

Inhaled Epoprostenol for the Treatment of Pulmonary Arterial Hypertension in Critically Ill Adults

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Pulmonary arterial hypertension (PAH) is a progressive disease without a cure. The primary treatment goal for patients with this disease is improving pulmonary blood flow through vasodilation of the pulmonary arteries. Several drugs are available that ameliorate walk distance and hemodynamics, but their maximum tolerated doses are limited in critically ill patients with PAH because of systemic vasodilation resulting in hypotension. The ideal vasodilator would be cost-effective, safe, and selective to the pulmonary vasculature; no such agent currently exists. Inhaled nitric oxide selectively reduces pulmonary pressures without systemic hypotension. However, it is expensive, potentially toxic, and requires complex technology for monitoring and administration. Inhaled epoprostenol may be an alternative therapy to minimize systemic hypotension, which often accompanies rapid intravenous titration. To evaluate the safety and efficacy of inhaled epoprostenol in critically ill patients with PAH, we conducted a literature search by using the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases (1966–August 2009) for relevant studies. Case reports and in vitro studies were excluded. Overall, 11 studies met the inclusion criteria. The PAH population included patients requiring cardiac surgery, lung or heart transplantation, or nonspecific intensive care. All trials showed that inhaled epoprostenol significantly decreased pulmonary pressures without lowering systemic blood pressure. The duration of therapy in most studies was 10–15 minutes, with one study evaluating its effects up to an average of 45.6 hours. Pulmonary pressures returned to baseline soon after drug discontinuation. Minimal adverse events were reported. Thus, inhaled epoprostenol in various subgroups of critically ill patients was effective in reducing pulmonary pressures. However, the significance of these effects on improving clinical outcomes remains unknown. Further studies are needed to determine the role of inhaled epoprostenol in critically ill patients with PAH.

Key Words: epoprostenol, inhalation, pulmonary arterial hypertension, PAH, critical illness.

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Pulmonary arterial hypertension (PAH) is a devastating disease characterized by a progressive impairment of the pulmonary vasculature.¹ The

pathogenesis is multifaceted, involving vascular endothelial dysfunction, smooth muscle hypertrophy, and fibrosis.¹ Insight into the pathogenesis of PAH has resulted in the development of drugs to improve survival.² Over the past 2 decades, the median survival has more than doubled with treatment, although a cure remains elusive.^{1,2}

Pulmonary arterial hypertension is a significant problem in patients undergoing cardiac surgery or heart or lung transplantation, as well as in patients in the medical intensive care unit (ICU). Surgery, particularly cardiothoracic, can result in acutely elevated pulmonary artery pressures both during and after the procedures.³ Subtle increases in pulmonary pressures can be particularly detrimental in critically ill patients with preexisting PAH, leading to sudden right ventricular failure, cardiogenic shock, and death.⁴⁻⁶ The rates of mortality and morbidity associated with persistent PAH in these critically ill populations are high.^{3,6} Pulmonary arterial hypertension is a risk factor for both early and late mortality after heart transplantation, with the highest risk occurring immediately after surgery.⁷⁻⁹ The grafted heart's right ventricle may not have the capacity to adapt to the high pulmonary pressures in the immediate postoperative period.¹⁰⁻¹² The magnitude of increased pulmonary pressures is proportional to the increased risk of death for heart transplant recipients.¹³ Although reversible PAH is associated with improved mortality and morbidity rates compared with nonreversible PAH, death rates still remain unacceptably high.^{3,14}

The causes of acute elevations in pulmonary artery pressures are multifactorial. Massive pulmonary embolism, acute lung injury or acute respiratory distress syndrome (ARDS), and septic shock are potential causes for acute pulmonary artery pressure elevations in patients in the ICU.^{5,6} Other factors include hypoxia, hypercarbia, acidosis, anesthesia, and hypervolemia.³ Furthermore, cardiopulmonary bypass (CPB) can lead to PAH in patients undergoing cardiac surgery, as well as in the heart and lung transplant populations.³ In patients with preexisting PAH, serum concentrations of endothelin-1, a

potent vasoconstrictor, are elevated during and after CPB, resulting in further pulmonary vasoconstriction; this has not been observed in patients without PAH.¹⁵ The upregulation and release of several endogenous vasoactive substances during CPB, including epinephrine, norepinephrine, and angiotensin II, may contribute to acute elevations in pulmonary pressures.¹⁶

Treatment of Pulmonary Arterial Hypertension

Medical therapies target the three major pathways identified in the pathogenesis of PAH: prostacyclin, endothelin-1, and nitric oxide.² Seven treatments have been approved by the United States Food and Drug Administration (FDA): prostacyclins (epoprostenol, treprostinil, iloprost), endothelin receptor antagonists (bosentan, ambrisentan), and phosphodiesterase inhibitors (tadalafil, sildenafil).¹ Combination therapy may offer additive or synergistic effects in some patients.¹

Intravenous Epoprostenol

Epoprostenol, a member of the prostaglandin family, was the first FDA-approved therapy for the treatment of PAH. Also referred to as prostaglandin I₂ or prostacyclin, it has vasodilatory, antiinflammatory, antiproliferative, and antithrombotic properties. Soon after its discovery in 1976, epoprostenol was synthesized as a chemical analog of endogenous prostacyclin.¹⁷ Epoprostenol is available as a lyophilized powder requiring reconstitution with an alkaline diluent. It is a highly unstable product with a plasma half-life of about 3 minutes, thus requiring continuous intravenous administration.¹⁷

Patients with PAH have a decreased expression of prostacyclin synthase within the vascular endothelium, resulting in a deficiency of endogenous prostacyclin production.¹⁸ Exogenous administration overcomes this deficiency and induces pulmonary vasodilation. Epoprostenol primarily exerts its effects acting as a prostaglandin I receptor agonist located in the vasculature.¹⁸ Adenylate cyclase activation from prostaglandin I receptor stimulation subsequently increases intracellular cyclic adenosine 3',5'-monophosphate (cAMP) concentrations.¹⁸ Vascular smooth muscle relaxation is the result of cAMP synthesis.¹⁸

Intravenous epoprostenol remains a first-line therapy because of its beneficial effects on exercise capacity, pulmonary hemodynamics, quality of life, and survival.^{19,20} Currently,

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intravenous epoprostenol is the only FDA-approved agent shown to reduce mortality in prospective, randomized clinical trials.^{19, 20} Intravenous epoprostenol has been shown to improve other outcomes as well as to delay the need for lung transplantation.^{19, 20} The long-term benefits with intravenous epoprostenol may be attributed to more than its vasodilating properties, such as its effects on smooth muscle proliferation and apoptosis (i.e., vascular remodeling).²⁰

The management of the critically ill patient with PAH remains a complex and poorly studied problem. The therapeutic challenge in critically ill patients with acute decompensation is to improve right ventricular function by reducing pulmonary pressures, maintaining adequate coronary perfusion as well as cardiac output, while avoiding systemic hypotension.^{6, 21} Intravenous pulmonary vasodilating agents, including epoprostenol, may be problematic during surgery or in the ICU because of systemic vasodilation. Systemic hypotension in these patients decreases right ventricular perfusion leading to further deterioration of right ventricular contractility, intrapulmonary ventilation-perfusion matching, and gas exchange.^{6, 21} Therefore, systemic hypotension frequently limits the dose escalation of these agents before optimal pulmonary pressure reduction occurs.^{6, 21} Unfortunately, published guidelines for the medical management of PAH do not address short-term treatment strategies in critically ill patients.²²

Inhaled Nitric Oxide, Nitroglycerin, and Milrinone

The use of inhaled vasodilating agents may be an option in providing selective pulmonary vasodilation without affecting systemic pressures. The ideal pulmonary vasodilator agent should display several key characteristics. First, it should be selective for the pulmonary circulation without systemic effects.²³ Other aspects to consider would be efficacy, safety, and cost.²³ Also, it should have a rapid onset and be easily titrated.²³ Since this ideal agent does not exist, clinicians have been searching for novel strategies among the available vasodilating agents.

Inhaled nitric oxide is a potent vasodilator selective to the pulmonary vasculature and exerting its effects by stimulating a cascade of pathways leading to relaxation of the vascular smooth muscle.²⁴ It has a short biologic half-life due to rapid inactivation after binding to

hemoglobin in the pulmonary capillaries; therefore, systemic effects are not typically observed.²⁴ Inhaled nitric oxide has been shown to reduce pulmonary vascular resistance (PVR) and intrapulmonary shunting, while improving ventilation-perfusion matching and arterial oxygenation.^{3, 5}

The effects of inhaled nitric oxide make it a feasible option for the short-term management of PAH in critically ill adults. However, inhaled nitric oxide is FDA approved only for the treatment of hypoxic respiratory failure associated with PAH in newborns.³ Unfortunately, the clinical data evaluating its use for PAH as a nondiagnostic agent in the adult population are very limited. This therapy has been shown to reduce pulmonary artery pressures and improve oxygenation in a variety of adult populations with PAH in the ICU (e.g., patients undergoing cardiac surgery, patients with ARDS, heart or lung transplant recipients).²⁵⁻³⁵ It has been successfully used in patients with ARDS and PAH despite its questionable impact on clinical outcomes.³⁴ One study found that inhaled nitric oxide improved cardiac performance in critically ill patients with ARDS associated with PAH, whereas other reports failed to confirm these findings.^{29-32, 36} However, the effects of inhaled nitric oxide on cardiac function may depend on the degree of dysfunction, with better response rates associated with more severe ventricular dysfunction.³

Unfortunately, inhaled nitric oxide has several disadvantages including cost, the development of methemoglobinemia and other toxic metabolites, and the need for dedicated equipment for administration.²³ Another concern is the potential for deterioration of oxygenation and rebound PAH associated with abrupt discontinuation.²³ Although this therapy remains an option for patients with PAH, its potential toxicity, cost, and need for dedicated equipment do not make it an ideal agent.

Other inhaled therapies have also been studied in critically ill adults with PAH. One study evaluated inhaled nitroglycerin in adults with PAH after mitral valve surgery.³⁷ Reductions in pulmonary pressures were found without any systemic effects, including cardiac output and mean arterial pressure (MAP). Another study found similar effects with inhaled milrinone in heart transplant recipients with PAH.³⁸ However, the few studies investigating inhaled milrinone and nitroglycerin are limited by small sample sizes and short duration of administration.^{37, 38}

Although inhaled milrinone and nitroglycerin demonstrated beneficial effects on pulmonary pressures without systemic effects, the paucity of data makes these options less attractive.

Inhaled Epoprostenol

Inhaled epoprostenol may be a feasible option in the short-term management of PAH in patients with acute critical illness. This agent may be a more suitable choice since it has similar efficacy and safety as inhaled nitric oxide without its drawbacks. It has been evaluated in patients in the ICU for treatment of ARDS and severe pneumonia with mixed results for improving gas exchange.^{34, 35, 39-43} Published reports of aerosolized prostacyclin for patients with PAH have increased over the years.⁴⁴⁻⁶⁰ Still, the role of inhaled epoprostenol in critically ill patients remains unknown. Therefore, to evaluate the safety and efficacy of inhaled epoprostenol for the management of PAH in critically ill patients, we conducted a systematic search of the literature

by using the MEDLINE and EMBASE databases and the Cochrane Central Register of Controlled Trials for English-language reports published from 1966–August 2009. The following terms were used in this query: epoprostenol, prostacyclin, prostaglandin, pulmonary hypertension, inhaled, aerosolized, and nebulized.

The overall search strategy was to identify clinical studies that evaluated the use of inhaled epoprostenol in critically ill patients with PAH. Studies meeting the following three criteria were included in this review: the route of administration for epoprostenol was inhalation, the study subjects were treated for PAH in an ICU or surgical setting, and the study was a clinical trial in the adult (≥ 18 yrs) patient population. Case reports were excluded as were studies that reported only in vitro data.

The titles and abstracts of all articles identified from the literature search were reviewed for relevance. Reports potentially meeting the criteria or those whose abstracts were indeterminate were

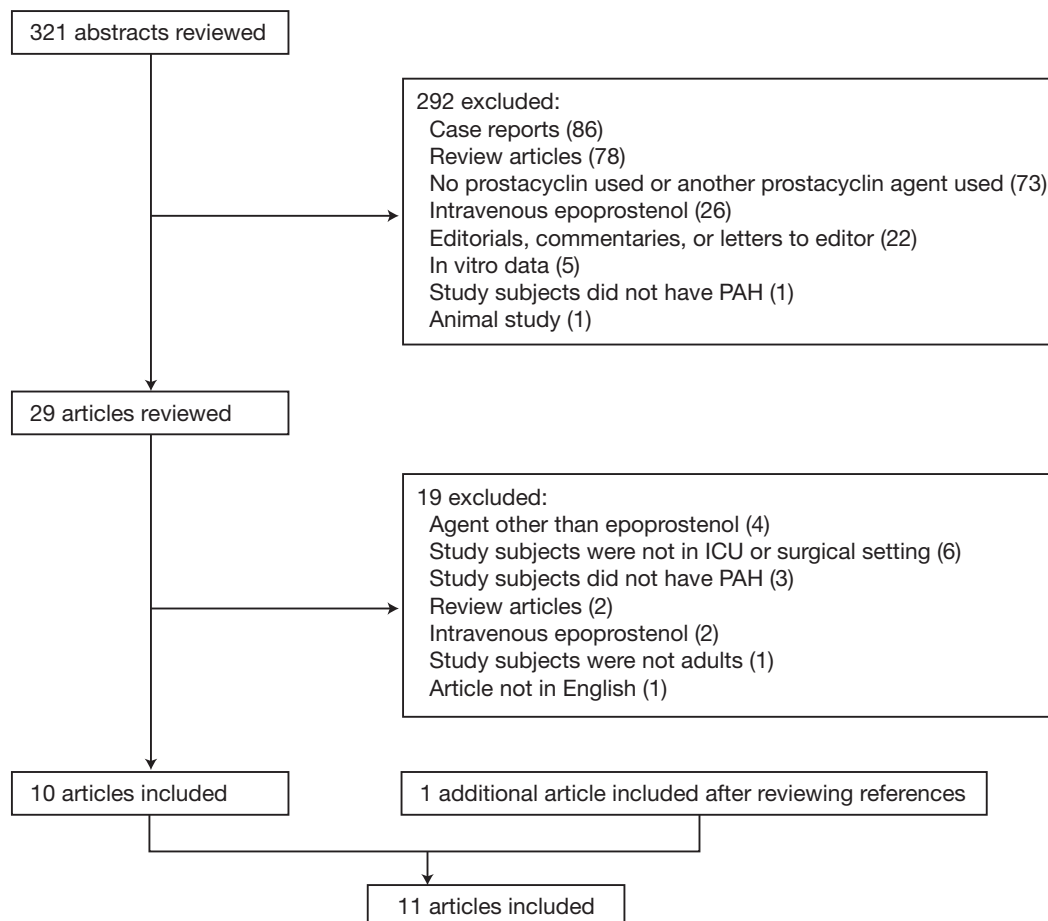


Figure 1. Schematic of the literature search process. PAH = pulmonary arterial hypertension; ICU = intensive care unit.

Table 1. Summary of 11 Studies of Inhaled Epoprostenol in Critically Ill Patients with Pulmonary Arterial Hypertension

Study Design	Population	Inhaled Epoprostenol Regimen
Prospective, dose-response (n=9) ⁴⁴	Cardiac surgery patients (n=7) and orthotopic heart transplant recipients (n=2) with PAH (PVR > 200 dyne•sec/cm ⁵)	2.5, 5, and 10 µg/ml nebulized in ICU after surgery or transplantation and given in 3 consecutive, incremental concentrations of 2.5, 5, and 10 µg/ml over 10 min each
Prospective, open-label (n=11) ⁴⁵	Cardiac surgery patients (n=10) and orthotopic heart transplant recipients (n=1) with PAH (PVR > 200 dyne•sec/cm ⁵ and MPAP > 25 mm Hg)	10 µg/ml nebulized alone and with inhaled milrinone 1 mg/ml over 10 min each after ICU admission after surgery
Prospective, randomized, double-blind, placebo-controlled (n=20) ⁴⁶	Cardiac surgery patients with PAH (SPAP > 30 mm Hg or MPAP > 25 mm Hg)	15 µg/ml (85 ng/kg/min, total dose ~60 µg) nebulized over 10 min after induction during CPB
Prospective, randomized, double-blind (n=58) ⁴⁷	Cardiac surgery patients after MVR and PAH (PVR > 200 dyne•sec/cm ⁵ and/or TPG > 10 mm Hg)	10 µg/ml (~85 ng/kg/min) nebulized over 30 min starting on ICU admission
Prospective, randomized, double-blind (n=58) ⁴⁸	Cardiac surgery patients with MV stenosis and PAH (SPAP > 45 mm Hg or MPAP > 25 mm Hg)	15 µg/ml nebulized before CPB weaning and continued ≥ 60 min; dosage regimen not reported
Prospective, open-label (n=126) ⁴⁹	Cardiothoracic surgery patients with PAH (MPAP ≥ 30 mm Hg or SPAP ≥ 40 mm Hg), RV dysfunction (CVP ≥ 16 mm Hg and CI < 2.2 L/min/m ²) or perioperative refractory hypoxemia (PaO ₂ :FiO ₂ < 150 mm Hg)	20 µg/ml (37 ng/kg/min) weaned by 50% every 2–4 hrs until final concentration of 2.5 µg/ml as tolerated (average duration of therapy 45.6 hrs, range 0.1–390 hrs)
Prospective, open-label (n=12) ⁵⁰	Single or bilateral sequential single lung transplant recipients with PAH ^a	10 µg/ml (10 ng/kg/min) nebulized over 15 min after clamping pulmonary artery during first lung implantation
Prospective, open-label (n=10) ⁵¹	Single or bilateral sequential single lung transplant recipients with PAH ^a	10 µg/ml (10 ng/kg/min) nebulized concomitantly with iNO 20 ppm over 15 min after clamping pulmonary artery during first lung implantation
Prospective, randomized (n=16) ⁵²	Patients with septic shock and PAH in the ICU ^a	10 µg/ml nebulized in incremental doses until 15% ↓ in MPAP and/or maximum dose 40 ng/kg/min (mean dose 18 ± 9 ng/kg/min)
Prospective, open-label (n=8) ⁵³	Patients with PAH in the ICU (MPAP ≥ 30 mm Hg)	5 ng/kg/min nebulized over 15 min ^b
Retrospective medical record review (n=35) ⁵⁴	Patients in operating room (n=2) or ICU (n=33) with PAH (SPAP > 30 mm Hg or MPAP > 25 mm Hg) or hypoxemia	15 µg/ml nebulized as bolus dose (60–120 µg), continuous inhalation (60–210 µg/hr), or combined; timing of initiation and duration not reported

Data are mean ± SD unless otherwise specified.

iEPO = inhaled epoprostenol; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; ICU = intensive care unit; MPAP = mean pulmonary artery pressure; NS = not statistically significant; SvO₂ = mixed venous blood oxygen saturation; PaO₂ = partial pressure of oxygen in arterial blood; SV = stroke volume; CI = cardiac index; SPAP = systolic pulmonary artery pressure; CPB = cardiopulmonary bypass; MVR = mitral valve replacement; TPG = transpulmonary pressure gradient; SVR = systemic vascular resistance; iNO = inhaled nitric oxide; BP = blood pressure; MV = mitral valve; RV = right ventricular; CVP = central venous pressure; PaO₂:FiO₂ = ratio of partial pressure of arterial oxygen: fraction of inspired oxygen; auto-PEEP = auto-positive end-expiratory pressure; QS/QT = intrapulmonary shunt.

^aPulmonary hypertension definition not reported for study inclusion criteria.

^bInhaled epoprostenol concentration not reported.

Table 1. (continued)

Control Regimen	Results	Adverse Events
None	Compared with baseline (39 ± 4 mm Hg), iEPO 5 $\mu\text{g/ml}$ \downarrow MPAP to 36 ± 4 mm Hg and iEPO 10 $\mu\text{g/ml}$ \downarrow MPAP to 32 ± 2 mm Hg ($p < 0.01$); no significant MPAP change with iEPO 2.5 $\mu\text{g/ml}$ (38 ± 3 mm Hg) Compared with baseline (332 ± 38 dyne $\cdot\text{sec/cm}^5$), iEPO 5 $\mu\text{g/ml}$ \downarrow PVR to 253 ± 29 dyne $\cdot\text{sec/cm}^5$ and iEPO 10 $\mu\text{g/ml}$ \downarrow PVR to 236 ± 28 dyne $\cdot\text{sec/cm}^5$ ($p < 0.01$); no significant PVR change with iEPO 2.5 $\mu\text{g/ml}$ (292 ± 37 dyne $\cdot\text{sec/cm}^5$) Compared with baseline (15 ± 2 mm Hg), iEPO 10 $\mu\text{g/ml}$ \downarrow CVP to 13 ± 2 mm Hg ($p < 0.01$); no significant CVP change with iEPO 2.5 $\mu\text{g/ml}$ (14 ± 1 mm Hg) or 5 $\mu\text{g/ml}$ (14 ± 1 mm Hg)	Not reported
None	iEPO alone: \downarrow MPAP (6%) and PVR (20%), \uparrow SvO ₂ and PaO ₂ ($p < 0.05$); iEPO + inhaled milrinone: \downarrow PVR further by 8% compared with iEPO alone ($p < 0.05$); combination \uparrow SV by 5% over iEPO alone ($p < 0.05$); no further \downarrow MPAP with inhaled milrinone; no effect on CI with single or dual therapy ($p = \text{NS}$)	Not reported
Placebo	iEPO \downarrow SPAP from 48.4 ± 18 to 38.9 ± 11.9 mm Hg ($p = 0.002$); no significant change in MPAP (32.9 ± 9.2 vs 28.2 ± 8.2 mm Hg), systemic hemodynamics, oxygenation variables, cardiac performance, or platelet aggregation tests ($p = \text{NS}$)	None
Both iNO 20 ppm and nitroprusside 2.5–25 ng/kg/min i.v. over 30 min on ICU admission	Compared with post-CPB measures, iEPO \downarrow PVR 50%, \downarrow TPG 64%, and \downarrow MPAP 20% ($p < 0.05$); iNO \downarrow PVR 45%, \downarrow TPG 62%, and \downarrow MPAP 19% ($p < 0.05$); nitroprusside \downarrow PVR 45%, \downarrow TPG 44%, and \downarrow MPAP 21%; only nitroprusside \downarrow SVR 51% ($p < 0.05$)	Nitroprusside ($n = 7$) caused \downarrow BP requiring drug “interruption”; iEPO ($n = 2$) was interrupted (reasons not reported)
Two control groups: iNO and i.v. vasodilators	Compared with baseline, both iEPO and iNO \downarrow MPAP, \uparrow CI, \downarrow CPB weaning times, \downarrow intubation times, and \downarrow ICU stay ($p < 0.05$); i.v. vasodilators had no effect on any end points ($p = \text{NS}$)	None
None	Baseline vs iEPO (30–60 min): \downarrow MPAP (36 ± 9 vs 30 ± 8 mm Hg, $p < 0.001$); baseline vs iEPO (4–6 hrs): \downarrow MPAP (36 ± 9 vs 25 ± 8 mm Hg, $p < 0.001$)	Ventilator exhalation valve stuck from “sticky” glycine diluent causing auto-PEEP and hypotension
None	Compared with baseline measurements after induction, iEPO \downarrow MPAP from 55 ± 15 to 49 ± 13 mm Hg ($p < 0.001$), \uparrow PaO ₂ :FiO ₂ , and \downarrow intrapulmonary shunting	Not reported
iNO 20 ppm nebulized over 15 min	Compared with baseline, both iNO only and iNO + iEPO therapy significantly \downarrow MPAP from 57 ± 12 to 53 ± 13 mm Hg and 46 ± 11 mm Hg, respectively ($p < 0.001$); iNO + iEPO combination \downarrow MPAP ($p < 0.05$) and \downarrow QS/QT ($p < 0.001$) compared with iNO alone; only iNO + iEPO significantly \uparrow PaO ₂ :FiO ₂	Not reported
iNO nebulized in incremental doses until 15% \downarrow MPAP and/or maximum dose of 25 ppm (mean dose 19 ± 10 ppm)	Baseline vs iEPO (90 min): \downarrow MPAP (34 ± 4 vs 30 ± 2 mm Hg, $p < 0.05$); baseline vs iNO (90 min): \downarrow MPAP (35 ± 4 vs 30 ± 4 mm Hg, $p < 0.05$); neither drug affected systemic hemodynamics or gas exchange; only iEPO improved splanchnic perfusion	None
None	Baseline vs iEPO: \downarrow MPAP (41.2 ± 6.7 vs 36.1 ± 6 mm Hg, $p < 0.05$); \uparrow PaO ₂ :FiO ₂ ($p < 0.05$)	Not reported
None	iEPO \downarrow MPAP from 34.8 ± 11.8 to 32.1 ± 11.8 mm Hg ($p = 0.0017$)	1 discontinuation due to \uparrow peak pulmonary pressures from nebulizer

obtained for full-article review. The references of the selected articles were also manually searched to identify additional studies.

The literature search strategy yielded 321

citations, of which only 11 studies met inclusion criteria (Figure 1, Table 1).^{44–54} Although several articles were identified as potentially meeting inclusion criteria from cross-referencing articles,

only one additional article was included after a full-article review. Most reports on inhaled epoprostenol were either randomized clinical trials or open-label evaluations. Most of these studies were evaluations without a control comparator. However, a few trials compared inhaled epoprostenol with other inhaled and intravenous therapies, as well as concurrent administration with other nebulized agents.

Populations with Pulmonary Arterial Hypertension

Cardiac Surgery Patients and Heart Transplant Recipients

A dose-response study examined the effects of various concentrations of inhaled epoprostenol after heart transplantation secondary to dilated cardiomyopathy and coronary artery bypass graft (CABG) and/or valve surgery.⁴⁴ All nine patients were administered three concentrations of inhaled epoprostenol in the ICU after surgery. Hemodynamic data and blood sampling were collected at baseline, after each incremental dose study period, as well as 10 and 20 minutes after final cessation of the aerosolized epoprostenol. The investigators found no significant changes in systemic hemodynamics, cardiac performance, or gas exchange with inhaled epoprostenol. The mean pulmonary artery pressure (MPAP) returned to baseline values at 10 and 20 minutes after stopping the inhalation. Similar findings were observed for PVR, with a significant reduction from baseline with the 5- and 10- $\mu\text{g}/\text{ml}$ concentration ($p < 0.01$); PVR did not change with the 2.5- $\mu\text{g}/\text{ml}$ concentration. The PVR continued to be significantly lower 10 minutes after terminating inhaled epoprostenol ($p < 0.01$) but returned to baseline values at the 20-minute follow-up. Also, the central venous pressure (CVP) was significantly lower with the 10- $\mu\text{g}/\text{ml}$ concentration compared with baseline (mean \pm SD 13 ± 2 vs 15 ± 2 mm Hg, $p < 0.01$). However, this significant difference was lost with discontinuation of the drug.

Another trial evaluated the adjunctive use of inhaled epoprostenol in combination with aerosolized milrinone in patients undergoing cardiac surgery.⁴⁵ Being a two-part study, the first phase was a dose-response evaluation of inhaled milrinone, whereas the second portion evaluated inhaled milrinone with concomitantly nebulized epoprostenol. Subjects undergoing CABG and/or valve surgery as well as a heart transplant recipient were included in the second part of this

study. Epoprostenol was nebulized over 10 minutes followed by concomitantly inhaled milrinone with epoprostenol for another 10 minutes. Hemodynamics and blood samples were obtained before study drugs, between single and dual therapy, as well as 20 minutes after the completion of milrinone with concomitant epoprostenol treatment. Inhaled epoprostenol monotherapy significantly decreased pulmonary pressures without any effects on systemic hemodynamics. The MPAP significantly decreased from baseline (35 ± 2 mm Hg) with inhaled epoprostenol and combination therapy (33 ± 2 and 33 ± 2 mm Hg, respectively, $p < 0.05$). Further improvements in other pulmonary hemodynamics did not significantly change with adjunctive milrinone use versus epoprostenol monotherapy. Sustained pulmonary hemodynamic effects from these inhaled therapies were observed at the 20-minute postinhalation measurements compared with the baseline control values.

One study investigated inhaled epoprostenol's effects on hemodynamics, oxygenation, echocardiographic examination, and platelet aggregation.⁴⁶ Five hemodynamic measurements were taken: just before induction of anesthesia, 10 minutes after induction, at the end of the nebulization period, 15 minutes after nebulization, and 25 minutes after nebulization. Blood samples for oxygenation parameters were collected simultaneously with the hemodynamic measurements for the first 4 times without the fifth and final measurement. Echocardiography was performed to assess left and right ventricular performance. Both the transesophageal echocardiography and platelet tests were completed before and after nebulization.

Baseline systolic pulmonary artery pressure (SPAP) and MPAP did not differ significantly between the placebo and epoprostenol groups. Pulmonary pressures returned to baseline 15 and 25 minutes after discontinuing epoprostenol. No significant change in SPAP was found in the placebo group except for the 10-minute post-induction measurement. Heart rate was significantly lower immediately after inhaled epoprostenol than before study drug administration (58.5 ± 11 vs 64.4 ± 8.8 beats/min, $p < 0.002$). Other systemic hemodynamic measurements such as MAP, CVP, and systemic vascular resistance index were not significantly different in either the epoprostenol or placebo groups compared with baseline. However, the epoprostenol group showed a nonsignificant trend of improved right and left ventricular

systolic function.

A prospective, randomized, double-blind study comparing the effects of inhaled epoprostenol with inhaled nitric oxide and intravenous sodium nitroprusside was conducted immediately after mitral valve replacement requiring CPB.⁴⁷ Hemodynamic and oxygenation variables were obtained at four periods throughout the study: before CPB; 30 minutes after CPB; during epoprostenol, inhaled nitric oxide, or nitroprusside therapy; and during the 15-minute control period (after active treatment administration finished). Patients were randomly assigned to one of three treatment groups in almost equal numbers: epoprostenol (18 patients), inhaled nitric oxide (22 patients), and nitroprusside (18 patients). Dosages in all study groups were titrated until a decrease in MAP or PVR occurred.

The investigators found no significant changes in heart rate, MAP, CVP, pulmonary capillary wedge pressure, cardiac output, or systemic vascular resistance with either inhaled epoprostenol or inhaled nitric oxide. The pulmonary pressure effects for all three study drugs are shown in Table 1. Nitroprusside was discontinued in almost 39% of patients because of significant reductions in MAP. The authors mentioned drug therapy was "interrupted" in some patients who were given epoprostenol and nitroprusside. However, it was not clearly stated if the drug therapy was permanently or temporarily discontinued.

These same investigators performed another study to investigate the effects of inhaled epoprostenol, inhaled nitric oxide, and intravenous vasodilating agents (nitroglycerin or nitroprusside) in patients with preoperative PAH undergoing mitral valve and/or tricuspid valve surgery.⁴⁸ Hemodynamic data were chronologically measured at six time periods throughout the study: at baseline before induction, after heparinization just before CPB, during study drug administration just before CPB weaning, after protamine after CPB, after closing the patient's chest, and 2 hours before ICU admission. Unfortunately, the investigators did not disclose the dosing protocol for the three study groups. Inhaled nitric oxide and epoprostenol showed beneficial effects on pulmonary pressures. Increased cardiac index was maintained for both inhaled agents throughout the study except during the fourth measurement period (after protamine). Neither study drug significantly affected heart rate or MAP.

Inhaled epoprostenol was evaluated in patients

with PAH, refractory hypoxemia, or right ventricular dysfunction who were undergoing cardiac surgery.⁴⁹ Although this study did not exclusively include patients with PAH, about 87% of subjects had PAH. This study was the largest of all the cardiothoracic surgery trials investigating inhaled epoprostenol; however, it was the least robust in study design. No significant changes in MAP or cardiac index were found at any time.

Robust study design was a strength in half of these studies.⁴⁶⁻⁴⁸ Another advantage of these trials was the comparison of inhaled epoprostenol's effects on pulmonary and systemic hemodynamics with that of standard therapies (inhaled nitric oxide and intravenous vasodilator agents) in this patient population. Although most of these studies found a significant reduction in pulmonary pressures with inhaled epoprostenol compared with baseline, one study failed to find a significant difference. Whereas inhaled epoprostenol failed to significantly reduce MPAP in this one study, a significant decline in SPAP was observed.⁴⁶ Small sample sizes and MPAP values before study drug administration may have resulted in its ineffectiveness. Baseline MPAP before induction was significantly lower at the 10-minute postinduction measurement (mean \pm SD 41.5 ± 9 vs 32.9 ± 9.2 mm Hg, $p < 0.001$). Overall, the major limitations of these studies were the small sample sizes and heterogeneous patient population. Although most patients underwent cardiac surgery, the surgeries varied from heart transplantation to CABG with or without various valve replacement procedures. Only one study mentioned control of mechanical ventilation and vasoactive agents by keeping settings or the infusion rates constant during the study period.⁴⁵ Failure to control these variables might have produced biased results in the other studies.

Lung Transplant Recipients

One prospective, open-label study evaluated inhaled epoprostenol in patients undergoing lung transplantation without CPB requirement.⁵⁰ Patients were scheduled for lung transplants secondary to cystic fibrosis (seven patients) or severe emphysema (five patients). Although several improvements on pulmonary pressures as well as other clinical end points were noted, no significant differences were found for heart rate, MAP, or cardiac index with inhaled epoprostenol.

Another trial by the same investigators

examined the hemodynamic and oxygenation effects of concomitant inhaled epoprostenol with inhaled nitric oxide in a similar study population.⁵¹ Systemic and pulmonary hemodynamics (e.g., heart rate, MAP, MPAP, and cardiac index) as well as oxygenation variables were collected at three time periods: at baseline (5 min after pulmonary artery clamping), at 15 minutes after administration of inhaled nitric oxide only, and at 15 minutes after adjunctive administration of inhaled nitric oxide and inhaled epoprostenol. Ventilator and vasoactive drug support was maintained constant during data collection phases.

These two studies consistently showed that inhaled epoprostenol lowered pulmonary pressures and improved oxygenation without systemic effects during lung transplantation. Further reductions in MPAP and improving gas exchange were observed when simultaneously administered with inhaled nitric oxide 20 ppm. It should be noted that hemodynamic support during transplantation was controlled with vasoactive and inotropic agents, including intravenous prostaglandin E₁. However, ventilation, cardiovascular drugs, and oxygen support were kept constant during baseline and inhaled epoprostenol hemodynamic measurements so that the effects of inhaled epoprostenol could be evaluated.

Nonspecific Critically Ill Patients

One prospective, randomized trial evaluated the effects of inhaled epoprostenol on hemodynamics and gas exchange in patients in the ICU.⁵² All patients meeting the American College of Chest Physicians–Society of Critical Care Medicine definition of septic shock and requiring vasopressor support were randomly assigned to either the inhaled epoprostenol group or inhaled nitric oxide group. Unfortunately, the investigators did not report details regarding the patients' PAH (acute vs chronic), nor did they specify inclusion criteria relating to pulmonary pressures (e.g., MPAP > 30 mm Hg). Baseline data were collected after a minimum of 90 minutes of a hemodynamically stable condition based on consistent cardiac index, vascular pressures, and arterial blood gases. After another consecutive 90 minutes in a stable condition with inhaled treatment, a second data set was collected. The third and final data measurements were obtained 90 minutes after the inhaled study agents were discontinued. All patients were administered incremental doses of the inhaled

therapies to achieve either a specific reduction from baseline MPAP and/or a predetermined maximum dose. However, the investigators did not disclose the dosage titration regimen for either group.

Baseline systemic and pulmonary hemodynamics as well as gas exchange and blood gas analysis did not differ significantly between the groups. Both epoprostenol and inhaled nitric oxide showed similar responses in lowering MPAP with return to baseline values on discontinuation.

The effects of inhaled epoprostenol on hemodynamics and gas exchange were also studied in patients requiring mechanical ventilation who experienced severe respiratory failure and acute PAH.⁵³ Patients developed acute PAH secondary to hypoxic pulmonary vasoconstriction. Hemodynamic and oxygenation variables were measured before administration, 15 minutes after epoprostenol was started, and 10 minutes after drug discontinuation. Aerosolized epoprostenol was not associated with a significant change in heart rate or systemic blood pressure. These investigators reported that the mean baseline cardiac index of 4.96 L/minute/m² decreased to 4.68 L/minute/m² ($p < 0.05$) during epoprostenol treatment, without any changes in systemic hemodynamics. These significant changes were not observed 10 minutes after discontinuing treatment.

A retrospective medical record review was conducted on the data of 35 patients who received inhaled epoprostenol for PAH or hypoxemia.⁵⁴ This 1-year evaluation of epoprostenol use in the ICU or operating room mostly included patients with hypoxemia; only eight patients had PAH. Inhaled epoprostenol was administered by various methods (bolus, continuous or combined nebulization approaches). Hemodynamics and gas exchange variables were noted before and after the initial treatment as well as the "best response" during inhaled epoprostenol. Only 27 patients (77%) had pulmonary artery pressure monitoring performed.

The results of this retrospective evaluation showed significantly lower MPAP with inhaled epoprostenol. The "best response" in MPAP (i.e., the lowest numeric value at any time during the study) was found to have been significantly reduced to a mean \pm SD of 27.5 \pm 11.1 mm Hg ($p < 0.0001$) compared with baseline. The mean reduction in MPAP was 22%, with most patients (77.8%) showing a decrease in MPAP within 1 hour after starting treatment. The ratio of partial pressure of arterial oxygen:fraction of inspired

oxygen improved from before treatment (108 ± 81) compared with during epoprostenol treatment (138 ± 105 , $p < 0.001$) as well as "best response" (224 ± 134 , $p < 0.0001$). Adverse events were reported in six patients who experienced hypotension; two patients developed subsequent pneumothoraces, and one patient had bronchospasm. Most hypotensive episodes developed before inhaled epoprostenol; however, one event was possibly associated with inhaled epoprostenol.

Although these studies in a nonspecific critically ill patient population showed improvement in pulmonary pressures and oxygenation in most patients, comparison of these findings is difficult due to major inconsistencies in study design, patient populations, and overall medical management. The first study included only patients in the ICU with septic shock and PAH.⁵² The investigators stated that ventilation and cardiovascular agents remained unchanged during study drug inhalation. Unfortunately, the other two studies were dissimilar by not defining septic shock nor did the authors disclose their control over variables (e.g., mechanical ventilation, cardiovascular agents), possibly affecting hemodynamic measurements during study drug evaluation.^{53, 54} The latter study had several significant limitations necessitating commentary.⁵⁴ First, the study design may have introduced bias. These investigators were not able to control for variables affecting pulmonary pressures such as mechanical ventilation, intravenous vasoactive agents, and concomitant inhaled nitric oxide. The timing of hemodynamic measurements as well as the epoprostenol dosage regimens were inconsistent. Finally, the heterogeneous study population is another major concern. This trial did not clearly define a study population with specific inclusion criteria. Rather, the investigators identified patients who were prescribed inhaled epoprostenol within their institution and reported their findings. Therefore, the effects of inhaled epoprostenol on pulmonary pressures could not have been well established in this particular study.

Comparison of Clinical Study Data and Study Limitations

In most of the published studies, inhaled epoprostenol consistently lowered pulmonary pressures. Although the reduction in pulmonary pressures met statistical significance in most of these studies, the clinical significance of this

reduction remains unclear. A dose-related response was observed on reducing pulmonary pressures.⁴⁴ The minimum effective concentration for inhaled epoprostenol was 5 $\mu\text{g}/\text{ml}$, whereas 2.5 $\mu\text{g}/\text{ml}$ was ineffective. Although the MPAP was lower with the 10- $\mu\text{g}/\text{ml}$ compared with the 5- $\mu\text{g}/\text{ml}$ concentration, the authors did not report if this further reduction met statistical significance. Most studies used a concentration of 10 $\mu\text{g}/\text{ml}$.^{44, 45, 47, 50-52} However, the highest concentration studied was 20 $\mu\text{g}/\text{ml}$.⁴⁹

Two studies evaluated the effects of epoprostenol concomitantly nebulized with another agent. The addition of inhaled milrinone was found to have an additive effect on lowering pulmonary pressures.⁴⁵ Stroke volume significantly increased with combination therapy, whereas inhaled epoprostenol alone had no effect.⁴⁵ However, cardiac output remained unchanged with dual therapy.⁴⁵ An additive effect of further lowering pulmonary pressures was also observed with concomitant administration of inhaled nitric oxide with inhaled epoprostenol.⁵¹ Three studies directly compared inhaled epoprostenol against inhaled nitric oxide.^{47, 48, 52} These trials included lung transplant recipients, patients undergoing cardiac surgery, and those with septic shock. All three trials showed that inhaled nitric oxide and inhaled epoprostenol resulted in similar improvements in measured end points.

Small sample sizes, inconsistent and poor study designs, heterogeneous patient populations, and variable dosage regimens limit the conclusions regarding inhaled epoprostenol's safety and efficacy. First, the optimal dosage regimen remains unclear because of inconsistent dose, concentration, and duration of aerosolization, as well as differences in nebulizer characteristics. Most of the studies evaluated inhaled epoprostenol over a short duration (i.e., < 15 min). However, one study examined the drug up to an average of almost 48 hours.⁴⁹ Furthermore, the precise amount of aerosolized drug reaching the alveolar epithelium in mechanical ventilation is less than 10%. Pulmonary deposition is dependent on several factors such as the type of nebulizer used, inhaled flow rate, droplet size, characteristics of the drug, patient factors, humidity and temperature within the nebulizer circuit, as well as the amount of drug remaining in the nebulizer.⁶¹⁻⁶⁴ Most of the studies did not describe the type of nebulizer, flow rate, and mean mass diameter for the droplet particles. Those studies describing nebulizer techniques delivered a mean mass particle diameter less than 5 μm .^{44-47, 52} Although

the most common flow rate used in these studies was 2–3 L/minute, this varied.^{44–49, 54} The glycine buffer diluent used to reconstitute epoprostenol for inhalation is “sticky.” In one study, the investigators changed the ventilator filters every 2 hours to prevent mechanical malfunction.⁴⁹ Despite their efforts, one patient experienced auto-positive end-expiratory pressure and hypotension due to a stuck exhalation valve on the ventilator from the “sticky” diluent. However, no other studies stated such precautions regarding the diluent, nor were any adverse events reported as a result of the diluent.

Another concern is epoprostenol’s effect on platelet function, especially in surgical patients requiring CPB. Although in vitro testing with inhaled epoprostenol showed significant impairment of platelet aggregation, in vivo data did not suggest clinically relevant platelet dysfunction.⁶⁵ Inhaled epoprostenol has not been associated with significant platelet dysfunction in critically ill patients.⁴⁶ Although safety was evaluated in this review, it should be noted that almost half of the included studies did not disclose adverse events. Whereas inhaled epoprostenol did not significantly affect systemic pressures, the overall safe use of this novel technique in delivering epoprostenol remains speculative.

Directions for Future Research

Although inhaled epoprostenol has been shown to reduce pulmonary pressures, further research is warranted. The noncontrolled study design in most of these trials inherently limits the investigators’ abilities to truly evaluate inhaled epoprostenol’s pulmonary and systemic effects. Multiple variables such as intravenous vasoactive agents, sedation, fluids, and mechanical ventilation changes during the study could have affected the results. Therefore, investigators of future studies should attempt to control for these factors. Moving forward, dosage regimens based on patient weight should be standardized and more clearly reported since all studies failed to disclose the weight (e.g., actual vs ideal) used in the dosage regimen. More important, future studies should more clearly define causes and severity of PAH within their study population. The therapeutic response of inhaled epoprostenol may vary based on the severity of chronic disease compared with those patients experiencing an acute elevation of pulmonary pressures without longstanding PAH. Extended duration of use in

patients in the ICU also requires further investigation. Studies should investigate the impact that short-term lowering of MPAP has on clinical outcomes such as improved cardiac function, ICU length of stay, survival rates, and safety.

Conclusion

The success over the past 20 years in the long-term management of PAH has resulted in more patients surviving long enough to develop other acute medical problems; however, the short-term treatment of PAH in the ICU remains a challenge. Inhaled therapies, particularly inhaled epoprostenol, may be a practical option in select critically ill patients intolerant to intravenous pulmonary vasoactive agents; however, limited data exist on the benefits and risks in critically ill patients. Relatively low cost, lack of dedicated administration equipment, and minimal toxicity favor further investigation of inhaled epoprostenol for the management of critically ill patients with PAH.

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