Physiologic Effect and Safety of the Pumpless Extracorporeal Interventional Lung Assist System in Patients With Acute Respiratory Failure—A Pilot Study

*Woo Hyun Cho, †Kwangha Lee, ‡Jin Won Huh, ‡Chae-Man Lim, ‡Younsuck Koh, and ‡Sang-Bum Hong

*Department of Internal Medicine, *Pusan National University Yangsan Hospital and †Pusan National University Hospital, Pusan National University School of Medicine, Busan; and ‡Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*

Abstract: Interventional lung assist (iLA) effectively reduces CO_2 tension and permits protective lung ventilation in patients with acute respiratory distress syndrome. However, there is little experience in using iLA in acute respiratory failure from various causes and no experience for small body sizes such as Asian patients. We evaluated the physiologic effect and safety of the iLA device in patients with acute respiratory failure from various causes. We enrolled 11 consecutive patients with severe respiratory failure from various causes. Wire-enforced cannulae (13–15 Fr) were inserted under ultrasound guidance and connected to iLA. Arterial blood gas analysis, ventilator parameters, hemodynamic parameter, and adverse events were recorded serially. During the first 24 h of iLA use, mean blood flow was 1.08 ± 0.15 L/min, $PaCO_2$ decreased from 83.9 ± 23.4 mm Hg to 40.7 ± 10.2 mm Hg, and PaO_2/FiO_2 ratio increased from 110 ± 37 to 141 ± 74. Minute ventilation decreased from 9.4 ± 2.5 to 6.3 ± 1.5 L/min, and peak inspiratory pressure decreased from 30.3 ± 7.1 cm H_2O to 28.8 ± 9.4 cm H_2O. No serious adverse events were observed during iLA use. iLA showed effective CO_2 removal, allowed for reducing the invasiveness of mechanical ventilation in patients with severe respiratory failure from various causes even using a small-sized catheter and was safe in small body-sized patients. **Key Words:** Respiratory failure—Interventional lung assist—Physiology—Safety.

Although mechanical ventilation has been used to support patients with acute respiratory failure, and is critical for their survival, it can cause additional lung injury that may delay or prevent resolution of respiratory failure (1). Ventilator-induced lung injury may be caused by overdistension of aerated lung regions, especially when large tidal volumes (V_T) are used (2–5). To protect injured lungs from stress failure during mechanical ventilation, various methods have been tried either totally or partially, from extracorporeal gas exchange (6,7). These methods, however, are very invasive and require sophisticated machines and experienced personnel, precluding widespread application at the bedside.

The introduction of small, easy-to-use devices such as the NovaLung interventional lung assist (iLA) has made extracorporeal gas exchange a treatment option in patients with severe respiratory failure (8,9). The NovaLung iLA is a low-gradient device, designed to operate without the help of a mechanical pump in an arteriovenous configuration. This device is attached to the systemic circulation and receives only part of the cardiac output (1–2 L/min) for extracorporeal gas exchange.

The iLA has been shown to reduce CO_2 tension and could be used to avoid the need for aggressive ventilation even in the most severe cases (10–18). As the iLA was studied mainly in acute respiratory distress syndrome (ARDS) patients, in other clinical situations and underlying lung conditions, however, little is known about the clinical role, physiologic effects, and safety of the iLA. Furthermore, this device has been rarely used in small body sizes such as Asian patients. We therefore evaluated the safety and physiologic efficacy of the iLA system in Asian patients with various clinical situations and underlying lung conditions, who required aggressive ventilation to achieve safe blood gas profiles.

PATIENTS AND METHODS

Patients

Between January and October 2010, we enrolled 11 consecutive patients with acute respiratory failure in whom lung protective ventilation strategy was aborted to achieve safe blood gas profiles. Lung protective strategies were defined as keeping plateau pressure <30 cm H_2O and applying a low V_T (6–8 mL/kg predicted body weight). Severe respiratory acidosis exceeding arterial pH of 7.2, and clinical situations, not in accordance with well-established strategies to protectively ventilate the lung, were considered mandatory for the implementation of iLA. Patients with severe hypoxemia (PaO_2/FiO_2 <70) at positive end-expiratory pressure (PEEP) of 10 cm H_2O, hemodynamic instability (mean arterial pressure <60 mm Hg), or severe peripheral vascular disease were not considered suitable for the iLA. All patients or their legal representatives provided

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Address correspondence and reprint requests to Dr. Sang-Bum Hong, Asan Medical Center, 388-1 Pungnap-2 Dong, Songpa-gu, Seoul 138-736, Korea. E-mail: sbhong@amc.seoul.kr

written informed consent, and the study protocol was approved by Asan Medical Center institutional review board.

Measurements

Patient baseline characteristics, such as age, gender, body mass index (BMI), days on ventilator before iLA commencement, duration of iLA use, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) score, were recorded. Physiologic parameters, such as PaO_2/FiO_2 ratio (PF ratio), PaO_2, $PaCO_2$, arterial oxygen saturation, and blood pH; respiratory parameters, such as minute ventilation (MV), V_T, respiratory rate (RR), and peak airway pressure; hemodynamic parameters, such as mean arterial pressure and requirement for a vasopressor; and routine laboratory findings were recorded immediately before iLA implementation, at 1, 6, 12, and 24 h after iLA implementation and daily thereafter. Any clinical complications and adverse events were recorded during routine daily checkups.

Technique

In all cases, the iLA system was implemented by an intensivist in our institution. Before implementation, an average arterial pressure of 60 mm Hg was required for the iLA membrane to function properly. Cannulae were placed percutaneously into femoral vessels using the Seldinger technique under ultrasound guidance. In case of vascular pathology, that is, severe atherosclerosis or intravascular thrombus, or in case of diameter of vessel less than 5 mm as confirmed by ultrasound, implementation of iLA was aborted. A 13 Fr-sized cannula was selected for arterial insertion, and a 15 Fr-sized cannula for venous insertion. Blood flow was monitored continuously and was always maintained around 1 L/min, if possible. Following vascular cannulation, 5000 units of unfractionated heparin were administered intravenously and PTT was titrated to 55 s or more.

RESULTS

Baseline characteristics

All patients had severe respiratory failure and were under mechanical ventilation. Patients had various underlying conditions, such as obstructive lung disease, post-lung resection, and interstitial lung disease (ILD) (Table 1). Respiratory failure was caused by pneumonia in six patients, acute exacerbation of ILD in three patients, massive hemoptysis in one patient, and near-fatal asthmatic attack in one patient (Table 1). Main indications for iLA use were refractory hypercapnia (seven patients), enabling of protective ventilation in ARDS (two patients), and therapy for pneumothorax (two patients) (Table 1). Mean height was 164.3 ± 6.9 cm and mean BMI was 19.5 ± 4.4 kg/m^2. Mean duration of mechanical ventilation before iLA implementation was 8.6 ± 12.6 days, and mean duration of iLA support was 8.6 ± 9.4 days. APACHE II and SOFA scores at 24 h were 25.3 ± 3.7 and 8.8 ± 1.8, respectively. The successful weaning of iLA was possible in three patients; however, there is one surviving case in near-fatal asthma and one patient transferred to another hospital.

Gas exchange and hemodynamics

The mean blood flow across the iLA remained stable, ranging from 0.89 ± 0.19 L/min at 1 h to 1.08 ± 0.15 L/min at 24 h and to 1.03 ± 0.11 L/min at 72 h. The average sweep flow was set at 3.5 ± 1.2 L/

TABLE 1. *Patient demographic and clinical characteristics at baseline*

Age (years)	58.0 ± 15.4 (33–75)
Sex (male/female)	8/3
Height (cm)	164.3 ± 6.9 (157–177)
BMI (kg/m^2)	19.5 ± 4.4 (13.7–26.1)
Days on ventilator prior to iLA	8.4 ± 12.6 (0–40)
Duration of iLA (days)	8.6 ± 9.4 (2–32)
APACHE II, 24 h	25.3 ± 3.7 (17–30)
SOFA, 24 h	8.8 ± 1.8 (6–11)
*Underlying lung disease	
Obstructive lung disease	4
ILD	3
Post-pneumonectomy or lobectomy	3
HCMP with pulmonary hypertension	1
No disease	1
Diagnosis	
Pneumonia	6
Acute exacerbation of ILD	3
Massive hemoptysis	1
Severe asthmatic attack	1
Indication for iLA	
Enable protective ventilation in ARDS	2
Refractory hypercapnia	7
Rescue for pneumothorax	2
Causes for weaning of iLA	
Improvement	3
Deterioration	7
Hypoxemia	5
Shock	2
Need for withdrawal	1

Values given as mean ± standard deviation (range).

* One or more underlying lung diseases are listed. Obstructive lung disease includes two chronic obstructive pulmonary diseases and one bronchial asthma.

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; HCMP, hypertrophic cardiomyopathy; ILD, interstitial lung disease.

TABLE 2. *Gas exchange and hemodynamics during iLA*

Variables	Baseline	1 h	6 h	12 h	24 h	48 h	72 h
Gas exchange							
pH	7.18 ± 0.13	7.34 ± 0.12	7.37 ± 0.13	7.44 ± 0.08	7.42 ± 0.06	7.44 ± 0.08	7.41 ± 0.05
$PaCO_2$ (mm Hg)	83.9 ± 23.4	56.5 ± 21.2	47.1 ± 11.6	39.1 ± 10.9	40.7 ± 10.2	43.6 ± 10.1	48.6 ± 14.3
PaO_2 (mm Hg)	84.3 ± 35.3	72.7 ± 21.4	83.8 ± 40.9	110 ± 108	80.2 ± 24.2	68.4 ± 15.2	69.9 ± 25.1
PF ratio (mm Hg)	110 ± 36.6	106 ± 43	112 ± 49	153 ± 114	141 ± 74	132 ± 89	89 ± 18
iLA data							
Gas flow(O_2) (L/min)		3.5 ± 1.2	8.0 ± 2.9	8.1 ± 2.5	8.4 ± 2.1	8.8 ± 2.4	9.4 ± 2.8
Blood flow (L/min)		0.89 ± 0.19	0.90 ± 0.34	1.08 ± 0.15	1.06 ± 0.11	1.08 ± 0.06	1.03 ± 0.11
Ventilator settings							
RR (breaths/min)	28.6 ± 4.7	25.8 ± 4.7	24.4 ± 5.1	24.3 ± 6.7	21.6 ± 6.7	22.0 ± 6.6	21.3 ± 8.6
V_T (mL)	331 ± 87	297 ± 79	245 ± 67	311 ± 81	328 ± 116	309 ± 88	324 ± 94
MV (L/min)	9.43 ± 2.50	8.15 ± 2.08	6.37 ± 2.09	7.09 ± 1.49	6.34 ± 1.45	7.74 ± 3.64	6.73 ± 1.85
PIP (cm H_2O)	30.3 ± 7.1	30.8 ± 7.8	32.6 ± 6.3	32.3 ± 6.5	28.8 ± 9.4	25.1 ± 11.4	24.5 ± 10.5
PEEP (cm H_2O)	3.0 ± 2.9	3.0 ± 2.9	3.6 ± 3.1	3.8 ± 3.2	4.4 ± 2.8	4.0 ± 3.1	5.6 ± 2.8
Hemodynamic data							
MAP (mm Hg)	85.3 ± 10.8	78.5 ± 11.5	83.0 ± 15.0	90.8 ± 17.2	78.9 ± 15.6	79.1 ± 10.7	81.1 ± 10.3
Norepinephrine (μg/kg/min)	0.19 ± 0.27	0.18 ± 0.27	0.28 ± 0.42	0.21 ± 0.25	0.16 ± 0.19	0.14 ± 0.23	0.11 ± 0.10

Values given as mean ± standard deviation (range).
MAP, mean arterial pressure; MV, minute ventilation; PEEP, positive end-expiratory pressure; PF ratio, PaO_2/FiO_2; PIP, peak inspiratory pressure; RR, respiratory rate; V_T, tidal volume.

min at 1 h and was further increased to 8.4 ± 2.1 L/min at 24 h and 9.4 ± 2.8 L/min at 72 h.

The effects of iLA on arterial oxygenation were dependent on underlying lung conditions. During the first 12 h of iLA implementation, a significant improvement in mean PF ratio was observed in three cases of ILD (from 99.0 ± 5.4 to 108.7 ± 6.4) and three cases of obstructive lung disease (from 129.0 ± 62.9 to 252.2 ± 132.6), whereas a deterioration of oxygenation was observed in three cases of post-lung resection, one hypertrophic cardiomyopathy patient with resting pulmonary hypertension, and one with late-stage ARDS (from 104.4 ± 31.1 to 78.9 ± 15.3). Mean PF ratio in the 11 patients increased from 110 ± 37 mm Hg at baseline to 112 ± 49 mm Hg at 6 h and to 141 ± 74 mm Hg at 24 h.

Although its effect on oxygenation varied, the iLA initiation resulted in a marked removal of $PaCO_2$ and a normalization of arterial pH level within 1 h after onset of therapy, allowing a rapid reduction in MV (Table 2). Mean $PaCO_2$ decreased from 83.9 ± 23.4 mm Hg at baseline to 56.5 ± 21.2 mm Hg at 1 h, to 47.1 ± 11.6 mm Hg at 6 h, and to 40.7 ± 10.2 mm Hg at 24 h.

Implementation of the iLA did not induce any hemodynamic instability and decreased the amount of continuously infused noradrenalin (Table 2).

Adverse events and laboratory variables

Complications observed during iLA use are shown in Table 3. Clotting in the iLA membrane ventilator was the most common adverse event, occurring in eight patients. In addition, hematoma at the cannulation site, dislocation of the cannula connection, and bleeding occurred in one patient each. None of these complications, however, affected iLA implementation or patient outcomes.

During iLA treatment, there was a moderate prolongation of partial thromboplastin time. However, platelet count and other laboratory variables were not affected.

DISCUSSION AND CONCLUSIONS

The main results of our study were that the iLA system was effective in rapidly reducing CO_2 and was sufficiently safe to implement in severe respiratory failure. The rapid reduction of carbon dioxide observed in most patients allowed a significant reduction in aggressive ventilation within hours. The effects of the iLA on oxygenation might be dependent on underlying lung conditions. Small arterial cannulae were suitable for small body-sized patients, without

TABLE 3. *Adverse events*

Event	Baseline
Hematoma	1
Limb ischemia	—
Air embolism	—
Kinking of the cannula	—
Clotting of the iLA membrane ventilator	8
Dislocation of the cannula	1
Bleeding	1

compromising the efficacy and safety of the iLA. We observed that iLA did not cause hemodynamic instability.

Our patients had various clinical situations, such as refractory hypercapnia and ARDS requiring protective lung ventilation, and pneumothorax, requiring preemptive iLA implementation. Most of our patients had underlying lung conditions with low physiologic reserve, such as post-lung resection, advanced ILD, and severe obstructive airway diseases. In seven of our patients, iLA was initiated to control refractory hypercapnia and to rescue them from life-threatening situations. One of these patients presented with massive hemoptysis and refractory hypercapnia; in this patient, the iLA was effective in reducing CO_2 without anticoagulation. Two of our patients had pneumothorax under mechanical ventilation. To avoid further aggravation of pneumothorax, we decreased V_T and preemptively initiated iLA, which successfully controlled pneumothorax in the absence of chest tubing. The iLA system has been used in ARDS patients to rescue them from life-threatening situations (19,20), showing that iLA was an effective and safe rescue therapy in patients with severe ARDS with hypercapnia. Clinical use of the iLA has recently been suggested in various other clinical situations, such as bridge therapy for lung transplantation, interhospital transportation of patients with respiratory failure, and preemptive CO_2 control for patients with head injuries (12,16,18). Few studies, however, have assessed the physiologic effects of the iLA in patients with underlying lung conditions such as chronic obstructive pulmonary disease, ILD, and post-lung resection. Therefore, our experience with the iLA may be helpful in extending its clinical role in various respiratory diseases.

In early clinical studies, extracorporeal membrane oxygenation failed to show outcome benefits in adult patients, despite its physiologic effects on blood gas and hemodynamics (21). This failure was due primarily to the occurrence of significant adverse events, such as bleeding, hemolysis, and technical problems. Therefore, minimizing complications is important for successful iLA implementation. We inserted a 13 Fr cannula into the femoral artery of each patient, resulting in a mean iLA flow of approximately 1.0 L/min. Despite this flow being lower than in previous studies (8,19), it resulted in effective CO_2 removal without serious complications. As the level of CO_2 became normalized, it became possible to reduce V_T, RR, and MV, leading to decreased peak inspiratory pressure. In a previous study, the size of the arterial cannula ranged from 13 to 21 Fr to establish a minimum iLA flow of 1.5 L/min (19). Limiting the size of the arterial cannula to 15 or 17 Fr was shown to reduce ischemic complications to the lower limbs (20). Most of these results, however, were obtained in European patients, suggesting that these arterial cannulae may be too large for small body-sized patients, due to differences in height, weight, and BMI. Although our study population was small, none of our patients experienced ischemic complications of the lower limbs or thrombosis of the cannula.

The main determinant of gas exchange from extracorporeal membrane system is the blood flow through the system. A previous study showed that iLA induced marked CO_2 removal and moderate oxygenation with approximately 1.5–2.0 L/min iLA flow (20). In our study, we found that early improvement of oxygenation effect disappeared on day 3 even though blood flow through iLA was maintained at 1.0 L/min. So it is possible that lower blood flow failed to improve oxygenation. Another explanation might be that our PEEP settings were relatively lower than previous data. Animal experimental study showed that iLA could cause deterioration of oxygenation due to increasing ventilation/perfusion mismatch (22). With regard to CO_2 removal, it is interesting that our data were similar to previous studies despite relatively lower blood flow. Terragni et al. also showed that lower blood flow could decrease CO_2 effectively, but this article did not mention the oxygenation effect (23). Taken together, we suggest that low blood flow via a small catheter is enough to remove CO_2 only; however, to improve oxygenation with CO_2 removal we should maintain a high flow via a large catheter and increased PEEP level.

We found that oxygenation through the iLA might vary due to underlying lung conditions. A moderate benefit was observed in three cases of ILD and three cases of obstructive lung disease. However, deterioration of oxygenation was observed in three post-lung resection patients. To our knowledge, few reports have assessed the oxygenation effects of the iLA, and these reports focused on ARDS models (15,22). Therefore, further study will be needed to confirm the effect of iLA on oxygenation according to underlying lung physiology.

This study had several limitations, including its small sample size and its inclusion of patients from a single center. We focused on the physiologic efficacy and safety of iLA in acute respiratory failure with various underlying lung diseases. The iLA showed efficient CO_2 removal following reduction of MV and

was both easy to implement and safe. However, the iLA should be applied cautiously because it may worsen hypoxemia in some patients. Technically, we found that 13 Fr arterial cannulae resulted in an iLA flow around 1 L/min and was safe for small body-sized patients.

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REFERENCES

1. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998;157:294–323.
2. Tsuno K, Miura K, Takeya M, et al. Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. *Am Rev Respir Dis* 1991;143:1115–20.
3. Dreyfuss D, Soler P, Basset G, et al. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988;137:1159–64.
4. Parker JC, Townsley MI, Rippe B, et al. Increased microvascular permeability in dog lungs due to high peak airway pressures. *J Appl Physiol* 1984;57:1809–16.
5. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–8.
6. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994;149:295–305.
7. Bartlett RH, Roloff DW, Custer JR, et al. Extracorporeal life support: the University of Michigan experience. *JAMA* 2000;283:904–8.
8. Tao W, Brunston RL Jr, Bidani A, et al. Significant reduction in minute ventilation and peak inspiratory pressures with arteriovenous CO_2 removal during severe respiratory failure. *Crit Care Med* 1997;25:689–95.
9. Liebold A, Reng CM, Philipp A, et al. Pumpless extracorporeal lung assist—experience with the first 20 cases. *Eur J Cardiothorac Surg* 2000;17:608–13.
10. von Mach MA, Kaes J, Omogbehin B, et al. An update on interventional lung assist devices and their role in acute respiratory distress syndrome. *Lung* 2006;184:169–75.
11. Cordell-Smith JA, Roberts N, Peek GJ, et al. Traumatic lung injury treated by extracorporeal membrane oxygenation (ECMO). *Injury* 2006;37:29–32.
12. Fischer S, Simon AR, Welte T, et al. Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. *J Thorac Cardiovasc Surg* 2006;131:719–23.
13. Kjaergaard B, Christensen T, Neumann PB, et al. Aeromedical evacuation with interventional lung assist in lung failure patients. *Resuscitation* 2007;72:280–5.
14. Kopp R, Dembinski R, Kuhlen R. Role of extracorporeal lung assist in the treatment of acute respiratory failure. *Minerva Anestesiol* 2006;72:587–95.
15. Zick G, Frerichs I, Schadler D, et al. Oxygenation effect of interventional lung assist in a lavage model of acute lung injury: a prospective experimental study. *Crit Care* 2006;10:R56.
16. Zimmermann M, Bein T, Philipp A, et al. Interhospital transportation of patients with severe lung failure on pumpless extracorporeal lung assist. *Br J Anaesth* 2006;96:63–6.
17. Elliot SC, Paramasivam K, Oram J, et al. Pumpless extracorporeal carbon dioxide removal for life-threatening asthma. *Crit Care Med* 2007;35:945–8.
18. Mallick A, Elliot S, McKinlay J, et al. Extracorporeal carbon dioxide removal using the Novalung(R) in a patient with intracranial bleeding. *Anaesthesia* 2007;62:72–4.
19. Bein T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med* 2006;34:1372–7.
20. Zimmermann M, Bein T, Arlt M, et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. *Crit Care* 2009;13:R10.
21. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979;242:2193–6.
22. Dembinski R, Hochhausen N, Terbeck S, et al. Pumpless extracorporeal lung assist for protective mechanical ventilation in experimental lung injury. *Crit Care Med* 2007;35:2359–66.
23. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 mL/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009;111:826–35.