The Dynamics and Clinical Significance of Alpha 2 Plasmin Inhibitor–Plasmin Complex and Thrombin–Antithrombin Complex in Postoperative Pleural Effusion Following a Pulmonary Lobectomy

FUMIHIRO SHOJI1,2, TOKUJIRO YANO1,2, ICHIRO YOSHINO3, DAIGO KAWANO3, TOMOYOSHI TAKENAKA1, NAOKO MIURA1, KENSAKU ITO1, YOSUKE MORODOMI1, and YOSHIHIKO MAEHARA1

1 Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
2 Department of Surgery, Saga Prefectural Hospital KOSEIKAN, Saga, Japan
3 Department of Thoracic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

Abstract

Purpose. The overall incidence of postoperative alveolar air leakage (AAL) remains high; however, the mechanism regarding how to adequately heal such postoperative AAL remains to be elucidated. The aim of this study was to determine any correlations between the activity of the fibrinolytic and coagulation system in the postoperative pleural effusion and appearance or disappearance of postoperative AAL.

Methods. This study prospectively investigated 25 patients who underwent a pulmonary lobectomy from July 2005 to March 2006. Pleural effusion was collected through the chest tube. Alpha 2 plasmin inhibitor–plasmin complex (PIC), as a fibrinolytic marker, and thrombin–antithrombin complex (TAT), as a coagulation marker, were measured.

Results. The activity of the coagulation system was higher than that of the fibrinolytic system. The concentration of TAT tended to increase (3rd vs 4th postoperative day [POD], P = 0.0907). The mean time of appearance and disappearance of postoperative AAL was 1.4 days and 3.2 days, respectively. The patients with postoperative AAL had a TAT level significantly below the average on the 3rd POD in comparison to the patients without postoperative AAL (P = 0.0163). Moreover, the concentration of TAT in patients with postoperative AAL was significantly lower than that in patients without postoperative AAL (1824.0 ± 137.3 ng/ml vs 3444.0 ± 287.6 ng/ml, P = 0.0113) on the 3rd POD. On the 4th POD, the concentration of TAT was almost same and there was no significance (P = 0.6759).

Conclusions. This study demonstrated for the first time the course of the fibrinolytic and coagulation activity in the pleural effusion after a pulmonary lobectomy, and showed that the delayed activity of the coagulation system is associated with the appearance of the postoperative AAL.

Key words Fibrinolytic and coagulation system · Postoperative pleural effusion · Pulmonary lobectomy · Lung cancer

Introduction

Most air leaks following general thoracic surgery result from an alveolar air leak (AAL) from the stumps of the resected lungs or stripped sites of pulmonary adhesion. Prolonged postoperative AAL can result in an extended hospital stay as well as an increased risk of postoperative complications such as infection. Therefore, direct sealants in the form of fibrin glue,1–3 synthetic gels and polymers,4–6 and adherent patches7 are applied during general thoracic operations.

Nevertheless, the overall occurrence of postoperative AAL remains above 60% during the early postoperative period.8 Despite the high incidence, most postoperative AAL disappears within a few days. However, the mechanism of repair has not yet been thoroughly analyzed.

Some factors in pleural effusion may be associated with preventing the occurrence of postoperative AAL, because most postoperative AAL spontaneously disappears. An adequate balance of the fibrinolytic and coagulation systems is required for the formation of fibrin deposition.9 Therefore, the hypothesis is that if the balance and activity of the fibrinolytic and coagulation system in the pleural effusion is changed, fibrin deposition in the pleural effusion will be delayed, thus resulting in postoperative AAL. However, no studies have previously investigated the activity of the fibrinolytic
Recently, the molecular markers associated with fibrinolysis and coagulation have been measured to investigate their activity more precisely. The stress of a major surgical procedure physiologically activates fibrinolysis and coagulation in the serum and, in these cases, the molecular markers could be elevated over normal levels because of their hypersensitivity. Figure 1 shows a representation of the molecular markers associated with fibrinolysis and coagulation. Specifically, alpha 2 plasmin inhibitor–plasmin complex (PIC) and thrombin–antithrombin complex (TAT) are sensitive markers for fibrinolysis and thrombin formation respectively. PIC is produced from plasmin immediately after fibrinolysis is activated, and an increase in the PIC level indicates fibrinolysis. TAT is produced from thrombin and has a rapid turnover; therefore, it is a sensitive variable of the latent activation of the coagulation pathways.

In the present study, 25 patients with AAL during the operation were assessed and investigated as follows. (1) The course of PIC and TAT levels in the pleural effusion following pulmonary lobectomies for lung cancers was observed. (2) Postoperative AAL prevalence was analyzed. (3) The correlation between the activity of the fibrinolytic and coagulation system in the postoperative pleural effusion and appearance or disappearance of postoperative AAL was examined.

### Patients and Methods

#### Patient Selection and Study Design

Prospectively, 25 patients, who underwent a pulmonary lobectomy for primary or metastatic lung cancer, thus resulting in intraoperative AAL, were evaluated from July 2005 to March 2006. Written informed consent was obtained from each patient for study of the pleural effusion. The institutional review board of Saga prefectural hospital, KOSEIKAN, gave approval for this study.

#### Surgical Procedure

A posterolateral thoracotomy was done through the 5th or 6th rib bed and a pulmonary lobectomy with a mediastinal lymphadenectomy (ND2a) was performed. After the completion of each surgical procedure, the thoracic cavity was filled with warmed normal saline. The lung was then mechanically ventilated with a pressure of 20 cmH₂O to inflate any atelectatic zone and detect air leak test. All AALs were sealed with fibrin glue (BOLHEAL, including 160 mg, 500 IU, and 150 IU of fibrinogen, thrombin, and factor XIII, respectively; Kaketsuken, Kumamoto, Japan). The PIC and TAT concentration in the postoperative effusion were not affected by the use of fibrin glue (data not shown). After repairing the intraoperative AAL, an air leak test was again performed with a pressure of 20 cmH₂O in warmed normal saline. After confirming that there was no AAL, one 24-F chest double-lumen tube was positioned into the thorax through the 6th or 7th intercostal space and the tube was placed on suction (~5 cmH₂O) after the closure.

#### Follow-Up

Chest radiographs were routinely performed every day until the chest tube was removed. When the pleural effusion was less than 200 ml in a 24-h period and no air leak was evident after the 4th postoperative day (POD), the chest tube was removed.

#### Collection of the Pleural Effusion

The pleural effusion was collected through the chest tube at the same time (08:00 h) from the 2nd to the 4th POD. Next, 5 ml of the collected effusion was transferred to a sample tube containing 3.2% of sodium acid citrate and was centrifuged immediately at 3000 rpm for 10 min.

#### Measurement of PIC and TAT Levels in Postoperative Pleural Effusion

PIC (serum normal range <0.8 μg/ml), as a fibrinolytic factor and TAT (serum normal range <3.0 ng/ml), as a coagulation factor were analyzed. PIC and TAT were measured by a latex photometric immunoassay and an enzyme linked immunosorbent assay, respectively.

#### Statistics

The value of all measurements was represented by the means ± standard error. A statistical analysis (comparison among three periods) was performed using an analysis of variance (ANOVA). When the ANOVA showed