TRD
Tuberculosis and
Respiratory Diseases

Thrombotic Complications during Interventional Lung Assist: Case Series

Eun Jung Kim, M.D.[1], **Woo Hyun Cho, M.D.**[1], **Eun Young Ahn, M.D.**[1], **Dae Gon Ryu, M.D.**[1], **Seung Eun Lee, M.D.**[1], **Doo Soo Jeon, M.D., Ph.D.**[1], **Yun Seong Kim, M.D., Ph.D.**[1], **Bong Soo Son, M.D.**[2] **and Do Hyung Kim, M.D.**[2]

Departments of [1]Internal Medicine and [2]Cardiovascular and Thoracic Surgery, Pusan National University Yangsan Hospital, Yangsan, Korea

Interventional lung assist (iLA) effectively reduces CO_2 retention and allows protective ventilation in cases of life-threatening hypercapnia. Despite the clinical efficacy of iLA, there are a few major limitations associated with the use of this approach, such as bleeding, thrombosis, and catheter-related limb ischemia. We presented two cases in which thrombotic complications developed during iLA. We demonstrated the two possible causes of thrombotic complications during iLA; stasis due to low blood flow and inadequate anticoagulation.

Keywords: Lung; Complications; Thrombosis

Introduction

Interventional lung assist (iLA), which is performed using a device manufactured by Novalung (Talheim, Germany), has been used as rescue therapy in life-threatening forms of refractory hypercapnic respiratory failure[1-4]. The iLA system is characterized by a heparin-coated poly(4-methyl-2-pentyne) membrane with optimized blood flow, which is integrated into an arteriovenous bypass established by cannulation of the femoral artery and vein[5]. A blood flow setting of 1.0–1.5 L has been considered sufficient to reduce catheter-related dis-tal limb ischemia and facilitate protective ventilation[6]. However, concerns regarding thrombotic complications exist at low blood flow settings with or without anticoagulation. These events can be fatal in critically ill patients. Here, we review two cases of thrombotic complications that developed during extracorporeal membrane oxygenation (ECMO) support.

Case Report

1. Case 1

A 70-year-old man, who had undergone lung cancer resection 32 months ago, was admitted to the anesthesia department for stump (amputated finger) pain management. During hospitalization, the patient developed pneumonia, and the peripheral capillary oxygen saturation (SpO_2) decreased to 89% with mild dyspnea. On day 11 of hospitalization, SpO_2 rapidly decreased to 68% while the patient was receiving 100% oxygen via a non-rebreather facemask, and conventional ventilation was initiated. Hypercapnia was intractable despite mechanical ventilation; therefore, he was placed on iLA (Table 1). On the second day of iLA, the iLA flow was zero due to clots in the circuit without anticoagulation (Figure 1); consequently, the iLA membrane was changed and heparin infusion was started. On the tenth day of iLA, clots formed again despite

Address for correspondence: Woo Hyun Cho, M.D.
Department of Internal Medicine, Pusan National University Yangsan Hospital, 20 Geumo-ro, Yangsan 626-787, Korea
Phone: 82-55-360-1414, **Fax:** 82-55-360-1757
E-mail: popeyes0212@hanmail.net

heparin infusion (Table 2). Ultimately, veno-venous ECMO was initiated for effective oxygenation. On the 11th day of ECMO, acute respiratory distress syndrome was not resolved, and the patient died of multi-organ failure.

2. Case 2

A 61-year-old man was admitted to the emergency room because of a near-fatal asthma attack. The initial arterial blood gas analysis revealed the following findings: pH, 7.15; $PaCO_2$, 66 mm Hg; PaO_2, 66 mm Hg, and O_2 saturation 86%. His mental functions gradually decreased despite conventional treatment for asthma. The patient's hypercapnia was intractable under conventional mechanical ventilation (Table 1). As such, iLA support was initiated within 2 hours after intubation with heparin infusion. After iLA insertion, hypercapnia resolved immediately. Extubation was done 32 hours after intubation, and iLA was removed 55 hours after insertion. After the removal of iLA, the patient complained about a new episode of dyspnea. Pulmonary embolism was diagnosed through a computed tomography scan (Figure 2) and anticoagulation treatment was initiated. On the ninth day, he was transferred to his hometown for follow-up treatment.

Discussion
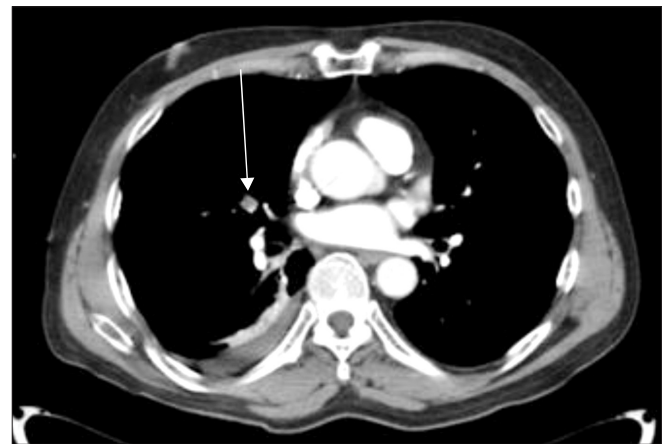
The iLA employs a low-gradient device designed to operate

Figure 1. Case 1. Clots in the circuit.

Figure 2. Case 2. Chest spiral computed tomography scan showing filling defect at pulmonary artery (arrow).

Table 1. Patient demographic and clinical data

Variable	Case 1	Case 2
Age, yr	70	61
Sex	Male	Male
SOFA score	6	3
SAPS-II score	43	36
Initial PaO_2/FiO_2 ratio	98	110
Lung injury score, Murray	3	1.75
Underlying disease	Pneumonia	Near-fatal asthma
Diagnosis	ARDS	Near-fatal asthma
Indication for iLA	Protective ventilation	Refractory hypercapnia
Days on iLA	9	3
Catheter size A/V, Fr	13/15	13/15

SOFA: sequential organ failure assessment; SAPS: simplified acute physiology score; ARDS: acute respiratory distress syndrome; iLA: interventional lung assist; A/V: artery/vein.

Table 2. Coagulation parameters, dose of heparin, changes in gas exchange, cardiovascular and respiratory variables before and during iLA treatment

Variable	Case 1			Case 2		
	Pre	2 hr	24 hr	Pre	2 hr	24 hr
PaO_2/FiO_2 ratio	98	135	100	136.6	247.75	344
Arterial pH	7.05	7.24	7.46	6.98	7.104	7.368
Partial pressure of CO_2, mm Hg	122	75	35	107	>81	28.4
Partial pressure of O_2, mm Hg	98	81	60	82	99.1	137.6
FiO_2	1	0.6	0.6	0.6	0.4	0.4
Tidal volume, mL	380	380	410	320	350	-
Peak inspiratory pressure, cm H_2O	32	28	24	24	22	-
PEEP, cm H_2O	12	10	10	8	4	-
MAP, mm Hg	96.85±12.06	100±11.41		60.5±2.07	91.6±6.8	
HR, bpm	116±14.02	103±4.99		113±5	98.2±9.6	
iLA flow, L/min	-	1.06±0.26		-	0.69±0.04	
Platelet count, 10^3/μL	299	160±41.3		214	98.75±35.25	
PT-INR	1.14	1.24±0.08		0.88	0.94±0.03	
aPTT, sec	32.3	72.8±5.74		27.1	64.65±23.26	
Hb, g/dL	13.4	12.7±0.41		13.8	13.4±1.76	
Heparin per iLA day, IU	23,406 ± 3,143			222,006±9,333		

Values are presented as number or mean±SD.
iLA: interventional lung assist; PEEP: positive end-expiratory pressure; MAP: mean arterial pressure; HR: heart rate; PT-INR: prothrombin international normalized ratio; aPTT: activated partial thromboplastin time; Hb: hemoglobin.

Table 3. Comparison in coagulation parameters, dose of heparin, catheter size, and flow rate between thrombosis and non-thrombosis group of during iLA

	iLA flow (min/L)	PT-INR	aPTT (sec)	Heparin per iLA day (IU)	Catheter size A/V (Fr)
Thrombosis group					
Case 1	1.06±0.26	1.24±0.08	72.8±5.74	23,406±3,143	13/15
Case 2	0.69±0.04	0.94±0.03	64.65±23.26	22,006±9,333	13/15
Non-thrombosis group					
Case A	0.93±0.39	1.24±0.08	91.5±5.44	35,000±12,535	13/15
Case B	0.96±0.22	1.44±0.17	84.8±4.04	34,166.67±12,416	13/15
Case C	1.41±0.60	1.65±0.22	85.8±2.04	20,937±12,951	13/15
Case D	0.92±0.32	-	-	-	13/15
Case E	0.97±0.12	-	-	-	13/15

Values are presented as mean±SD.
iLA: interventional lung assist; PT-INR: prothrombin international normalized ratio; aPTT: activated partial thromboplastin time; A/V: artery/vein.

without a mechanical pump in an arteriovenous configuration[7]. The natural arteriovenous blood pressure gradient determines the flow through the oxygenator[4]. The patient's oxygenation predominantly depends on arteriovenous shunt volume, which is influenced by the cannula diameter and the patient's mean arterial blood pressure[5]. Jayroe et al.[6] suggested that a blood flow of 1.0–1.5 L/min is sufficient to remove CO_2 effectively, and a smaller cannula decreases the incidence of cannula-related limb ischemia. Further, other data showed that low blood flow settings decreased distal limb ischemia

as well as effectively removed CO_2 level in Asians with petite body figures[7]. However, stasis which originates from low flow may have an impact on venous thrombosis. Our cases suggest that this concern is not groundless.

Catheter thrombosis occurred 24 hours after iLA device insertion in case 1, and pulmonary thromboembolism was diagnosed 55 hours after iLA device insertion in case 2. From January 2012 to August 2013, we recorded two cases of thrombotic (28.5%) complications out of the seven cases in which iLA was employed. The incidence of thrombotic complications was exceptionally higher than that in previous studies, which showed cannula thrombosis rates of 1.9%[5]. In all seven cases, the diameter of the arterial cannula was 13 French (Fr), whereas the venous cannula was selected to be 2Fr larger so that flow resistance was not compromised. Our anticoagulation strategy used a similar protocol (activated partial thromboplastin time [aPTT] level≥1.5 times the upper normal limit) to other studies[1-8]. To achieve a prolongation of the aPTT time, heparin (Heparin-Natrium-25,000; 200–600 IU/hr) was continuously infused into the arterial cannula before the gas-exchange membrane. However, in case D and E in nonthrombotic group, anticoagulation was not initiated because of hemoperitoneum and hemoptysis (Table 3).

The first factor to be considered for the high incidence of thrombosis is the maintenance of low blood flow through iLA. Generally, the blood flow was maintained below 1 L/min in all cases of iLA in our hospital. Jayroe et al.[6] suggested that a low blood flow of 1.0–1.5 L/min was sufficient to remove CO_2 effectively; however, it possibly caused the stasis and formation of thrombosis. Furthermore, the biggest difference between our study and previous studies is the mean blood flow. In a previous prospective pilot study[5], the thrombosis incidence was 1.9% when the mean blood flow was above 1.5 min/L. As we mentioned before, the blood flow depends on arteriovenous shunt volume, which is influenced by the diameter of the cannula and the patient's mean arterial blood pressure[5]. Even though the mean arterial pressure in these cases was maintained above 70 mm Hg, which is enough to produce adequate iLA flow, the blood flow was below 1.0 L/min. In previous studies from European countries and the United States, cannula sizes of 17Fr for veins and 15Fr for arteries had been used[1-6]; however, we used 15Fr for veins and 13Fr for arteries in proportion to the petite Asian body size to reduce catheter-related limb ischemia[7]. We assumed that the small size of the cannula caused low blood flow and stasis. Therefore, we suggest that an optimal cannula size be chosen to maintain a balance between prevention of thrombosis and distal limb ischemia. We recommend checking the femoral arterial diameter using Doppler ultrasound to determine an optimal cannula size that can maintain sufficient blood flow with adequate anticoagulation to reduce thrombosis. Unless a small cannula can sufficiently maintain flow rate, the transition to pump-driven ECMO should be considered for maintenance of blood

flow and gas exchange.

The second factor to be considered for the high incidence of thrombosis is inadequate anticoagulation. Although our anticoagulation strategy used a similar protocol (aPTT level≥1.5 times the upper normal limit) to other studies[1-8], aPTT level was not reaches to >1.5 times the upper normal limit. Even though the target aPTT level is between 55–70 seconds in iLA protocol of our hospital, aPTT level was ranged to 36.6–70.2 seconds between the first and the second catheter thrombosis in case 1 with heparinization. And the level was ranged to 27.1–81.1 seconds with heparinization in case 2. Therefore, strict target-achieved anticoagulation is important to prevent thrombosis. Furthermore, Bein et al.[8] recently demonstrated that adding acetylsalicylic acid to heparin for anticoagulation management reduces thrombotic complications without bleeding. Addition of acetylsalicylic acid can also be considered as one of the techniques for prevention of thrombosis.

However, our cases show some limitations to the general hypothesis that low blood flow and stasis are the causes of thrombosis. In addition, reviews assessing coagulopathy with antithrombin III activity were not evaluated although underlying antithrombin III deficiency, which would cause heparin resistance, would be a possible cause of thrombosis. Therefore, if thrombotic events occur despite adequate anticoagulation, combined antithrombin III deficiency must be considered and evaluated[9,10].

In conclusion, thrombotic complications are one of the common complications in iLA. A small-sized cannula may be beneficial in reducing limb ischemia but not thrombosis in low blood flow settings. The arterial diameter should be evaluated using Doppler ultrasound before insertion of the cannula. In patients with a small femoral artery, pump-driven venovenous ECMO should be considered as an alternative treatment. Also, strict target-achieved anticoagulation is important to prevent thrombosis.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

References

1. Tao W, Brunston RL Jr, Bidani A, Pirtle P, Dy J, Cardenas VJ Jr, 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.

2. Liebold A, Reng CM, Philipp A, Pfeifer M, Birnbaum DE. Pumpless extracorporeal lung assist: experience with the first 20 cases. Eur J Cardiothorac Surg 2000;17:608-13.

3. Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med 2006;34:1372-7.

4. Zick G, Frerichs I, Schadler D, Schmitz G, Pulletz S, Cavus E, 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.

5. Zimmermann M, Bein T, Arlt M, Philipp A, Rupprecht L, Mueller T, et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. Crit Care 2009;13:R10.

6. Jayroe JB, Wang D, Deyo DJ, Alpard SK, Bidani A, Zwischenberger JB. The effect of augmented hemodynamics on blood flow during arteriovenous carbon dioxide removal. ASAIO J 2003;49:30-4.

7. Cho WH, Lee K, Huh JW, Lim CM, Koh Y, Hong SB. Physiologic effect and safety of the pumpless extracorporeal interventional lung assist system in patients with acute respiratory failure: a pilot study. Artif Organs 2012;36:434-8.

8. Bein T, Zimmermann M, Philipp A, Ramming M, Sinner B, Schmid C, et al. Addition of acetylsalicylic acid to heparin for anticoagulation management during pumpless extracorporeal lung assist. ASAIO J 2011;57:164-8.

9. Villaneuva GB, Danishefsky I. Evidence for a heparin-induced conformational change on antithrombin III. Biochem Biophys Res Commun 1977;74:803-9.

10. Oliver WC. Anticoagulation and coagulation management for ECMO. Semin Cardiothorac Vasc Anesth 2009;13:154-75.