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Innovative use of EIT-guided prone positioning and inhaled nitric oxide therapy for refractory hypoxemia in primary graft dysfunction: a case report

Yan Dong[1], Zhongping Xu[1], Jing Tian[1], Dapeng Wang[1], Jingyu Chen[2] and Hongyang Xu[1*]

Abstract

Primary graft dysfunction Grade 3 (PGD 3) following lung transplantation significantly increases the incidence of acute and chronic complications. These effects complicate clinical perioperative management and significantly increase mortality. Here, we report a case of PGD 3 and refractory hypoxemia after bilateral lung transplantation at our center. Despite ongoing extracorporeal membrane oxygenation (ECMO) support, the patient's partial pressure of oxygen (PaO_2) remained suboptimal at 71.7 mmHg on postoperative day 4, precluding safe discontinuation of ECMO support. Consequently, EIT-guided interventions—including prone positioning optimization and inhaled nitric oxide (iNO) therapy—were implemented to improve oxygenation. After undergoing a rigorous treatment process, the patient was successfully weaned off ECMO on the 10th day and transitioned out of the intensive care unit (ICU) on the 24th postoperative day. The combination of prone positioning and iNO therapy, tailored through EIT-guided interventions, provided an innovative approach to post-lung transplant management and had the potential to save patients' lives.

Keywords Lung transplantation, Electrical impedance tomography (EIT), Prone ventilation treatment, iNO therapy.

Introduction

Lung transplantation is the most effective treatment for end-stage pulmonary disease. Primary graft dysfunction (PGD) occurs in up to 30% of patients within 72 h after surgery and is a significant factor contributing to early mortality among lung transplant recipients [1, 2].

*Correspondence:
Hongyang Xu
xhy1912@aliyun.com
[1]Department of Critical Care Medicine, Wuxi People's Hospital, Wuxi Medical Center, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Nanjing Medical University, Wuxi, China
[2]Lung Transplant Center, Department of Thoracic Surgery, Wuxi People's Hospital, Wuxi Medical Center, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Nanjing Medical University, Wuxi, China

Current clinical assessment of pulmonary function primarily relies on clinicians' interpretation of diagnostic test results and application of empirical knowledge, while frequently lacking access to advanced visualization technologies that could enhance diagnostic intuition through spatial representation of respiratory parameters. In recent years, electrical impedance tomography (EIT) has advanced significantly. This technology dynamically displays changes in bioimpedance associated with pulmonary functional alterations, enabling real-time dual monitoring of regional ventilation and perfusion dynamics [3].

Prone ventilation offers a survival advantage for patients with moderate to severe acute respiratory distress syndrome (ARDS), which enhances the distribution

of ventilated blood flow due to gravity and promoting the drainage of sputum from the lungs, ultimately leading to improved oxygenation [4]. As a selective pulmonary vasodilator, inhaled nitric oxide (iNO) has the effects of dilating pulmonary blood vessels, increasing pulmonary blood flow, reducing pulmonary artery pressure and improving oxygenation, and is mostly used in the treatment of pulmonary hypertension and refractory hypoxemia [5]. EIT has demonstrated clinical utility across diverse research settings, particularly in guiding individualized PEEP titration through dynamic monitoring of regional ventilation distribution. Emerging applications further extend to one-lung ventilation and pathological conditions such as pulmonary edema, where EIT provides real-time spatial resolution of fluid redistribution patterns [6, 7]. Although prone positioning maneuvers and iNO therapy have been clinically validated for ARDS, their implementation in lung transplantation protocols remains underexplored, particularly regarding the integration with dynamic visualization techniques for postoperative respiratory management [4, 8].The details of the case are outlined below.

Case report

The 54-year-old female patient was diagnosed with pulmonary interstitial fibrosis at the age of 52, treated with oral pirfenidone and prednisone. However, after the patient self-discontinued pirfenidone in April 2023, whcih resulted in worsening dyspnea, and necessitated continuous home oxygen therapy. Minimal exertion triggered significant asthmatic symptoms, rendering the patient unable to be weaned off oxygen. A lung biopsy confirmed the presence of usual interstitial pneumonia (UIP). During the pre-transplant evaluation for lung transplantation, pulmonary function tests showed FVC: 1.0 L, 35.6%; FEV1: 1.093 L; 39.1%; FEV1/FVC: 92.94%. The patient was listed for a lung transplant in late December and underwent bilateral lung transplantation with veno-venous extracorporeal membrane oxygenation (VV ECMO) support on January 26, 2024. The surgery lasted 7.8 h, with a peak cold ischemia time of 630 min. Intraoperative blood loss was 1200 ml, and blood transfusions totaled 1450 ml. Postoperatively, the patient remained hemodynamically stable but required additional ECMO support in the intensive care unit (ICU) due to suboptimal oxygenation.

Initial management

Upon admission to the ICU, the patient was provided with mechanical ventilatory support and V-V ECMO (via internal jugular-femoral vein) cardiopulmonary support. Treatment included anti-infective therapy with imipenem/cilastatin sodium in combination with caspofungin, immunosuppressive therapy using methylprednisolone and tacrolimus, sedation, analgesia, muscle relaxation, blood transfusion support, expectorant therapy, and acid suppression, among other interventions. Despite the support from ventilator and VV ECMO (the ECMO gas flow rate was 2.35 L/min and the fraction of oxygen delivered by ECMO to 1.0), the arterial blood gas (ABG) indicated oxygenation with PaO_2: 78.5mmHg, and FIO_2: 80% (Fig. 1). A chest X-ray showed bilateral pulmonary

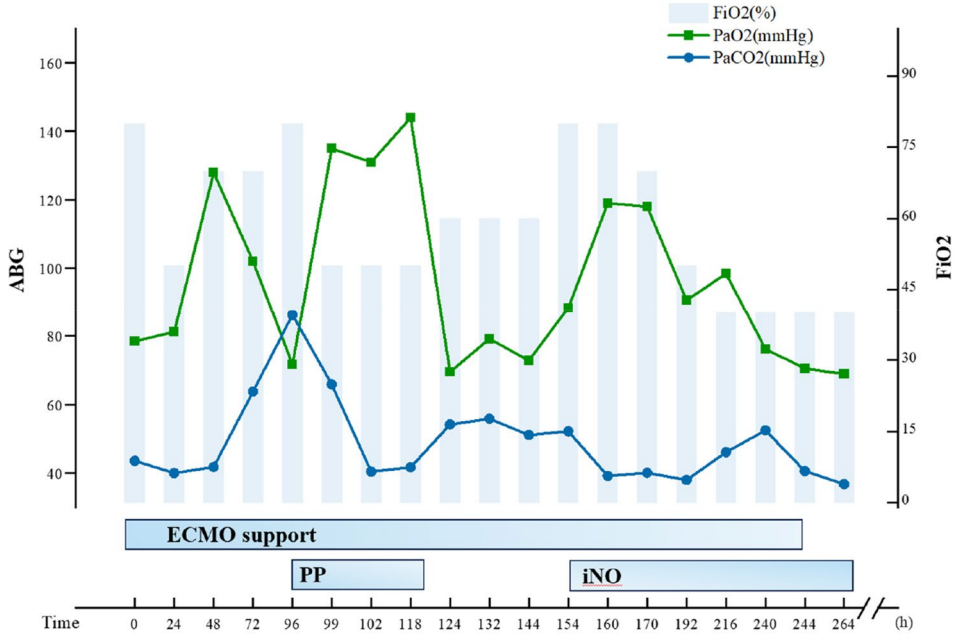

Fig. 1 ABG and treatment measures at various time points. ABG, arterial blood gas; ECMO, extracorporeal membrane oxygenation; PP, prone positioning; iNO, inhaled nitric oxide

exudative changes (Fig. 2, A). Lung ultrasonography revealed scattered B-lines in the anterior and lateral thoracic walls, and extensive confluent B-lines with a few fragmentary signs in the posterior thoracic wall. EIT examination showed center of ventilation (CoV) of 48%, left lung heterogeneity index (LHI) of 67, and global inhomogeneity index (GI) of 79.6. The treatment strategy was temporarily altered to enhance diuresis and replenish colloidal osmotic pressure to reduce pulmonary edema.

Within the first 3 days post-operation, the patient's oxygenation remained inadequate. Intermittent fiberoptic bronchoscopy was performed, revealing moderate congestion and edema in the airways, with a small amount of edema fluid observed bilaterally. Given that the patient was experiencing PGD 3, ECMO support was continued alongside enhanced fluid management.

Prone positioning phase

On the morning of the 4th day post-operation, an evaluation revealed that the removal of ECMO was not feasible. A subsequent bronchoscopy indicated significant airway contamination with moderate yellow mucus, and the patient's oxygenation remained suboptimal. EIT showed that the patient's tidal volume was uneven, with the ventilation center located near the dorsal side. Consequently, it was decided to initiate prone ventilation therapy. At the same time, the ventilator tidal volume was set at 300–400 ml to reduce the risk of atelectasis and emphysema, as well as to minimize the physical damage caused by mechanical ventilation to the alveoli. The initial session of prone positioning lasted 22 h, during which ABG analysis showed improved oxygenation. The EIT results showed that the distribution of tidal volume was more uniform than before; however, the ventilation flow ratio remained mismatched (Fig. 3). Additionally, oxygenation deteriorated again once prone positioning was discontinued.

INO therapy phase

On the 6th day post-operation, given the patient's significant dependence on ECMO, the prone position proved ineffective, and the patient experienced refractory hypoxemia (PaO2: 88.3mmHg, FIO2: 80%). INO therapy (iNO will N200 Nitric Oxide Generator and Delivery System, Novlead Biotech, China) was administered to optimize pulmonary ventilation-perfusion (V/Q) matching through selective pulmonary vasodilation. The NO concentration was set at 20 ppm (monitored concentration 17 ppm) with the NO_2 concentration maintained at 0.2 ppm. Six hours after the initiation of iNO treatment, arterial blood gas analysis revealed the following: PaO2: 119 mmHg, PaCO2: 39.2 mmHg, FIO2: 80% (Fig. 1). Oxygenation improved significantly, and EIT results indicated a substantial optimization of ventilation-perfusion ratio (GI improved from 68 to 79, Fig. 3, A). Blood circulation remained stable, and lung fields were cleared.

Follow-up treatment phase

On the morning of the 10th day post-surgery, the patient was in a stable condition. ECMO was successfully removed after 3 h based on adequate evaluation, and EIT showed: LHI: 80, GI: 63, and ventilation-blood flow matching was satisfactory. Unfortunately, during the bronchoscopy, a significant amount of sputum was still observed, accompanied by moderate congestion and edema of the respiratory mucosa; the mucosa of the right airway appeared grayish-black. Sputum culture revealed pan-resistant Acinetobacter baumannii and Pseudomonas aeruginosa. Consequently, the anti-infective treatment regimen was altered to include a combination of eravacycline, ceftazidime-avibactam, and isavuconazole. Due to the patient's poor oxygenation and reduced lung compliance, inability to independently expectorate sputum, and challenges in weaning off the ventilator and

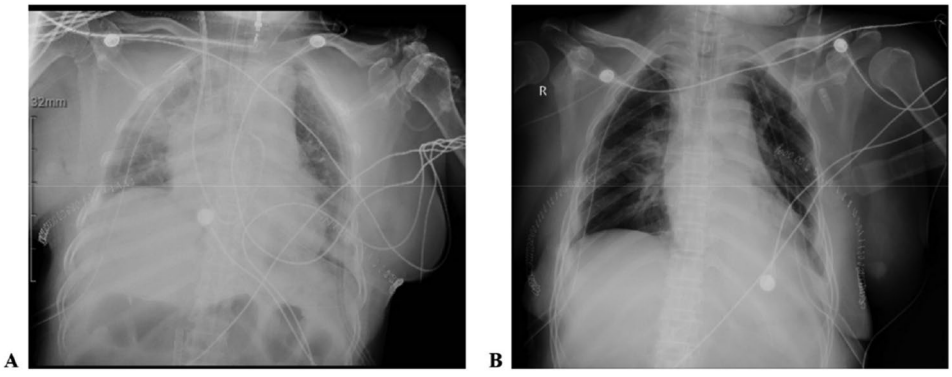

Fig. 2 Chest imaging of the patient. (**A**) Postoperative chest imaging revealed exudative changes in both lungs following bilateral lung transplantation, an enlarged cardiac silhouette in the supine position, and a small amount of pleural effusion on both sides associated with bilateral thoracic drainage. (**B**) When discharge from ICU, the chest imaging examination revealed significant absorption of the exudate in both lungs, although the lung texture remained thickened

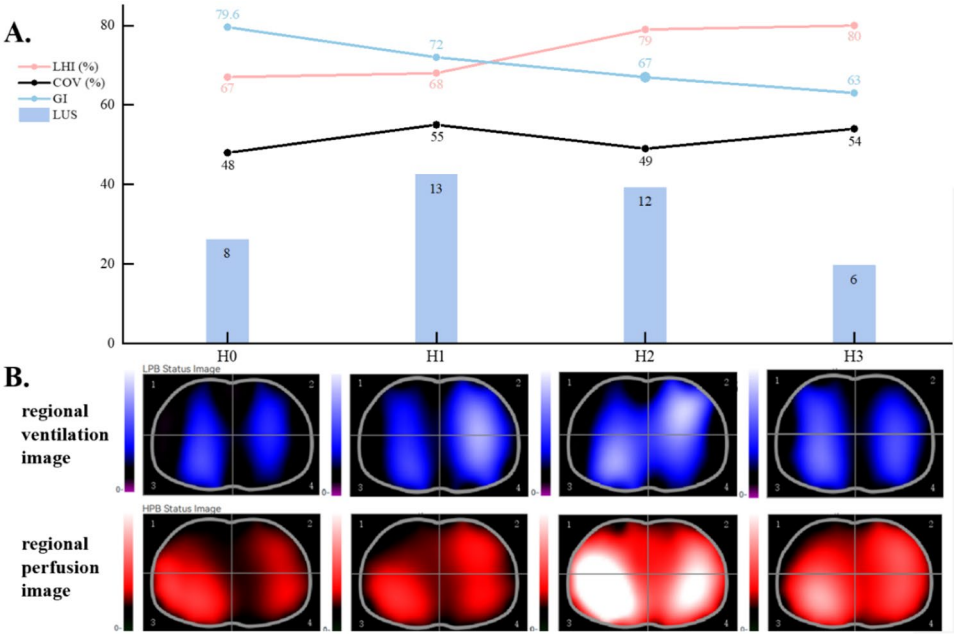

Fig. 3 EIT data and LUS score at each points in time. H0: Transferred to ICU. H1: Prone position for 6 h. H2: iNO application for 6 h. H3: Transferred out of ICU. EIT, electrical impedance tomography; LUS, lung ultrasound score. CoV, center of ventilation; LHI, lung heterogeneity index; GI, global inhomogeneity index

extubating in the short term, a tracheotomy was scheduled for the following day.

After the tracheotomy, bronchoscopy showed a reduction in the amount of sputum and an enhancement in its characteristics. The edema of the airway mucosa had improved compared to previous assessments, infection markers gradually decreased without any fluctuations, and the use of antibiotics were gradually reduced. The level of ventilator support was also decreased compared to prior levels. On the 24th day post-operation, the patient was successfully transferred out of the ICU (Fig. 2, B). 52 days after the operation, the patient was successfully weaned off the ventilator, and the tracheostomy tube was removed.

Discussion

This patient developed severe hypoxemia within 72 h post-lung transplantation. Bronchoscopy demonstrated moderate-to-severe mucosal congestion and edema, while chest X-ray revealed bilateral diffuse exudative infiltrates. These findings met the diagnostic criteria for PGD 3, indicating a poor prognosis [2, 9].

Despite the support of VV ECMO, the patient experienced persistent hypoxemia. Our department used EIT technology to provide real-time data of regional pulmonary ventilation and blood perfusion, combined with bedside chest ultrasound, to facilitate visual respiratory management. Data were recorded by an EIT device. Lung perfusion was evaluated by pulsatility-based EIT methods. The pulsatile technique assesses variations in electrical impedance resulting from alterations in pulmonary vascular structure caused by cardiac pulsation, and uses filtering technology to obtain perfusion signals, so it is unnecessary to inject hypertonic saline and interrupt the patient's breathing. Zhang et al. [10] found that during VV ECMO, the ECMO blood flow rate, which is closely related to recirculation fraction, has a stronger influence on the distribution of bolus saline across the regional lung, thus affecting the accuracy of lung perfusion assessment using hypertonic saline bolus-based EIT. It is evident that the pulsatility-based method does not present such concerns. EIT has been extensively used in clinical settings for individualized PEEP titration, guiding lung recruitment maneuvers, and treating patients with conditions such as one-lung ventilation and pulmonary edema [11, 12].

Prone ventilation could improve the ventilation-perfusion ratio [13], facilitate the drainage of pulmonary secretions, and enhance oxygenation [14, 15]. Given that the patient had a large surgical wound and underwent multiple intubations, the initial long-term prone positioning lasted for 22 h to avoid serious complications, such as dislodgment of the intubation. During the prone ventilation treatment, the patient did not experience any associated complications. Unfortunately, the effect of prone position did not significantly increase the ventilation-perfusion ratio (LHI increased from 67 to 68) and could not be maintained after the patient was returned to the supine position (PaO2: 69.5mmHg, FiO2:60%).

EIT suggested that while the patient's ventilation appeared to improve in the prone position, perfusion remained inadequate, leading to a mismatch between ventilation and blood flow. Therefore, we promptly initiated iNO treatment as a remedial measure. At this time, the sputum cultures indicated an infection with pan-resistant Acinetobacter baumannii and Pseudomonas aeruginosa, which could potentially contribute to the observed refractory hypoxemia. Previous basic studies have shown that NO can inhibit the proliferation and replication of various pulmonary pathogens while suppressing the production of pulmonary inflammatory chemokines [16, 17]. After 6 h of continuous inhalation of NO, the patient's oxygenation index increased significantly, with PaO_2 improving from 88.3mmHg to 118mmHg while the ventilator settings remained unchanged. Although there was a gradual decline in benefits following prolonged use, iNO continued to demonstrate positive effects on enhancing ventilation and blood perfusion. During the treatment, there was a gradual reduction in the patient's reliance on ventilator support, the circulatory status remained stable, and the treatment proved effective.

Conclusion

We presented a novel strategy to improve outcomes for patients suffering from severe PGD through advanced monitoring and diagnostic techniques to establish visual respiratory management. Prone positioning and iNO therapy also have unique effects in the treatment of severe PGD and refractory hypoxemia. We emphasized the promising role of EIT in real-time evaluations and individualized management. However, further extensive studies on EIT-guided respiratory management are necessary.

Abbreviations

PGD	Primary graft dysfunction
ECMO	Extracorporeal membrane oxygenation
VV ECMO	Veno-venous extracorporeal membrane oxygenation
EIT	Electrical impedance tomography
ICU	Intensive care unit
UIP	Usual interstitial pneumonia
ARDS	Acute respiratory distress syndrome
FVC	Forced vital capacity
FEV1	Forced expiratory volume in 1 s
LUS	Lung ultrasound score
CoV	Center of ventilation
LHI	Lung heterogeneity index
GI	Global inhomogeneity index
ABG	Arterial blood gas

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Author contributions

All authors contributed to this case report. All provided input and critique on the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

The present case complies with *the Regulations on Human Organ Transplantation in China* and other relevant laws and regulations. Written informed consent for both clinical procedures and case publication was obtained from the patient's legal surrogate. All personal identifiers have been removed to protect patient confidentiality.

Consent for publication

Written informed consent was obtained from the patients for publication of this article.

Competing interests

The authors declare no competing interests.

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