



Case report

Successful use of inhaled epoprostenol as rescue therapy for pediatric ARDS

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A B S T R A C T

Severe pediatric ARDS remains a significant challenge for clinicians, and management strategies are essentially limited to lung protective ventilation strategies, and adjunct approaches such as prone positioning, steroids, surfactant, and inhaled nitric oxide in unique situations. Inhaled nitric oxide produces pulmonary vasodilation in ventilated regions of the lung, shunting blood away from poorly ventilated areas and thus optimizing the ventilation perfusion ratio. A subset of patients with ARDS are known to be non-responders to nitric oxide, and selective pulmonary vasodilators such as Epoprostenol can be useful as rescue therapy in such cases. We describe a case of severe pediatric ARDS in the setting of pre-existing pulmonary hypertension and Trisomy 21, whose clinical course improved remarkably once inhaled Epoprostenol was initiated.

1. Introduction

While the incidence of pediatric acute respiratory distress syndrome (ARDS) remains low, studies have reported an overall mortality of 18–27% [1]. Insults causing ARDS can directly or indirectly (extrapulmonary) injure the lungs. Pneumonia, aspiration, and smoke inhalation are examples of direct lung injuries that can precipitate pediatric ARDS, whereas sepsis, near-drowning, concomitant cardiac disease, and other clinical conditions damage lungs indirectly [2]. The direct alveolar epithelial and indirect alveolar capillary injury leads to the breakdown of the alveolar-capillary barrier, resulting in the influx of protein-rich fluid into the air spaces and a decrease in the ability of the alveolar epithelium to remove excess alveolar fluid [3–5]. These lead to further downstream consequences such as poor lung compliance secondary to dysfunctional surfactant, ventilation perfusion mismatching, and hypoxemia.

Management for pediatric ARDS includes lung protective strategies such as low tidal volumes with high positive end expiratory pressure (PEEP) and adjunct approaches such as prone positioning, steroids, surfactant, and inhaled nitric oxide (INO). Pediatric Acute Lung Injury Consensus Conference (PALICC) does not recommend routine use of these adjunct therapies, except in unique circumstances [6,7]. INO may be indicated in ARDS in patients with pulmonary hypertension and clinically important right-ventricular dysfunction [8]. With administration of INO, pulmonary vasodilation predominantly occurs in ventilated regions of the lung, shunting blood away from poorly ventilated areas thus optimizing the ventilation perfusion ratio. Other selective pulmonary vasodilators such as Epoprostenol have demonstrated

improvement in hemodynamic parameters and oxygenation in ARDS patients, however, the data is currently limited [9]. We focused on a case at our center in which a pediatric patient developed ARDS in the setting of pre-existing pulmonary hypertension and Trisomy 21, whose clinical course greatly improved once inhaled Epoprostenol was initiated. In this report, we describe this pediatric case in further detail and outline the benefits of inhaled Epoprostenol, particularly in the setting of non-responders to INO.

2. Case report

Our patient was a 7-month old male with complex past medical history including Trisomy 21, pulmonary hypertension controlled on Sildenafil and Bosentan, and baseline supplemental oxygen requirement of ¼ liter per minute (lpm) during the day and 2 lpm at night. He was admitted to the Pediatric Intensive Care Unit (PICU) for acute respiratory failure with hypoxemia and hypercarbia in setting of parainfluenza viral illness. Prior to transfer to the PICU, the patient was intubated and mechanical ventilation was initiated with high PEEP of 10 cmH₂O. Inhaled nitric oxide (INO) was also administered at 20 parts per million (PPM), with marginal improvement in oxygen saturation from 85% to 92% on FiO₂ of 0.6. Almost 24 hours after admission to the PICU, patient experienced pulmonary hypertensive crisis resulting in arrest with absent pulses, and required brief period of chest compression and manual bag-mask ventilation. Low dose epinephrine (0.03 mcg/kg/min) and phenylephrine (0.03 mcg/kg/min) infusions were initiated for hemodynamic support, patient was deeply sedated, and INO was continued. Over the next few days, patient's oxygenation worsened despite use of

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muscle relaxants, INO, escalating PEEP and other ventilatory support to optimize his oxygenation. During this time his hemodynamic parameters remained stable on low dose epinephrine only (0.03 mcg/kg/min).

High Frequency Oscillation ventilation (HFOV) was initiated on 5th day of admission, and patient developed a new left-sided pneumothorax the following day. Needle decompression was performed, and chest tube was placed. Further escalation in mean airway pressure of HFOV to optimize his oxygenation was halted due to concern of air-leak and worsening pulmonary hypertension secondary to high positive intrathoracic pressure. Continuous inhaled Epoprostenol was initiated at this point to enhance his oxygenation without increasing mean airway pressure and to optimize his pulmonary vascular resistance. Almost immediately his oxygenation improved significantly with 40 ng/kg/min of inhaled Epoprostenol (Fig. 1). No significant change was noted in his hemodynamic profile following initiation of Epoprostenol.

Of note, ECMO was considered for the patient following development of air-leak in setting of high mean airway pressure. However, trial of Epoprostenol at that point produced an immediate marked improvement in oxygenation allowing rapid weaning of mean airway pressure, thereby avoiding potential morbidities associated with ECMO. He tolerated HFOV wean and was transitioned back to the conventional ventilator three days later. Patient continued to tolerate FiO₂ and PEEP wean on conventional ventilation. He was subsequently transitioned to Neurally Adjusted Ventilation Assist (NAVA) mode to continue weaning ventilatory support and optimize patient-ventilator synchrony. The chest tube was discontinued on hospital day 17 and endotracheal tube was removed on day 27. He was placed on 15 LPM high flow nasal cannula which was gradually weaned off during his hospital stay. Inhaled NO and Epoprostenol were both weaned off gradually prior to extubation. Epoprostenol dose was adjusted by decrements of 10 ng/kg/min until discontinued on day 26 of admission. He remained on home medications Sildenafil and Bosentan to control his chronic pulmonary hypertension, and dosage were adjusted as recommended by pediatric cardiologist.

3. Discussion

Acute Respiratory Distress Syndrome was first described in a 12-patients case series in 1967 as a disorder with respiratory distress, cyanosis refractory to oxygen, and diffuse pulmonary infiltrates. In 1994, the

American-European Consensus Conference formulated clinical criteria for diagnosis of adult ARDS, which was then revised in 2012 by the Berlin definition [8]. The first pediatric specific ARDS definition and management guideline was proposed by PALICC in 2015 [6–8], and pediatric intensivists and pulmonologists continue efforts to improve outcomes of pediatric ARDS.

Disruption of alveolar-capillary by direct or indirect injuries has numerous consequences and is a key event in the development of ARDS. It leads to increased capillary permeability and flooding of alveoli with protein-rich fluid. It also impedes the fluid removal by damaging type II alveolar epithelial cells. Damage to type II alveolar cells further impairs lung compliance by curtailing surfactant production. The protein-rich fluid escalates alveolar damage by releasing proinflammatory cytokines including tumor necrosis factor (TNF) and interleukins (IL-1, IL-6, IL-8). These cytokines amplify inflammatory response by activating neutrophils which in turn release proteases, oxidants, leukotrienes, and other proinflammatory substances. Depending on host response to profound inflammation, lungs in ARDS either completely recover or develop diffuse fibrosis.

In patients with ARDS, impaired gas exchange occurs due to ventilation-perfusion (VQ) mismatching. Hypoxemia results because blood flows to poorly ventilated lung regions, resulting in wasted perfusion. Correction of the VQ mismatch is one of the main targets of treatment for ARDS. In terms of pharmacologic treatment, INO and its effects in improving VQ mismatch in the setting of pediatric ARDS has been studied. When INO is delivered to the respiratory tract, the principal effect occurs in adequately ventilated areas of the lung, producing localized short-term pulmonary vasodilation [10]. Research has shown that inhaled NO acutely improves oxygenation and decreases pulmonary vascular resistance in children with severe acute hypoxemic respiratory failure and ARDS [11]. Despite this short-term benefit, multiple randomized controlled trials performed in children with ARDS have shown that INO does not improve outcomes [12–14]. However, as mentioned in the introduction, INO may be indicated for ARDS in patients with documented pulmonary hypertension as a bridge to extracorporeal membrane oxygenation (ECMO) cannulation, and in those with clinically important right-ventricular dysfunction [8].

Despite INO's short-term effects, there are patients who receive this medication and are non-responders. In the Clinical Inhaled Nitric Oxide Research Group Investigation (CINGRI) study, treatment with INO was

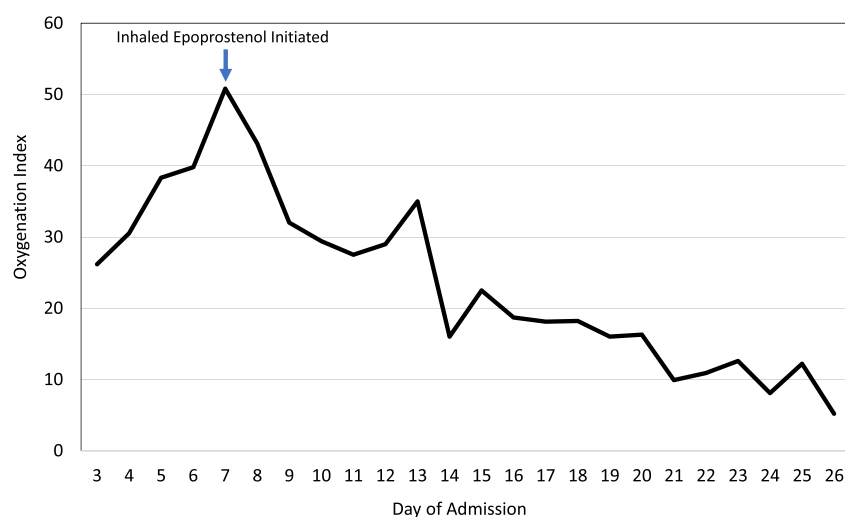


Fig. 1. Oxygenation Index trend during admission and relationship with Epoprostenol initiation.

$$\text{Oxygenation Index} = \frac{\text{Mean Airway Pressure} \times \text{FiO}_2}{\text{PaO}_2}$$

considered a failure when patients could not tolerate a reduced dose at 24 hours, or when the study gas could not be discontinued within 96 hours [15]. One particular subset of patients who are more likely to be INO non-responders are those with the diagnosis of Down syndrome, like the case presented here. Due to pathologic changes of the endothelial cells in individuals with Down syndrome, patients have a poorer response to nitric oxide inhalation. Blood levels of arginine and nitric oxide are lower, but the level of asymmetric dimethylarginine is increased, which has been reported as a possible reason for the reduced production of intrinsic NO [16]. Cannon et al. studied changes in pulmonary vascular resistance (PVR) following administration of 100% oxygen and INO, and discovered that patients with Trisomy 21 only demonstrated a 21% decrease in PVR whereas patients without chromosomal abnormalities had a 42% decrease [17]. When patients are non-responders to INO, inhaled Epoprostenol can be considered as an alternative treatment to help improve VQ mismatching. It may be argued that our patient's clinical improvement following Epoprostenol could be attributed to decreased PVR and associated improvement in comorbid pulmonary hypertension. Although this could certainly be a factor in his clinical improvement, we want to highlight that patient's hemodynamic parameters remained reassuring on low dose epinephrine infusion and did not improve remarkably following initiation of inhaled Epoprostenol, suggesting that improvement in VQ mismatch was the dominant physiology at play.

Epoprostenol is a prostacyclin analog. Prostacyclin is a naturally occurring prostaglandin which exerts its effects on vascular smooth muscle through a mechanism of action that is uniquely different from INO, and this probably accounts for its additional benefits in various pathologic conditions. It increases the concentration of cyclic adenosine monophosphate in vascular smooth muscle cells while INO produces cyclic guanosine monophosphate [18]. Prostacyclin also increases endogenous surfactant production, which is beneficial in ARDS because it may decrease the need for toxic ventilator settings by improving lung compliance [10]. Additionally, prostacyclin suppresses the synthesis of TNF α in activated monocytes, which is implicated in the pro-inflammatory state of ARDS [19,20]. Beyond these additional benefits, Epoprostenol has also been shown to have a better safety profile when compared to INO [9]. INO has been associated with platelet aggregation, renal failure, methemoglobinemia, and cytotoxic properties through the formation of peroxynitrite in the presence of oxygen free radicals [9]. While there are different routes of administration of Epoprostenol, the inhaled formulation should be used in ARDS to ensure selective pulmonary vasodilation within the relatively healthier and ventilated lung segments rather than indiscriminate vasodilation of all lung segments that would ensue following systemic administration. Unlike inhaled Epoprostenol, intravenous Epoprostenol has been associated with worsening V/Q matching, hypotension, inhibition of platelet aggregation, and tachycardia in most patients [9]. The only prospective trial in the pediatric population (less than 18 years old), while small [n = 14], failed to identify any adverse effects in children receiving inhaled Epoprostenol [9].

In conclusion, our case demonstrates that inhaled Epoprostenol can be a valuable tool for pediatric intensivists and pulmonologists dealing with severe pediatric ARDS cases, particularly for children that are non-responders or minimally responsive to INO. It can improve oxygenation index significantly without increasing mean airway pressure and thereby prevent ventilator associated barotrauma, and may be considered as a rescue therapy in situations where INO fails.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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