CASE REPORT

Independent lung ventilation for the management of acute allograft rejection after single-lung transplantation for end-stage emphysema

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Abstract : Background : We herein report the use of independent lung ventilation (ILV) for managing acute allograft rejection after single-lung transplantation (SLT) for end-stage emphysema. Case presentation : A 54-year-old woman was transferred to our hospital with severe hypoxemia and respiratory distress due to unilateral lung disease with diffuse alveolar damage in the right donor lung associated with acute allograft rejection and with hyperinflation of the left native lung due to emphysema. She was unresponsive to immunosuppressive medications and conventional ventilation strategies, so different ventilator settings for each lung were required. A double-lumen endotracheal tube (DLT) was inserted, and ILV was initiated. The right lung was ventilated with high positive end-expiratory pressure (PEEP), intended for lung recruitment, and the left lung was ventilated with lung protective strategies using a low tidal volume and low levels of PEEP to avoid hyperinflation. Two days later, her lung function was dramatically improved, and the DLT was replaced with a single-lumen endotracheal tube. Gas exchange was maintained, and she was successfully weaned from mechanical ventilation on intensive-care unit day 15. Conclusions : ILV appears to be effective and safe for managing acute allograft rejection after SLT for emphysema. J. Med. Invest. 69 : 323-327, August, 2022

Keywords **:** *independent lung ventilation, acute allograft rejection, single-lung transplantation, emphysema*

INTRODUCTION

End-stage emphysema is the most common indication for lung transplant surgery (1, 2). Single-lung transplantation (SLT) is an accepted procedure for managing emphysema, and its five-year survival benefits were reported to be similar to those of bilateral-lung transplantation in patients with end-stage emphysema in some studies, especially in patients over 60 years old (3-6).

However, SLT often causes native lung hyperinflation (NLH), which may be induced by asymmetrical distribution of gas flow with air-trapping in the native lung due to the marked difference in compliance between the highly compliant native lung and restrictive donor lung (2, 7). NLH is particularly prone to occur under positive-pressure mechanical ventilation and may be worsened by donor lung edema due to ischemic reperfusion injury, ventilator-induced lung injury or primary allograft dysfunction (8, 9). NLH may cause mediastinum shift and extrinsic allograft compression, resulting in atelectasis, impaired gas exchange and hemodynamic instability, which may require specific ventilator strategies or lung volume reduction surgery (2, 8, 9).

Independent lung ventilation (ILV) is a ventilation procedure used in patients with differing mechanics between the lungs due to asymmetrical lung diseases when conventional ventilation techniques fail to maintain optimal oxygenation and ventilation (9). The common indications of ILV are unilateral parenchymal lung diseases, post-operative complications of SLT, massive hemoptysis and bronchopleural fistulas (9, 10). Although reports of post-operative SLT for emphysema have largely been limited to case reports or small case series, ILV has mainly been used to minimize acute NLH in the early post-operative period (11-14).

However, a clinical case of ILV use for a patient with unilateral lung disease due to acute allograft rejection, which commonly occurs within one year from transplantation, in the chronic phase when more than two years have been passed since SLT has not been reported. In addition, ILV itself is rarely used in the ICU (9, 10) ; therefore, the rationale concerning the indication of ILV use and optimal ventilator strategies for each lung have not been established, in contrast to thoracic anesthesia.

We herein report an SLT patient treated with asynchronous ILV who experienced respiratory distress due to acute worsening of allograft rejection at 28 months after lung transplant surgery.

CASE PRESENTATION

A 54-year-old woman with severe chronic pulmonary emphysema underwent right SLT 28 months ago at another hospital. After transplant surgery, her respiratory condition was maintained, and chest radiography and computed tomography (CT) showed good aeration of the right donor lung without signs of chronic lung allograft dysfunction (Fig. 1a). However, she had a medical history of psychotic disorder (diagnosed as bipolar

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disorder), and her medical adherence was gradually decreased.

Five days after she completely refused to take immunosuppressive drugs (methylprednisolone 12 mg/day, mycophenolate mofetil 1500 mg/day, tacrolimus hydrate 2 mg every other day), she was admitted to our hospital with hypoxemia and respiratory distress. On chest radiography and CT, ground-glass opacity in the right donor lung and hyperinflation with reduced vascular markings of the native left lung without apparent mediastinum shift were observed (Fig. 1b). Her serum blood concentration of tacrolimus was low (1.4 ng/mL), and cytomegalovirus (CMV) antigen and CMV-positive cells were not detected. She was diagnosed with acute allograft rejection due to poor immunosuppressive medication adherence.

After admission, she was treated with intravenous hydrocortisone 500 mg/day for 3 days followed by hydrocortisone tapering, mycophenolate mofetil 1500 mg/day, tacrolimus hydrate 2 mg/day, and intravenous azithromycin, tazobactam/piperacillin and itraconazole empirically for infectious pneumonia ; however, she was unresponsive to medication therapy, and progressive worsening of the respiratory function was observed. Six days later, her oxygenation worsened to an S_pO_2 of 92% when oxygen was delivered at 15 L/min via a non-rebreather mask, and further worsening of the arterial blood gas analysis (ABGA) findings occurred (pH 7.31, P_aO_2 85 mmHg, P_aCO_2 59 mmHg, estimated P_aO_2/F_IO_2 94 mmHg). Chest X-ray and CT showed severe consolidation of the right lung (Fig. 1c). She was transferred to our intensive-care unit (ICU) and intubated with a single-lumen endotracheal tube, and conventional mechanical ventilation was initiated (pressure assist-control ventilation, pressure control 14 cmH_2O, positive end-expiratory pressure [PEEP] 8 cmH_2O, respiratory rate 16/min, F_IO_2 0.6). She received intravenous immunoglobulin 5 g/day for 3 days. On ICU day 4, despite no improvement in her radiograph findings, her oxygenation and ventilation improved (ABGA : pH 7.46, P_aO_2 90 mmHg, P_aCO_2 43 mmHg, F_IO_2 0.3, P_aO_2/F_IO_2 300 mmHg), and she was extubated after a spontaneous breathing trial (pressure support ventilation, pressure support 5 cmH_2O, PEEP 5 cmH_2O, F_IO_2 0.3), with high-flow nasal cannula (HFNC) oxygen therapy initiated (Flow 40 L/min, F_IO_2 0.45).

However, on ICU day 8, she was re-intubated due to recurrent hypoxemia and respiratory distress (pH 7.47, P_aO_2 53 mmHg, P_aCO_2 38 mmHg, P_aO_2/F_IO_2 118 mmHg, respiratory rate 30/min). On ICU day 8, she received methyl prednisolone 1,000 mg/day for 3 days, followed by oral prednisolone tapering. On ICU day 10, despite an attempt to optimize ventilator support and medical therapy, further worsening of the ABGA findings occurred (pH 7.26, P_aO_2 79 mmHg, P_aCO_2 70 mmHg, F_IO_2 0.6, P_aO_2/F_IO_2 130 mmHg). Chest radiography revealed severe consolidation of the right donor lung and hyperinflation of the left native lung (Fig. 2a). To improve oxygenation and ventilation, we changed the body position, including adopting the left lateral decubitus position, which is known to attenuate ventilation/perfusion mismatch and asymmetrical lung compliance in both lungs. However, this postural change did not influence her respiratory function. Given the conflicting requirements of a non-high driving pressure and PEEP for the native lung, which had end-stage emphysema with a risk of barotrauma, and the need for high PEEP for the graft in the setting of a low-compliance lung, the single-lumen endotracheal tube was replaced with a left double-lumen endotracheal tube (DLT ; Portex®, BlueLine®, Endobronchial Tube, Left, 35-Fr ; ICU Medical, San Clemente, CA, USA), and ILV was started.

The left native lung was connected to a PB980 ventilator (Medtronic, Dublin, Ireland) with a lung-protective strategy, involving pressure assist-control ventilation, peak inspiratory pressure (PIP) 20 cmH_2O, PEEP 6 cmH_2O, respiratory rate 16/min, inspiratory time 1.0 sec, achieving tidal volume (V_T) of 230 mL, and F_IO_2 0.25. We intended to set PEEP as counter PEEP for mitigating small airway resistance and intrinsic PEEP to avoid dynamic hyperinflation (15). The right donor lung

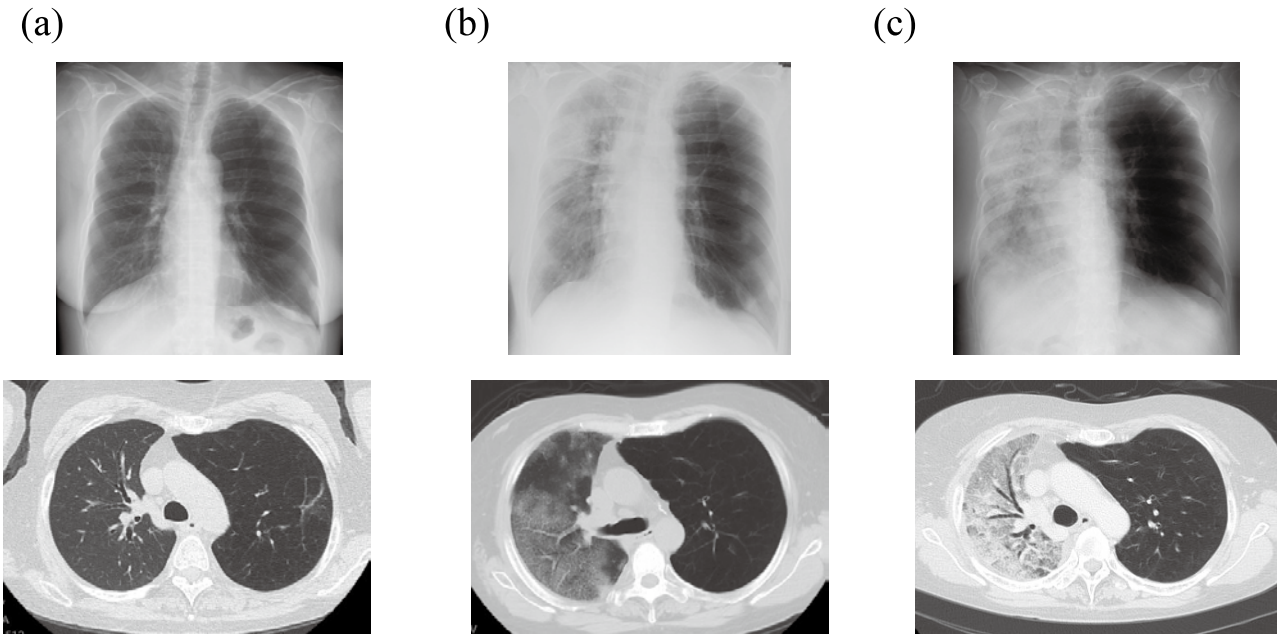

Figure 1. (a) Chest X-ray and CT findings at 24 months after lung transplant surgery. Chest X-ray and CT showed good aeration of the right donor lung and slight hyperinflation of the left naïve lung without apparent mediastinum shift. (b) Chest X-ray and CT findings at hospital admission. Chest X-ray and CT showed ground-glass opacification of the right donor lung and hyperinflation with reduced vascular markings of the native left lung without apparent mediastinum shift. (c) Chest X-ray and CT at ICU admission. Chest X-ray and CT showed the severe consolidation of the right lung. Chest CT showed marked densification of the right donor lung, hyperinflation with reduced vascular markings of the native left lung and mediastinum shift. CT, computed tomography ; ICU, intensive-care unit.

was connected to a Hamilton-C6 ventilator (Hamilton Medical, Bonaduz, Switzerland), intended for lung recruitment, with a PIP 26 cmH_2O, PEEP 16 cmH_2O, respiratory rate 16/min, inspiratory time 1.2 sec, achieving V_T of 140 mL, dynamic respiratory system compliance of 14 mL/cmH_2O and F_IO_2 0.4.

We identified the optimal PEEP setting providing the highest lung compliance and adequate oxygenation. We also identified the optimal values for other ventilator settings, as follows : driving pressure < 15 cmH_2O, plateau pressure < 28 cmH_2O, and respiratory rate < 35/min in accordance with lung protective strategies for acute respiratory distress syndrome (ARDS) patients (15, 16). This strategy was effective for recruiting the right donor lung without worsening the hyperinflation of the left native lung (Fig. 2b). During ILV, we used midazolam, dexmedetomidine and fentanyl to manage the patient under deep sedation (Richmond agitation-sedation scale -5 to -4) in order to avoid patient discomfort due to the use of two ventilators. The introduction of ILV resulted in progressive improvement of the patient's respiratory conditions and functional parameters without any hemodynamic instability.

On ICU day 12, the dynamic respiratory system compliance of the right donor lung reached 31 mL/cmH_2O, and given the improvement in the ABGA findings (pH 7.45, P_aO_2 90 mmHg, P_aCO_2 48 mmHg, F_IO_2 0.4, P_aO_2/F_IO_2 225 mmHg), the DLT was exchanged for a single-lumen endotracheal tube. Chest X-ray and CT showed the improved aeration of the right donor lung (Fig. 3). Adequate gas exchange was maintained with conventional ventilation, and the patient was successfully weaned from mechanical ventilation on ICU day 15.

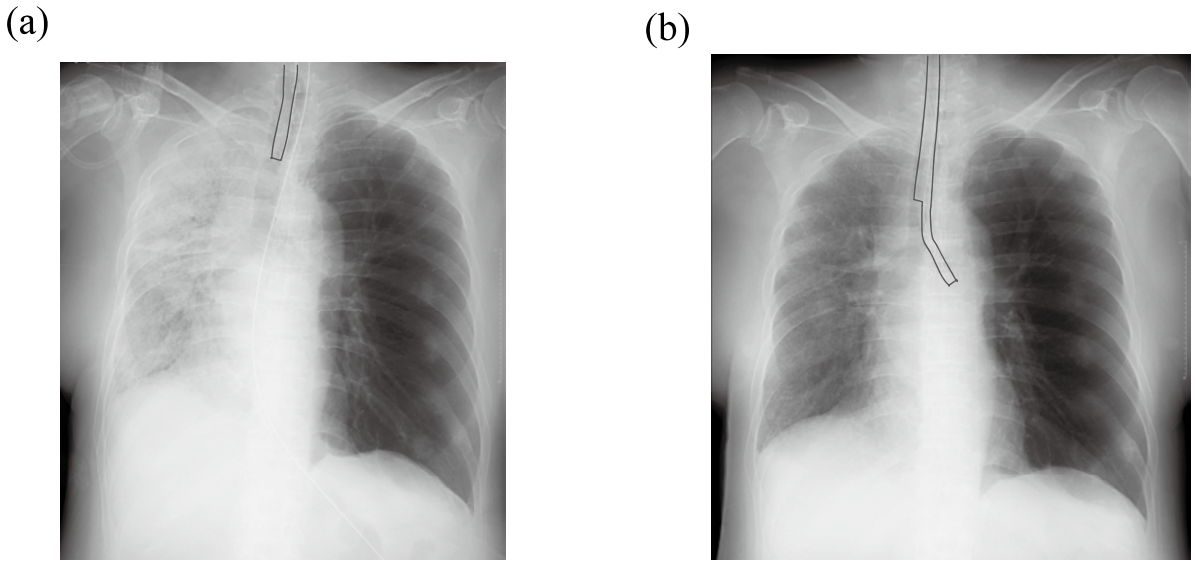

Figure 2. (a) Chest X-ray during conventional ventilation on ICU day 10. Chest X-ray showed severe consolidation of the right lung. The gray line indicates single-lumen end-tracheal tube intubation in the trachea. (b) Chest X-ray at day 1 after ILV initiation. Chest X-ray showed the improved aeration of the right lung compared with before ILV. The gray line indicates double-lumen end-tracheal tube intubation in the left main bronchus. ILV, independent lung ventilation.

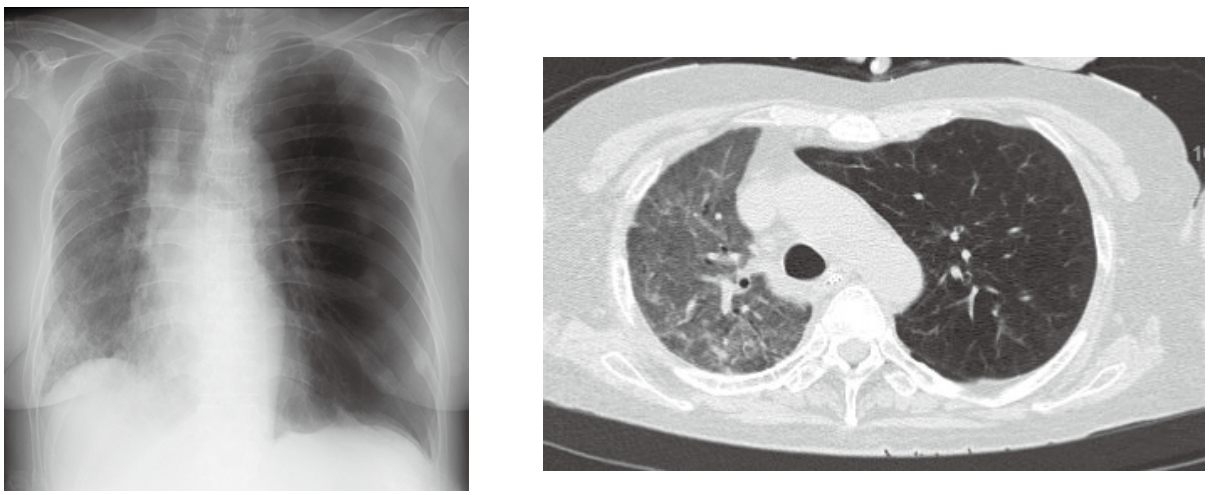

Figure 3. Chest X-ray and CT findings at ICU discharge. Chest X-ray and CT showed the improved aeration of the right donor lung despite remnant hyperinflation of the left native lung and mediastinum shift.

DISCUSSION

ILV, especially one-lung ventilation, is commonly used in anesthesia for thoracic surgery but more rarely in critical care settings (9, 10). ILV in the critical care setting has been used mainly as a rescue strategy for refractory hypoxemia and respiratory distress in patients with asymmetrical lung diseases for which conventional mechanical ventilation with a single-lumen endotracheal tube proved ineffective in maintaining optimal oxygenation and ventilation. Some case studies have reported that ILV was an effective strategy in patients who developed primary graft dysfunction following SLT in the perioperative period, manifested as low compliance of a donor lung and hyperinflation of a native lung with markedly different lung pathologies (11-14).

The management of ventilator strategies for each lung should be performed based on the underlying pathology and principles of lung protective ventilation. Since the compliance of diseased and non-diseased lungs differs significantly, the best PEEP for each lung should be determined independently (9). As with conventional ventilation for restrictive lung diseases, such as ARDS, the application of PEEP for a collapsed donor lung should be determined based on the established protocol of the PEEP titration method so that the PEEP setting can provide the highest lung compliance, the lowest driving pressure and adequate oxygenation (15, 16). In our patient, we applied a high PEEP of 16 cmH_2O for the right donor lung, which achieved effective lung recruitment, increased the dynamic lung compliance (14 mL/cmH_2O to 31 mL/cmH_2O) and improved oxygenation (P_aO_2/F_IO_2 : 130 to 225 mmHg). The application of a conversely low PEEP of 6 cmH_2O for the native lung, which was based on the ventilation strategy for obstructive lung disease, did not exacerbate the hyperinflation. Some previous studies have reported the application of ILV for asymmetrical lung diseases, such as unilateral lung contusion, unilateral bacterial pneumonia or primary graft dysfunction after SLT, including successful treatment with similar PEEP settings (diseased lung : 10-15 cmH_2O, non-diseased lung : 5-8 cmH_2O) (11, 17, 18).

The optimal duration of ILV in the critical care setting is unclear. One case series of ILV after SLT for emphysema reported that the duration of ILV varies among patients, ranging from 2 to 66 days (12). The use of prolonged ILV gives rise to several concerns regarding the use of a DLT, such as inadequate pulmonary hygiene, vocal cord trauma, tracheal membrane erosion and stenosis, increased airway resistance due to the narrow lumen, the need for deep sedation and/or paralysis to avoid patient-ventilator asynchrony and malposition of a DLT (9). In our patient, the duration of ILV was only two days. However, we believe that this duration was long enough to improve the respiratory function without obvious complications related to DLT placement. Considering that DLT placement itself may be invasive and require particular skills and experience for application in ICU settings, including preparation for bronchoscopy and experienced intensivists and nursing staff, it may be better to wean patients from ILV as soon as possible if they show improved gas exchange and equality in compliance between the lungs.

Acute allograft rejection commonly occurs weeks to months following surgery (19). According to the registry of the International Society of Heart and Lung Transplantation (ISHLT), 29% of patients who received primary lung transplant surgery were treated for at least 1 episode of acute allograft rejection in the first-year post-operation, and acute allograft rejection was responsible for about 4% of deaths in the first 30 days following lung transplantation (20). In our case, acute allograft rejection occurred 28 months after lung transplantation, mainly due to poor medical adherence. This means that we should remain alert, as acute allograft rejection may occur any time over the life of the donor lung, and we should be familiar with optimal ventilator management methods for asymmetrical lung pathology, especially in patients post-SLT for end-stage emphysema. ILV can still be a treatment option for complications in the chronic phase of SLT.

Regarding treatment for acute allograft rejection, most cases are treated with high-dose steroid regimens, included methylprednisolone 10-15 mg/kg/day for 3 days, followed by oral prednisolone tapering. Since the initial high-dose steroid is effective in 55% to 74% cases of acute allograft rejection (21, 22), optimal ventilation strategies are mandatory to allow the patient more time to recover until the effectiveness of medical therapy manifests. Although the significant improvements in her respiratory parameters and imaging findings were mainly due to the success of fundamental medical treatments other than mechanical ventilation therapy, we believe that, without ILV in this case, it would have been difficult for the patient to recover from her respiratory deterioration, or more time would have been needed to overcome this situation due to progressive acute hypoxemia and respiratory acidosis during conventional mechanical ventilation.

In conclusion, ILV is feasible and may increase the likelihood of successful treatment of atelectatic lungs due to acute allograft rejection and hyperinflating native lung after SLT that is refractory to conventional ventilation strategies. ILV should be included as a treatment option for critically ill patients with unilateral lung disease and severe respiratory distress in the chronic phase of SLT for end-stage emphysema.

CONFLICT OF INTERESTS

All authors have no conflict of interests.

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