

Intrabronchial Infusion of Autologous Blood Plus Thrombin for Intractable Pneumothorax After Bronchial Occlusion Using Silicon Spigots

A Case Series of 9 Patients With Emphysema

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Background: Bronchial occlusion therapy using silicon spigots is effective for intractable pneumothorax. However, sometimes the pneumothorax is refractory to bronchial occlusion because of collateral ventilation. For such difficult pneumothoraces, we attempted an intrabronchial infusion of autologous blood plus thrombin to control collateral ventilation and stop air leaks.

Methods: We performed bronchial occlusions using silicon spigots in patients with spontaneous pneumothorax secondary to emphysema and refractory to chest drainage, but which was inoperable owing to each patient's poor surgical candidacy and poor overall health condition. When bronchial occlusion proved ineffective, we undertook intrabronchial infusion of autologous blood plus thrombin, 2 to 4 days after bronchial occlusion. A catheter was inserted into the subpleural area, through a gap between the silicon spigot and the bronchial wall, using a flexible bronchoscope under fluoroscopic guidance. Autologous blood, followed by a thrombin solution, was infused using the catheter. We repeated the same infusion a total of 4 to 6 times while changing the target bronchi. All interventions were performed under local anesthesia.

Results: The subjects were 9 men, aged from 61 to 88 years, with smoking histories. Three patients also had interstitial pneumonia, and 6 patients had undergone pleurodesis in vain before bronchial occlusion. For 4 of the 9 patients, autologous blood plus thrombin infusions successfully stopped air leaks, and in 3 patients, intrabronchial infusions and pleurodesis halted leaks altogether.

Conclusion: Intrabronchial infusion of autologous blood plus thrombin was effective for intractable pneumothoraces that could not be clinically managed, even by bronchial occlusion using silicon spigots.

Key Words: autologous blood, bronchial occlusion, emphysema, silicon spigot, pneumothorax

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The development of a pneumothorax is one of the most serious complications of emphysema. From August 2014 to July 2015, 68 emphysema patients presented at our hospital with spontaneous secondary pneumothorax that required a chest tube placement. Of these, 46 patients had a persistent air leak after chest tube placement that required further intervention (an operation in 35 cases and bronchial occlusion using silicon spigots in 11 cases).

Bronchial occlusion using silicon spigots (EWS, Novatech, La Ciotat, France) has proven effective for intractable pneumothorax that is refractory to chest drainage, and that is inoperable owing to the patient's poor surgical candidacy and poor overall health condition.^{1–3} However, in some cases, bronchial occlusion cannot stop air leaks because of the existence of collateral ventilation, seen especially in patients with emphysema. For such intractable cases, we attempted the intrabronchial infusion of autologous blood plus thrombin after bronchial occlusion. Here, we report the outcomes of this treatment and discuss the effectiveness and problems associated with this procedure.

PATIENTS AND METHODS

Patients

The subjects of this study were 9 patients with emphysema and who had also developed a secondary, spontaneous pneumothorax. Each patient's pneumothorax was refractory to chest

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drainage, with or without pleurodesis, and inoperable owing to the patient's poor surgical candidacy and poor overall health condition. In addition, each pneumothorax could not be clinically managed, even by bronchial occlusion using silicon spigots.

Methods

The bronchi responsible for each air leak were identified using chest computed tomography, and/or a balloon occlusion test. In patients for whom bronchial occlusion using silicon spigots was ineffective, we subsequently performed an intrabronchial infusion of autologous blood plus thrombin, 2 to 4 days after the bronchial occlusion.

Intervention

Each patient was placed under local anesthesia and mild sedation with 1.5 to 3 mg intravenous midazolam, and a bronchoscopy was then performed whereby silicon spigots (EWS) were inserted through an endotracheal tube. If a satisfactory decrease in each air leak was not obtained within 2 to 4 days, autologous blood plus thrombin were infused in an intrabronchial manner. The infusion was performed as follows: a catheter (PW-1L-1 or PW-5L-1; maximum external diameter: 2.45 mm; working length: 1650 mm; Olympus, Tokyo, Japan) was inserted through a gap between the silicon spigot and the bronchial wall into the subpleural area using a flexible bronchoscope (BF-1T260 or BF-1TQ290; Olympus) under fluoroscopic guidance. Autologous blood was drawn from a venous cannula that had been placed in the patient's median cubital vein, and the blood (3 to 4 mL) was immediately infused using a catheter, followed by 2500 U of thrombin solution (Mochida, Tokyo, Japan), and flushed by air (10 mL). We repeated the same infusion a total of 4 to 6 times while changing target bronchi.

We repeated the intrabronchial infusion at intervals of 3 to 5 days (mean 3.8 d) until the air leak resolved. However, if the air leak did not stop completely, additional insertions of spigots or even pleurodesis were performed as necessary.

We obtained authorization to perform this study in advance from the Ethics Committee of the National Organization Himeji Medical Center, Japan (registration number 26-11, approval date: August 11, 2014). We obtained informed consent from each enrolled individual, allowing us to provide treatment using the

specific procedure outlined above and to use the data obtained for research purposes.

RESULTS

The subjects studied were 9 men aged from 61 to 88 years and all with a history of smoking. Three patients also had interstitial pneumonia as well as emphysema. Before the onset of a pneumothorax, all patients had severe dyspnea (Modified Medical Research Council dyspnea scale: MMRC grade 4) and had undergone long-term oxygen therapy. Six of the 9 patients had undergone pleurodesis between 3 and 19 days (mean 10.7 d) before the bronchial occlusion, but air leaks had not stopped in any patients. The remaining 3 patients did not undergo pleurodesis before the bronchial occlusion because of a collapsed lung with massive air leaks.

The outcomes of combination therapy for the 9 cases examined are summarized in Table 1. Figure 1 shows 3 representative cases (cases 1, 3, and 4). In all 9 cases, the reduction in air leaks after bronchial occlusion using silicon spigots was a partial one and, consequently, an intrabronchial infusion of autologous blood plus thrombin was attempted.

The total number of bronchoscopies performed per patient was between 2 and 5 times (mean 3.9 times). Of these, intrabronchial infusions of autologous blood and thrombin were performed 1 to 2 times (mean 1.6 times) per patient. The total volume of blood that entered each patient's bronchi during each bronchoscopy was between 12 and 24 mL (mean 18.2 mL). Despite severe emphysema, complications secondary to repeated bronchoscopy and sedation were not seen.

In 4 patients, air leaks stopped within a few days of an infusion. In 3 patients, the effects of the intrabronchial infusions were incomplete and air leaks were finally stopped after an additional pleurodesis from between 2 and 6 days (mean 3.8 d) after the last intrabronchial infusion. Finally, air leaks did not stop for 2 patients, although a reduction in air leaks and reexpansion of the lung were achieved. These 2 cases eventually died due to an exacerbation of chronic obstructive pulmonary disease (COPD) during hospitalization for 13 (case 6) and 11 days (case 7), respectively, after intrabronchial infusion.

For case 1, we removed a silicon spigot 3 months after recovery from a pneumothorax. However, for the other 8 patients, spigots were

TABLE 1. Outcomes of Combination Therapy for Bronchial Occlusion Using Silicon Spigots With IBI-ABT

Case	Age (y)	Sex	Past History	Pleurodesis Before Bronchial Occlusion	Target of Bronchial Occlusion	No. Bronchial Occlusions	Total No. Silicon Spigots	No. IBI-ABT	Pleurodesis After IBI-ABT	Air Leak
1	88	Male	E and IP	+	Lt B3	1	1	1	-	Stopped
2	80	Male	E and IP	-	LtB1+2,3,6	3	5	2	-	Stopped
3	77	Male	E	-	Rt B4,5,8,9,10	2	4	2	+	Stopped
4	61	Male	E	+	Rt B1,2,3,6,9,10	3	6	1	-	Stopped
5	86	Male	E	-	Lt B3,4,5,8	3	8	2	+	Stopped
6	72	Male	E	+	Rt B1,2,3,4,5	2	5	1	+	Reduced
7	69	Male	E	+	Rt B1,3,4,6,8,10	3	9	2	-	Reduced
8	66	Male	E	+	Rt B1,2,3,4,5	3	7	2	+	Stopped
9	63	Male	E and IP	+	LtB1+2,3,4,5	1	6	1	-	Stopped
Mean	73.6					2.3	5.7	1.6		

E indicates emphysema; IBI-ABT, intrabronchial infusion of autologous blood plus thrombin; IP, interstitial pneumonia; Lt, left; Rt, right.

not removed because of the patients' poor overall health condition; but the expectation of a sustained therapeutic effect remained. No adverse effects were seen in relation to the remaining spigots.

In all cases, a consolidation shadow was transiently seen in the lung field of the infused side, a day after the intrabronchial infusion of autologous blood plus thrombin. Low-grade fever (4 cases) and hypoxemia (3 cases) were also

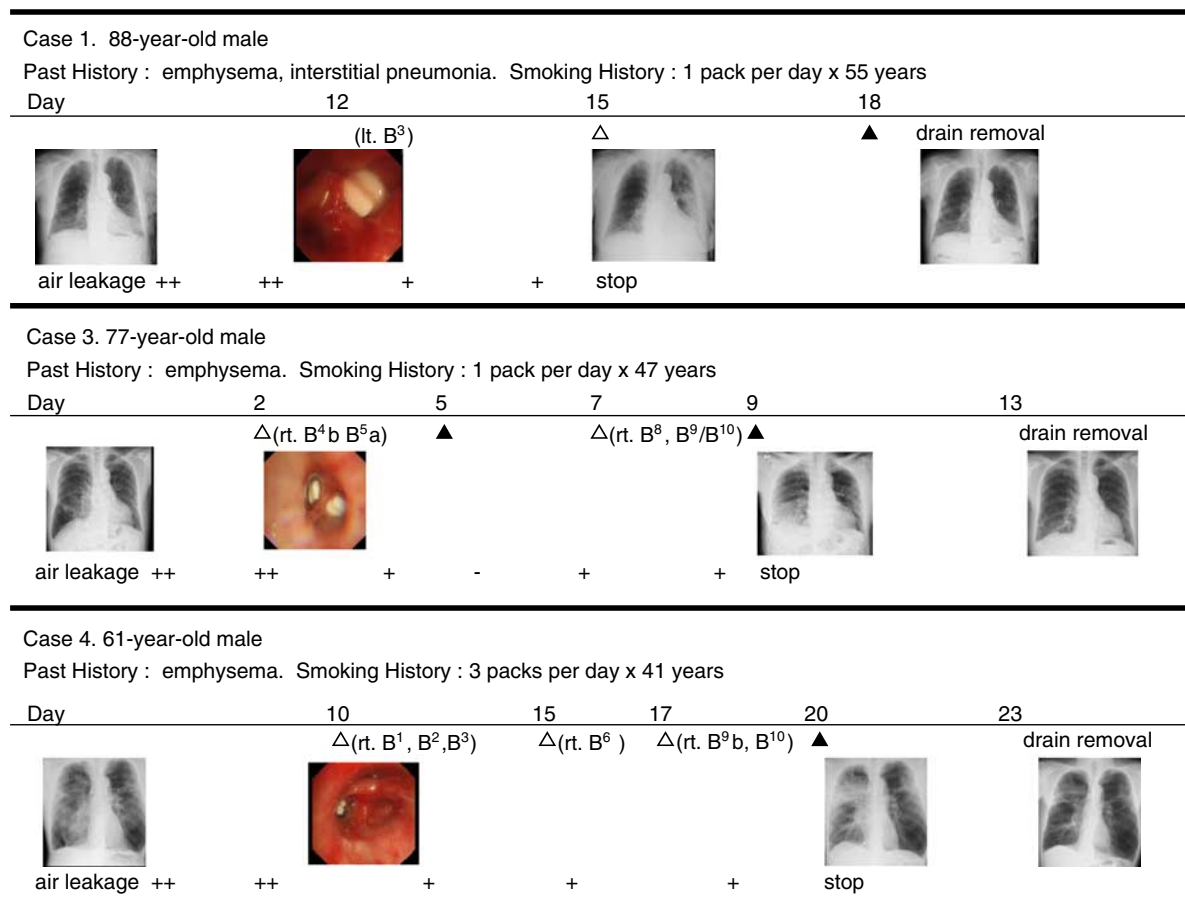


FIGURE 1. Clinical courses for 3 representative patients (cases 1, 3, and 4). A white triangle indicates a bronchial occlusion with silicon spigots. A black triangle indicates an intrabronchial infusion of autologous blood and thrombin. **u+**

transiently seen. Patients recovered from hypoxemia (SpO₂ 85% to 93% on oxygen) within 3 days and without the need for positive pressure ventilation. Because of the difficulty in differentiating inflammation caused by an intrabronchial infusion from bacterial pneumonia based on clinical presentation or imaging findings, penicillin antibiotics were given to all patients, with a consequent relief of symptoms within 3 days. Antibiotics were given for 3 to 10 days (mean 7 d).

DISCUSSION

Bronchial occlusion therapy using silicone-based plugs as a treatment for intractable pneumothorax was originally developed by Watanabe et al.^{4,5} In Japan, the silicon spigot (EWS) has been available and covered by health insurance since 2013; this technique is now recognized as a well-established treatment for intractable pneumothorax.

The effectiveness of combined therapy for intractable pneumothorax using both bronchial occlusion and chemical pleurodesis has also recently been reported.^{3,6} However, in several severe cases, bronchial occlusion and/or pleurodesis have been completely inadequate for various reasons. For example, high collateral ventilation may have developed,^{7,8} with collateral pathways traversing lobar fissures.^{9,10} This explains the difficulty in controlling air leaks from the pneumothorax by bronchial occlusion in severely emphysematous lungs. For the same reason, the outcome of lung volume reduction therapy with endobronchial valves depends largely on the presence of fissure completeness in the treated lobe.¹¹

As for the identification of the responsible bronchus, in only 1 case (case 1) could we identify the culpable bronchus using a balloon occlusion test. For the other cases, the responsible bronchi were inferred from computed tomographic scans. In other words, it appeared difficult to identify responsible bronchi using the balloon occlusion test in patients with emphysema because of collateral ventilation.

Ingenito et al,¹² in a study of biological lung volume reduction upon the instillation of a fibrin hydrogel and thrombin into the emphysematous area of a sheep model, reported that this procedure promoted fibroblast attachment and collagen synthesis. Their intention was to remodel the hyperinflated emphysematous lung into contracted scar tissue. On the basis of this study,

Kanoh et al^{13,14} reported the intrabronchial infusion of autologous blood in lung volume reduction therapy.

Kanoh and Kobayashi used autologous blood as the injection material, mainly because of its bioadhesive properties but also because it is relatively safe, as it has few side effects, and is inexpensive. They also used thrombin to promote blood clotting in the lung to enhance a reduction in lung volume.¹⁵ We hypothesize that this technique may seal collateral pathways and thus enhance the effectiveness of bronchial occlusion with silicon spigots. However, it is unclear how such a small volume of instilled blood of approximately 12 to 24 mL could have such effects, but we believe inflammation evoked by blood and thrombin in emphysematous regions may have had some role.

Wiaterek et al¹⁶ reported a case of intractable pneumothorax that was successfully treated with intrabronchial, oxidized regenerated cellulose (Surgicel Absorbable Hemostat; Ethicon), and 3 mL of the patient's blood delivered through a cut Fogarty balloon onto the absorbable hemostat. Compared with the absorbable hemostat, however, silicon spigots were thought to be fixed more firmly to the target bronchus.

The complications of bronchial occlusion by silicon spigot were thought to be acceptable, even after long-term placement in patients with a risk from their removal because of their poor overall health condition or with the necessity of long-term placement to prevent recurrence.^{2,6,17} However, when the benefit of the long-term placement of silicon spigots ends, these need to be removed within 3 months to a year of placement.^{17,18}

Watanabe¹⁸ reported that 4 of 22 cases of bronchial occlusion showed subsequent obstructive pneumonia that was relieved by antibiotic agents during a follow-up of >1 year (median 24.5 mo). However, in all our intractable cases except for 1, in which bronchial occlusion treatment, with or without pleurodesis, was inadequate, >4 silicon spigots per patient were needed to reduce air leaks. Therefore, the risk of obstructive pneumonia was thought to be high. In addition, as the intrabronchial injection of autologous blood may carry a certain risk of infection, we recommend that antibiotics be used during such a procedure and that patients be placed under careful observation.

Careful analysis is also required of the circumstances surrounding the deaths of 2 patients after intrabronchial injection of autologous blood plus thrombin. The cause of death for the 2 was thought to be an exacerbation of COPD. Both patients seemed to have had particularly bad prognoses due to poor baseline conditions, such as hypercapnia ($P_{CO_2} > 50$ Torr), and had shown a poor performance status (PS4). A decline in the overall health conditions of the 2 cases was seen > 1 week after the resolution of lung consolidation caused by intrabronchial infusion. Therefore, we believe that the intrabronchial injection of autologous blood plus thrombin was not directly related to their deaths, although any relationship between the procedure and the late-onset exacerbation of COPD is unclear. We believe that a reduction in air leaks and a reexpansion of the lung after the procedure may have had a beneficial impact, at least, temporarily.

In 4 cases, pleurodesis was performed after the intrabronchial infusion of autologous blood plus thrombin. We, therefore, could not assess the benefit of the intrabronchial infusion on its own. Further study is necessary to evaluate the effectiveness of the proposed intervention in other settings.

CONCLUSIONS

This study suggests that the intrabronchial infusion of autologous blood plus thrombin may be effective in cases of intractable pneumothorax, in which air leaks are partially reduced but not completely stopped by bronchial occlusion using silicon spigots. However, our report of this procedure does have a major limitation in that it still represents a small case series with multiple interventions. In addition, the deaths of 2 patients, in response to what was thought to be an exacerbation of COPD, is problematic as we cannot completely exclude a relationship between these deaths and the procedure. Further investigations with a larger patient population are required.

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