and critical care setting,[73,74] but the impact on reducing mortality has not been demonstrated and is not supported by evidence from randomized controlled trials.[75,76]

Despite the potentially serious toxic effects, the relative risks of INO therapy are small, given proper use of the approved delivery system and recommended dose range. The importance of endogenous NO inhalation, occult NO contamination of hospital compressed air, and the array of complex biological effects of NO need further study to fully understand the benefits and adverse effects. The widespread use of INO therapy is justified by the demonstrated short-term physiologic benefit; however, because of the complexity of administration, the unproven mortality benefit, and the cost of treatment, there are strong incentives to search for alternative pulmonary vasodilators.

Nitric Oxide Donors

NO is released by a number of synthetic agents, either spontaneously or by enzymatic cleavage, that can deliver NO to the site of action in vascular smooth muscle and thus mediate vasodilation. Several available NO donor drugs delivered via inhalation are selective pulmonary vasodilators that are potential alternatives to INO.

Sodium nitroprusside is a potent short-acting vasodilator that is FDA-approved for intravenous treatment of acute hypertensive crisis.[77] Low-dose intravenous sodium nitroprusside causes pulmonary vasodilation and reduces PAP, PVR, and right-ventricular afterload, but is not selective.[78] Achieving pulmonary selectivity by aerosolizing sodium nitroprusside and other NO-donor drugs was first demonstrated in an in vitro animal model of PAH.[79] In intact animals, nebulized sodium nitroprusside reduced PAP[80,81] and improved oxygenation,[81] with no systemic vasodilation. Both INO and inhaled sodium nitroprusside produced significant pulmonary vasodilation without altering systemic hemodynamics in piglets with hypoxia-induced PAH.[82] Inhaled sodium nitroprusside significantly increased oxygenation, without adverse effects, in 60–90% of pre-term and term infants with hypoxic respiratory failure.[83,84]

Potential toxic effects during intravenous administration of sodium nitroprusside include cyanide toxicity and methemoglobinemia, which correspond in severity to higher infusion rate and cumulative exposure. Sodium nitroprusside is also photosensitive and must be protected from light.[77]

Nitroglycerin is another NO donor that has selective pulmonary vasodilation effects when delivered via aerosol.[79,85] In a study of animals with induced hypoxic pulmonary vasoconstriction, inhaled (but not infused) nitroglycerin reduced PAP and PVR; however, both routes of administration decreased systemic blood pressure.[86] In contrast, in patients undergoing mitral valve replacement and in children with congenital heart disease, inhalation of nitroglycerin effectively reduced PAP without systemic vasodilation.[87–89]

Developing tolerance and endothelium dysfunction after prolonged intravenous exposure to nitroglycerin are potential adverse effects,[90] but have not been detected during short-term use for up to 24 hours.[91] Other potential adverse effects include methemoglobinemia at high doses for prolonged periods. Also, nitroglycerin readily migrates into plastics in intravenous administration sets (and possibly nebulizers) and can significantly reduce the delivered dose. Nitroglycerin is also absorbed through skin.[92]

Another class of NO donors agents, NO nucleophile adducts have been studied in animals (via aerosol)[93–96] and in a small, phase I clinical trial in humans with ARDS.[97] The long-term safety and efficacy of NO nucleophile adduct compounds have not been demonstrated.

Given their comparable effects to INO, inhaled NO donor drugs might be an effective, readily available, inexpensive alternative or bridge to INO therapy, especially in areas where INO and extracorporeal membrane oxygenation are inaccessible.

Prostacyclins

Prostacyclins (prostaglandin I-2 and prostaglandin E-1) are naturally occurring prostanoids that are endogenously produced as metabolites of arachidonic acid in the vascular endothelium.[98] In vascular smooth-muscle cells, prostacyclins stimulate soluble adenylate cyclase and convert adenosine triphosphate to cyclic adenosine monophosphate (cAMP). In turn, protein kinases mediate a cAMP-induced decrease in intracellular calcium and produce relaxation and vasodilation (see Fig. 3).[99,100] Prostaglandin I-2 and prostaglandin E-1 are both potent pulmonary vasodilators and inhibitors of platelet aggregation. A relative deficiency of endogenous prostacyclin may be a contributing factor to the pathogenesis of some forms of PAH.[101,102] Clinical studies have focused on the potential benefit of long-term supplementation of exogenous prostaglandin I-2. Several prostacyclin compounds, administrated via different routes, are currently available for the treatment of PAH.

Epoprostenol, a short-acting prostaglandin I-2, is FDA-approved for the treatment of PAH via continuous intravenous infusion in ambulatory patients. In randomized controlled trials, epoprostenol improved hemodynamic function, exercise capacity,[103–105] and survival in patients treated over a 3–18-month treatment period.[106] Problems and adverse effects related to this treatment are due primarily to the requirements of the complicated delivery system and characteristics of the drug. Pain and infection associated with the long-term presence of an indwelling intravenous catheter are common. Other rare but serious adverse events include pneumothorax, deep venous thrombosis, and pulmonary embolus. Additionally, the drug solution needs to be prepared with a special diluent at a specific pH balance, stored and used under refrigerated conditions, and a mechanical pump must be carried by the patient. Furthermore, because of the short half-life (3–6 min), interruptions in epoprostenol therapy related to catheter displacement or pump malfunction may be life-threatening secondary to acute rebound PAH.[107] The development of more stable long-acting compounds with alternative delivery routes has solved some of these problems and improved the prospects of long-term pulmonary vasodilator therapy with prostacyclins.

Aerosolized epoprostenol is an effective alternative to INO in the acute care setting.[2,108] In numerous case reports and observational trials, aerosolized epoprostenol has been effective in treating primary and secondary PAH, cardiac-surgery-associated PAH and right-ventricular failure, lung-transplantation-related reperfusion injury, portopulmonary hypertension following liver transplantation, and hypoxemia due to single-lung ventilation and ARDS.[108] Aerosol systems for epoprostenol include various pneumatic and ultrasonic nebulizers.[109–111] Because of its short half-life, epoprostenol is continuously inhaled at 10–50 ng/kg/min.[109] Although high-level evidence is lacking to support its use, use of aerosolized epoprostenol is justified by the lower cost of treatment, in comparison to INO.

Beraprost sodium is the only orally administered prostacyclin analog used to treat PAH and is taken 4 times a day. Evidence that oral beraprost induces selective pulmonary vasodilation in PAH was first reported in 1996.[112] Several small clinical trials reported functional benefits from reduced PAP, which was associated with lower mortality.[113–116] Subsequently, 2 randomized controlled trials revealed improved exercise capacity and symptoms.[117,118] However, cardiopulmonary hemodynamics and functional classification did not improve significantly,[117] initial benefits were attenuated over time,[118] and drug-related adverse events were common, especially during the initial dose-titration phase. Substantial hypotension, nausea, and vomiting one hour after a single dose, and lasting up to 3 hours, has been reported.[119] Beraprost has pulmonary vasodilating effects comparable to INO, which suggests its potential use during cardiac catheterization.[120] Beraprost sodium has been approved in Japan and South Korea for idiopathic PAH, but currently its development appears to have been stopped in the United States and Europe.[5]

Iloprost is the first prostaglandin I-2 that is FDA-approved for the treatment of PAH via direct pulmonary delivery by aerosol inhalation. Iloprost is a stable prostaglandin I-2 analog, with a half-life of 20–30 min and duration of effect of up to 120 min.[121,122] Dose administration is achieved using a specified breath-actuated nebulizer system.[121] In a randomized controlled trial, inhaled doses of 2.5–5.0 μg administered 6–9 times daily improved functional classification, exercise tolerance, and quality of life.[123] In small clinical trials, a single dose of inhaled iloprost was more potent than INO as a pulmonary vasodilator in adults during acute vasoreactivity testing,[124] and similar effects have been demonstrated in children with congenital heart disease.[125] In a comparison of iloprost and epoprostenol via continuous intravenous infusion, both significantly improved exercise tolerance and right-heart hemodynamics,[126,127] but only inhaled iloprost demonstrated pulmonary selectivity.[127] Intravenous iloprost treatment has also been reported following failure of inhaled iloprost.[128] Periodic doses of inhaled iloprost at 2–3 hour intervals during awake hours was found to be ineffective in 25% of patients during an uncontrolled trial of inhaled iloprost. The majority of these patients were subsequently successfully treated with intravenous iloprost.[129] In 3 patients with severe PAH receiving continuous intravenous epoprostenol, the addition of inhaled iloprost profoundly reduced PAP and PVR, and increased cardiac output, but the effects were brief. All 3 patients failed to transition to inhaled iloprost treatment because of signs of increasing right heart failure, and intravenous epoprostenol was reinstituted.[130] In a more recent uncontrolled study, inhaled iloprost was effective as a primary treatment of PAH in only 42% of patients after 12 months.[131] The remaining patients showed substantial disease progression that required other forms of treatment, including endothelin receptor antagonist, oral and intravenous prostacyclin, or lung transplantation. The authors concluded that, given the presence of multiple treatment options currently available, iloprost inhalation as a single primary therapy may have a limited role in the treatment of chronic PAH.

Treprostinil is a long-acting stable prostaglandin I-2 analog, with a duration of action up to 3 hours, and is FDA approved for subcutaneous infusion. The safety and effectiveness of treprostinil were demonstrated in a several small clinical trials[132,133] and a large randomized controlled trial with 470 patients.[134] Improvement in exercise capacity, improved indices of dyspnea, a reduction in signs and symptoms of pulmonary hypertension, and improved hemodynamics were noted in the patients who received subcutaneous treprostinil. The most common adverse effect was infusion-site pain, in 85% of patients, which led 8% of the patients to withdraw from the study. Three patients in the treprostinil treatment group developed an episode of gastrointestinal hemorrhage, which was attributed to other concomitant therapies. The authors concluded that treprostinil is effective and has an acceptable safety profile in patients with PAH.[134] Treprostinil was also found to pose no additional anti-coagulation risk in patients who received warfarin.[135] In comparison to intravenous epoprostenol, patients transitioned to subcutaneous treprostinil without clinical deterioration; however, infusion-site pain was moderate to severe in 88% of the patients.[136] Compared to epoprostenol, treprostinil has greater stability at room temperature, lacks the preparation and handling restrictions, and obviates the indwelling catheter; however, infusion-site pain is a major complaint with treprostinil.

Aerosolized treprostinil studied in sheep had a greater vasodilator effect, with minimal alterations in systemic hemodynamics, when compared with intravenous treprostinil.[137] In a small clinical trial with 3 patients with severe PAH, a single 15-μg dose of inhaled treprostinil, administered in 3 breaths with a modified ultrasonic nebulizer, was more effective than INO in lowering PAP and PVR. Two of these patients elected to continue the inhaled bolus dosing regimen 4 times daily, on a compassionate use basis. Over 3 months the patients experienced improved functional classification and exercise tolerance, without reported adverse effects.[138]

In a series of randomized controlled pilot studies that included 123 patients, inhaled treprostinil and iloprost provided a comparable decrease in PVR, though treprostinil showed a more sustained response and fewer systemic adverse effects. The effects of treprostinil inhalation were observed for 3 hours with near-maximal acute PVR decrease observed at a dose of 30 μg. Treprostinil inhaled at increasing concentrations from a pulsed ultrasonic nebulizer, so that a dose of 15 μg could be delivered in 1–3 breaths, mimicking a metered-dose inhaler, achieved comparable, sustained pulmonary vasodilation without substantial adverse effects.[139] Inhaled treprostinil is currently undergoing phase III clinical trials.[140] An inhaled liposomal treprostinil formulation[141] that may improve therapeutic response[142] is also undergoing pre-clinical trials.

Alprostadil is a prostaglandin E-1 prostanoid that is FDA-approved for intravenous use in neonates with congenital heart defects to maintain the patency of the ductus arteriosus until corrective surgery can be performed. When administered intravenously, alprostadil is rapidly metabolized, has an estimated half-life of 5–10 min, and up to 80% is removed via the pulmonary vascular bed in a single pass-through.[143] In a comparison with INO, intravenous alprostadil decreased PAP and PVR, and improved right-ventricular ejection fraction, but was not a selective pulmonary vasodilator.[144] A comparison of dose-response characteristics of alprostadil and epoprostenol in infants with pulmonary hypertension found that both were effec-

tive pulmonary vasodilators, but epoprostenol was 6 times more potent.[145]

Aerosolized alprostadil has been reported to improve gas exchange in adults patients with acute lung injury and multiple organ system failure,[146] and in infants with hypoxic respiratory failure.[147] In animals with pharmacologically induced pulmonary vasoconstriction, inhaled alprostadil appeared to be less effective than inhaled epoprostenol or INO in reducing PAH.[148,149] It has been demonstrated that, because of extensive pulmonary metabolism, plasma levels of prostaglandin E-1 do not correlate with increasing inhaled dose or duration of administration. This characteristic may enhance local action in the lungs, offer improved pulmonary selectivity, and limit systemic spillover.[150]

Aerosol delivery of prostacyclins offers the primary advantage of avoiding some of the systemic effects of intravenous, subcutaneous, and oral administration. Direct delivery to the lung for selective pulmonary vasodilation is an appealing and logical approach for long-term prostacyclin therapy. The development of efficient and effective inhaled delivery systems with an acceptable impact on the patient's quality of life may become attractive alternatives to current treatment options. Other potential benefits of inhaled prostacyclins, related to platelet-aggregation inhibition, anti-thrombotic, and anti-inflammatory effects, need further study.[151] The continued use of inhaled prostacyclins in the acute care setting as an effective alternative to INO is justified by the difference in cost.

Phosphodiesterase Inhibitors

Phosphodiesterases are enzymes that inactivate cGMP and cAMP. Use of phosphodiesterase inhibitors to prevent the breakdown of cGMP and cAMP in vascular smooth-muscle cells can augment or prolong the vasodilator signaling pathways of both NO and prostacyclin (see Fig. 3).

Phosphodiesterase type 5 inhibitors prevent the breakdown of cGMP, enhance NO-induced vasodilation, and improve hemodynamic abnormalities of PAH by enhancing endogenous NO effects (via inhibition of cGMP breakdown).[152,153]

Sildenafil, a phosphodiesterase type 5 inhibitor, approved for the treatment of erectile dysfunction, has been shown to be an effective treatment for PAH in several randomized controlled trials in adult patients[154–156] and was approved by the FDA in June 2005 as an oral PAH therapy. Sildenafil was also found to be an effective treatment for infants with persistent pulmonary hypertension of the neonate,[157] and it improved pulmonary hemodynamics and exercise capacity in children with severe PAH.[158] Oral sildenafil was reported to prevent rebound PAH following withdrawal of INO in infants.[159] This effect was demonstrated in a recent randomized trial in infants and children, which also showed a reduction in the duration of mechanical ventilation.[160] In patients with PAH secondary to end-stage COPD and idiopathic pulmonary fibrosis, treatment with oral sildenafil reduced PAP and PVR, and improved exercise tolerance.[161] In patients waiting for heart/lung transplant, the pulmonary vasodilation effects of oral sildenafil were found to be as effective as INO, but more effective when the two were combined.[162]

The short-term hemodynamic profile effects of sildenafil have been compared to other phosphodiesterase type 5 inhibitors, vardenafil and tadalafil, in patients with chronic PAH. Vardenafil showed the most rapid onset, but lacked the pulmonary selectivity of sildenafil and tadalafil. The pulmonary vasodilation response to tadalafil appeared to be the most long-lasting. In contrast with sildenafil, vardenafil and tadalafil did not improve arterial oxygenation.[163]

Phosphodiesterase-3 and phosphodiesterase-4 inhibitors amplify and prolong the effects of prostacyclin-induced increase of smooth-muscle-cell cAMP.[164,165] The phosphodiesterase-3 and phosphodiesterase-4 inhibitor tolafentrine, administered via aerosol, enhances and doubles the duration of effect of inhaled iloprost in rabbits[166] and in patients with severe PAH.[167]

Inhalation of other phosphodiesterase inhibitors also provides selective pulmonary vasodilation. The inhaled phosphodiesterase type 5 inhibitors zaprinast and sildenafil potentiated the effects of INO in lambs with induced PAH.[168,169] Aerosolized milrinone, a phosphodiesterase-3 inhibitor, selectively dilated the pulmonary vasculature in heart-transplant candidates with elevated PAP, without producing systemic adverse effects.[170]

The potential dose-related adverse effects from oral phosphodiesterase inhibitors include headache, flushing, dyspepsia, and hypotension, especially when taken with other antihypertensive vasodilator agents that contain nitrates.[171]

Phosphodiesterase inhibition offers another mechanism for pulmonary vasodilation. The potential additive benefit of phosphodiesterase inhibition when incorporated with other vasodilators is currently under investigation.

Endothelin Receptor Antagonists

Endothelin-1 is a potent modulator of vasoconstriction, trigger of smooth-muscle cell division, cell proliferation, and vascular hypertrophy,[172] which plays an important pathogenic role in the development and progression of PAH.[173] Plasma and pulmonary tissue endothelin-1 are elevated in patients with pulmonary hypertension[174,175] and correlate with disease severity.[176] Two distinct types of endothelin receptor have been identified in the pulmonary vasculature. Endothelin type A receptors are found in pulmonary vascular smooth-muscle cells. Endothelin type B receptors are located primarily in pulmonary vascular endothelial cells, and to a lesser extent in pulmonary vascular smooth-muscle cells (see Fig. 3).[177] Activation of endo-

thelin type A receptors promotes vasoconstriction and cell proliferation. In contrast, activation of endothelin type B receptors in the vascular endothelium stimulates the release of NO and prostacyclin, and mediates the pulmonary clearance of endothelin, whereas in smooth-muscle cells endothelin type B receptor activation stimulates vasoconstriction.[178] This dual effect of endothelin type B receptor activation makes it unclear whether it is preferable to block both endothelin type A and type B receptors or to selectively target the endothelin type A receptor alone, as both types of agent are effective in treating PAH.

Bosentan is an orally administered nonspecific endothelin type A and type B endothelin receptor antagonist that is FDA-approved for the treatment of PAH. In several animal models of PAH,[172,179–181] bosentan prevented and reversed the development of PAH, right-ventricular failure, and pulmonary vascular remodeling. Clinical trials in humans showed that bosentan improves hemodynamic function, exercise tolerance and capacity, and increases the time to clinical worsening.[182–184] Potential toxicities associated with bosentan include abnormal hepatic function, development of anemia, possible teratogenic effects, testicular atrophy, and male infertility.[4] Because of the risks of hepatic toxicity, the FDA requires monthly liver function tests and recommends regular monitoring of hemoglobin and hematocrit,[4] which increases the cost of bosentan treatment.

Sitaxsentan[185,186] and ambrisentan,[187] which are selective endothelin type A receptor antagonists, are undergoing phase III clinical trials and awaiting FDA approval. There are also over 50 other endothelin type A,B or endothelin type A-specific compounds under evaluation in preclinical studies and clinical trials.[178]

Selective pulmonary vasodilation has also been demonstrated by inhaled endothelin receptor antagonist. In animals following surfactant-depleted acute lung injury induced by saline lavage, inhalation of a selective endothelin type A receptor antagonist, LU-135252 (darusentan), at a dose of 0.3 mg/kg, improved oxygenation, reduced shunt fraction, and decreased PAP, without systemic vasodilation, for 4–6 hours.[188,189] In saline-lavaged pigs, both inhaled darusentan (at 0.3 mg/kg) and INO (at 30 ppm) significantly improved gas exchange and prevented an increase in mean PAP, without significant systemic effects, when compared with controls.[190] Inhaled endothelin receptor antagonists may reduce potential systemic toxicities by allowing smaller doses delivered to the target site of action in the lungs.

Endothelin receptor antagonists improve exercise capacity and hemodynamic function in patients with PAH, but the effect on mortality does not currently show a significant benefit from endothelin receptor antagonists. Additional assessment of this outcome in studies with longer follow-up is required.[191]

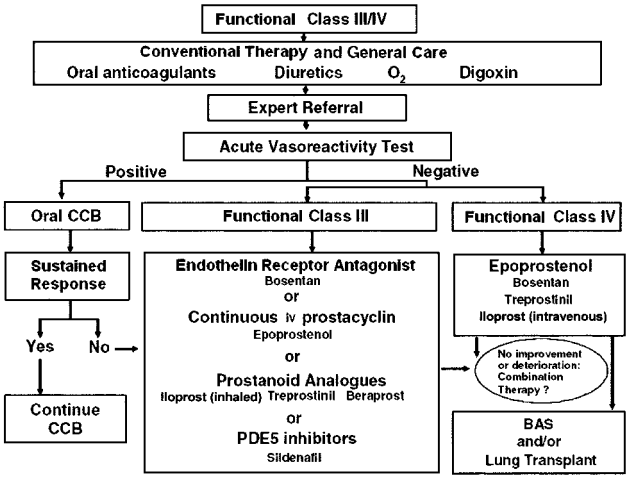

Fig. 4. Evidence-based treatment algorithm recommendations. The algorithm is focused on patients in functional class III (marked limitation of physical activity, no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain or pre-syncope) and class IV (unable to perform any physical activity and who may have signs of right-ventricular failure at rest, dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity). Patients in functional class III and class IV represent the largest population included in controlled clinical trials. Treatments have been evaluated mainly in patients with sporadic idiopathic pulmonary arterial hypertension (PAH), and in pulmonary arterial hypertension associated with scleroderma or anorexigen use. Extrapolation of these recommendations to the other PAH subgroups should be done with caution. It is strongly recommended that consideration be given to referral of patients with PAH to a specialized center. The acute vasoreactivity test should be performed in all patients with PAH. A positive acute response to vasodilators is defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to $\leq$ 40 mm Hg, with an increase or unchanged cardiac output during acute challenge with inhaled nitric oxide, intravenous epoprostenol, or adenosine. Sustained response to calcium channel blockers (CCBs) is defined as the patient improves to functional class I (no limitation of usual physical activity, and ordinary physical activity does not cause increased dyspnea, fatigue, chest pain or pre-syncope), or class II (mild limitation of physical activity, no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain or pre-syncope) with near normal hemodynamics after several months of treatment. In patients in functional class III, first-line therapy may include oral endothelin receptor antagonists, long-term intravenous epoprostenol or prostanoid analogues, or sildenafil. PDE = phosphodiesterase. BAS = balloon atrial septostomy. (Adapted from References 4 and 5.)

Combined Therapies

The availability of pulmonary vasodilators with different mechanisms of action makes combination therapy an attractive option to address the multiple pathophysiological mechanisms in PAH. Combination therapy can be simultaneously initiated treatments or the addition of a second or third treatment to a previously initiated therapy that is insufficient (Fig. 4). Which of these 2 strategies is the

best choice is currently unknown.[5] Prostaglandins may be more effective in conjunction with endothelin receptor antagonists[192–194] or phosphodiesterase inhibitors,[195] and an increasing number of studies are addressing the long-term safety and efficacy of these combinations. The short-term use of phosphodiesterase inhibitors combined with inhaled prostacyclins[167,196,197] and INO[162,198,199] demonstrated synergistic pulmonary vasodilation effects, which suggests that combined treatments may be useful in the acute care setting as well. The growing experience with combined pulmonary vasodilator treatment suggests that different mechanisms of action may produce additive benefit in some patients, or allow use of doses less likely to produce adverse effects.

Implications for Respiratory Therapists

PAH is a condition that respiratory therapists (RTs) will see and treat in patients with chronic lung disease, throughout their professional careers. The lungs act as a resister to blood flow and are situated in the hemodynamic circuit between the right and left sides of the heart. The impact of pulmonary vasodilators on right and left heart function and their potential hemodynamic and pulmonary gas-exchange effects are important concepts for the RT to understand. RTs will be involved in administering inhaled therapy, diagnostic cardiopulmonary testing, and care of patients with PAH in both the acute care and long-term care settings. The expertise of RTs will be needed to assist with the research and development of new treatments and evaluation of aerosol delivery systems for pulmonary vasodilators. The support and knowledge of RTs in the care of patients with PAH will contribute to reducing the incidence of treatment failure and the need for other more aggressive interventions such as extracorporeal membrane oxygenation and lung transplantation.

Summary

The evolution of pulmonary vasodilator therapy in the management of PAH has altered the prognosis and survival of patients with PAH in the last decade. RTs will take on an essential function in the administration of these developing therapies via inhalation. Investigational therapies on the horizon include multi-receptor phosphodiesterase inhibitors, selective endothelin A receptor antagonists, and prostacyclin analogues with alternative delivery routes (eg, inhaled, oral). The future of PAH therapy will probably include combinations of these therapies based on the multiple mechanisms of action. Based on the available evidence, there appear to be several potentially effective combined pulmonary vasodilator therapies. Continued research will be required to determine whether these combined agents have any advantage over currently available treatments in regard to altering patient outcome and costs of treatment.

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