DOI: 10.1002/pul2.12396

CASE REPORT

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

# Severe bronchospasm and acute respiratory failure associated with inhaled prostacyclin therapy

**Donna Steinbacher**[1] | **Brian Murray**[2] | **Thomas Devlin**[3] | **Shannon S. Carson**[4] | **H. James Ford**[5]

[1]Department of Pharmacy, University of North Carolina Health, Chapel Hill, North Carolina, USA

[2]Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado, USA

[3]Department of Respiratory Therapy, University of North Carolina Health, Chapel Hill, North Carolina, USA

[4]University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

[5]Pulmonary Hypertension Program, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

**Correspondence**
Donna Steinbacher, Department of Pharmacy, University of North Carolina Health, Chapel Hill, NC 27514, USA.
Email: Donna.Steinbacher@unchealth.unc.edu

**Funding information**
None

**Abstract**

Prostacyclin therapy is a mainstay of the management of pulmonary arterial hypertension (PAH). Inhaled prostacyclins present safe and effective options for the management of PAH that limit systemic side effects. We describe the first reported case of life-threatening bronchospasm and acute respiratory failure associated with inhaled prostacyclin administration.

**KEYWORDS**

epoprostenol, pulmonary hypertension, treprostinil

## CASE DESCRIPTION

A 33-year-old African American male with past medical history of congenital heart disease, bronchopulmonary dysplasia complicated by severe obstructive airway disease (FEV1 22.4% predicted), and pulmonary hypertension (Groups 1 and 3, mean pulmonary artery pressure 37 mmHg, pulmonary arterial wedge pressure 12 mmHg, pulmonary vascular resistance 4.8 Wood units) on 3 L oxygen by nasal cannula at baseline presented with hypoxemia, shortness of breath (SOB), and productive cough. His medication list included budesonide-formoterol, ipratropium-albuterol, furosemide 100 mg daily, sildenafil 20 mg 3 times daily, and nebulized inhaled treprostinil 9 breaths (54 mcg) 4 times daily initiated 2 years prior. Both sildenafil and inhaled treprostinil were self-discontinued by the patient 4 months prior due to SOB. Work-up revealed a dilated right ventricle with low-normal systolic function, abnormal septal motion due to right ventricular volume and pressure overload, and elevated tricuspid regurgitant jet velocity on echocardiogram. A chest radiograph on presentation was concerning for acute pneumonia.

The patient was managed for exacerbation of obstructive lung disease, pneumonia, fluid overload, and decompensated pulmonary hypertension with bronchodilators, corticosteroids, antibiotics, and diuretics. Nebulized inhaled iloprost was initiated at 2.5 mcg nine times daily on day 2 of hospitalization and titrated to 5 mcg nine times daily on day 5, with plans to transition to inhaled treprostinil dry powder inhaler (DPI) before discharge. On day 11 of hospitalization, the first dose of treprostinil DPI was administered. Within 10 s of receiving the dose, the patient endorsed SOB that

progressed to cardiopulmonary arrest. He received 12 min of cardiopulmonary resuscitation (CPR) and emergent intubation. An arterial blood gas at the time revealed pH 6.95, $PaCO_2 > 100$ mmHg, and $PaO_2$ 161 mmHg on 1.0 FiO2. Once intubated, peak inspiratory pressure (PIP) was measured from 50 to 60 $cmH_2O$, raising concern for airway obstruction related to bronchospasm. Inhaled epoprostenol via Aerogen® Solo nebulizer in line with the ventilator circuit was initiated to replace the longer-acting inhaled prostacyclin therapy during invasive mechanical ventilation. Overnight, PIP was elevated to 62 $cmH_2O$ (plateau pressure 42 $cmH_2O$, autoPEEP 24 $cmH_2O$) with minimal response to ventilator maneuvers.

Over the next 2 days, PIP remained elevated (50 to 60 $cmH_2O$) despite adequate sedation, corticosteroids, aggressive bronchodilators, a trial of heliox, and ventilator maneuvers. Pressure control ventilation was not attempted given consideration of variable airway narrowing, the potential impact on delivered tidal volumes, and the need to maintain adequate ventilation. Extracorporeal membrane oxygenation support was discussed but not pursued while conventional ventilation measures were deemed sufficient. On day 13 a chest radiograph demonstrated interval development of pneumomediastinum with extensive subcutaneous emphysema. A subsequent cardiopulmonary arrest in the ensuing hours raised clinical suspicion for development of pneumothorax causing cardiac tamponade. Two rounds of CPR and a needle decompression were performed with return of spontaneous circulation, and bilateral surgical chest tubes were emergently placed. Around this time, a nebulizer malfunction caused a temporary pause in inhaled epoprostenol administration. PIP was noted to be 30 $cmH_2O$ at that time (Figure 1), and inhaled epoprostenol was re-initiated. PIP returned to elevated levels (55 $cmH_2O$, autoPEEP 27 $cmH_2O$) until inhaled epoprostenol was finally paused on the evening of day 13, with PIP immediately decreasing to 20 to 30 $cmH_2O$ with autoPEEP 8 $cmH_2O$ (Figure 1). Ventilator mode, target tidal volumes, and positive end expiratory pressure were unchanged during this time. After discontinuation of inhaled epoprostenol therapy, airway pressures returned to normal levels and remained so for the remainder of

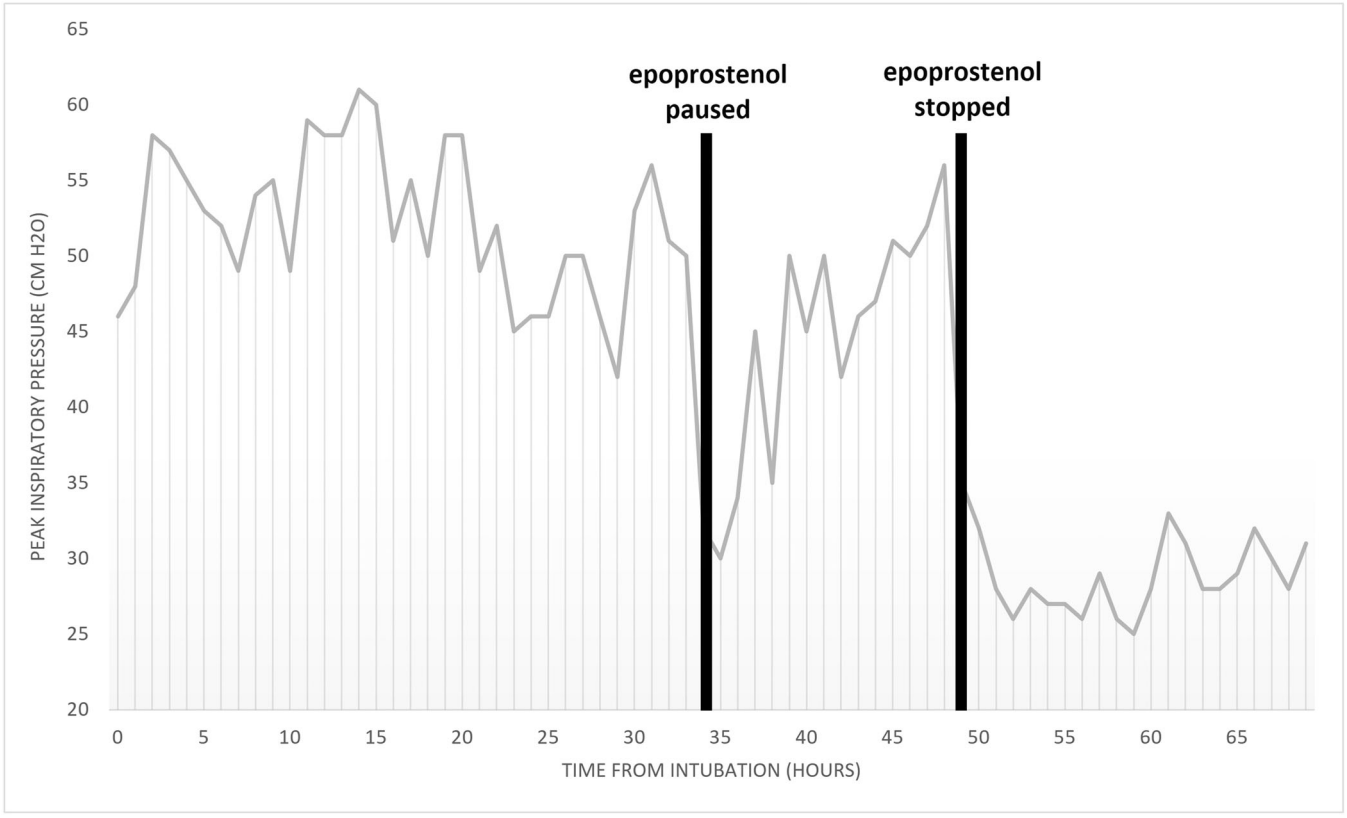


**FIGURE 1** Peak inspiratory pressure over time after initiation of invasive mechanical ventilation. After intubation, the patient experienced elevated peak inspiratory pressures consistent with airway obstruction. These pressures were not responsive to aggressive medical management with corticosteroids and bronchodilators. Peak airway pressures decreased during a brief pause in inhaled epoprostenol administration and increased upon re-initiation. Immediately after discontinuation of inhaled prostacyclin therapy, peak inspiratory pressures returned to normal and remained so throughout the remainder of the hospital stay.

the hospitalization. The patient was discharged to a long-term acute care hospital with a tracheostomy on day 63 of hospitalization, and was decannulated several days later.

## DISCUSSION

Pulmonary arterial hypertension is a progressive disease characterized by poor outcomes, and prostacyclin analogues are a mainstay of therapy.[1] Inhaled prostacyclins deliver medication directly to the lung, limiting systemic side-effects and pitfalls of more invasive routes of administration.[2] This case describes a life-threatening reaction seconds after administration of treprostinil DPI, a first-in-class formulation with similar pharmacokinetic properties, pulmonary hemodynamic effects, and safety profile compared to nebulized treprostinil.[3]

Initial clinical suspicion was for a "bolus" effect of the DPI formulation leading to severe systemic hemodynamic side-effects or alterations to gas exchange via disruption of ventilation-perfusion matching resulting in hypoxemia. However, current evidence demonstrates a low risk of systemic side-effects or disruptions to gas exchange metrics with inhaled treprostinil.[4] Pharmacokinetic and transition studies do not support the idea of a "bolus" effect.[5]

After intubation the patient demonstrated high peak airway pressures, peak-to-plateau difference, and autoPEEP, suggesting significant airway resistance. While the delivery of nebulized medications during mechanical ventilation can contribute to pressure changes, the Aerogen® Solo device used in this case is a vibrating mesh nebulizer and does not contribute flow or otherwise affect ventilator parameters in the process of drug delivery. Given the patient's history of obstructive lung disease, severe bronchospasm secondary to inhaled prostacyclin administration was a consideration. The treprostinil package insert provides a warning regarding use in patients with asthma or chronic obstructive pulmonary disease and recommends optimizing treatment for reactive airway disease before initiation of therapy.[6] However, there are few documented incidents of bronchospasm in the literature.[7] Suspected bronchoconstriction was managed with corticosteroids and aggressive bronchodilators without resolution. Ultimately, only discontinuation of inhaled epoprostenol led to resolution of bronchospasm and associated high airway pressures.

While the mechanism for bronchospasm in this case is unclear, Naranjo criteria for a probable adverse drug reaction are met including a temporal relationship between initiation and discontinuation of inhaled prostacyclin therapy and indices of airway resistance, positive rechallenge when epoprostenol was paused and re-initiated, alternative explanations were explored and ruled out, and potential similar reactions in the past (noncompliant with home nebulized treprostinil therapy related to cough and SOB that in retrospect could have indicated a milder bronchospastic response).[8] However, inhaled iloprost therapy was well tolerated – it was only after transition to treprostinil DPI that the patient had a significant event, which persisted after switching to inhaled epoprostenol. The reason for this differential response is unclear. Treprostinil DPI has a different mechanism of delivery and is formulated with fumaryl diketopiperazine (FDKP) as a unique inactive excipient,[6] but these factors do not explain continued bronchospasm with epoprostenol. Examination of other inactive excipients of the inhaled prostacyclins does not reveal any obvious explanations of bronchospasm. Iloprost and epoprostenol were delivered via the same nebulizer device, which would seem to rule out delivery mechanism as an explanation. While there are structural similarities between epoprostenol and treprostnil, there are notable structural differences and iloprost also shares significant structural similarities. Iloprost, treprostinil, and epoprostenol have different prostaglandin receptor affinities which may have played a role in the differential response; however, treprostinil has the highest affinity for the DP1, EP2 and IP receptors, all of which cause smooth muscle relaxation.[9] Stimulation of prostaglandin IP receptors on the tachykinin-containing sensory nerves in the tracheobronchial airways directly elicits cough, the most common side effect of inhaled prostacyclins, but none of the relevant prostaglandin receptors have been directly or convincingly linked to bronchospasm.[10]

This case represents the first report of life-threatening bronchospasm with inhaled prostacyclin therapy, and strongly argues for exercising caution when initiating or titrating inhaled prostacyclin therapy in patients with clinically significant reactive or obstructive airway disease.

## GUARANTOR

All authors assume responsibility for the content of this manuscript.

### AUTHOR CONTRIBUTION

All authors contributed significantly to this work. Brian Murray, Shannon S. Carson, and Thomas Devlin directly participated in the care of the patient. Donna Steinbacher performed background research and chart audits related to the case presentation. H. James Ford served as a

pulmonary hypertension content expert. Shannon S. Carson served as an expert in critical care pharmacotherapy. Thomas Devlin provided expertise on ventilator management and inhaled medication administration. Brian Murray drafted and revised the manuscript.

## ACKNOWLEDGEMENTS

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

## ETHICAL STATEMENT

All feasible attempts to obtain informed consent from the patient reported in this case were undertaken, including attempts to contact via phone, email, and EHR. After 3 months the patient was deemed to be lost to follow-up. All patient identifiers, elements of dates, etc. have been removed from case details to limit any risk to patient privacy.

## ORCID

*Brian Murray* http://orcid.org/0000-0001-6660-9749

## REFERENCES

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023;61(1):2200879.
2. El-Kersh K, Jalil BA. Pulmonary hypertension inhaled therapies: an updated review. Am J Med Sci. 2023;366(1):3–15.
3. Spikes LA, Bajwa AA, Burger CD, Desai SV, Eggert MS, El-Kersh KA, Fisher MR, Johri S, Joly JM, Mehta J, Palevsky HI, Ramani GV, Restrepo-Jaramillo R, Sahay S, Shah TG, Deng C, Miceli M, Smith P, Shapiro SM. BREEZE: open-label clinical study to evaluate the safety and tolerability of treprostinil inhalation powder as tyvaso DPI$^{TM}$ in patients with pulmonary arterial hypertension. Pulm Circ. 2022;12(2):e12063.
4. Zamanian RT, Levine DJ, Bourge RC, De Souza SA, Rosenzweig EB, Alnuaimat H, Burger C, Mathai SC, Leedom N, DeAngelis K, Lim A, De Marco T. An observational study of inhaled-treprostinil respiratory-related safety in patients with pulmonary arterial hypertension. Pulm Circ. 2016;6(3):329–37.
5. Kumar P, Thudium E, Laliberte K, Zaccardelli D, Nelsen A. A comprehensive review of treprostinil pharmacokinetics via four routes of administration. Clin Pharmacokinet. 2016;55(12):1495–505.
6. *Tyvaso DPI$^{TM}$ (treprostinil inhalation powder) [package insert].* Research Triangle Park, NC: United Therapeutics; 2022.
7. Krishnan U, Takatsuki S, Ivy DD, Kerstein J, Calderbank M, Coleman E, Rosenzweig EB. Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children. Am J Cardiol. 2012;110(11):1704–9.
8. Comfort S, Dorrell D, Meireis S, Fine J. Modified NARanjo causality scale for ICSRs (MONARCSi): a decision support tool for safety scientists. Drug Saf. 2018;41(11):1073–85.
9. Whittle BJ, Silverstein AM, Mottola DM, Clapp LH. Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist. Biochem Pharmacol. 2012;84(1):68–75.
10. Chapman RW, Corboz MR, Fernandez C, Sullivan E, Stautberg A, Plaunt AJ, Konicek DM, Malinin V, Li Z, Cipolla D, Perkins W. Characterisation of cough evoked by inhaled treprostinil and treprostinil palmitil. ERJ Open Res. 2021;7(1):00592–2020.

**How to cite this article:** Steinbacher D, Murray B, Devlin T, Carson SS, Ford HJ. Severe bronchospasm and acute respiratory failure associated with inhaled prostacyclin therapy. Pulm Circ. 2024;14:e12396. https://doi.org/10.1002/pul2.12396