Author’s response to reviews

Title: Very Late Unusual Thrombosis of the Remnant Pulmonary Vasculatures after Lung Resection Complicated by Embolic Events

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<<Answer to the Comments from the Reviewers>>

Reviewer #1:

1. Very late thrombosis is very rare, and this article provides a well-documented and complete description of these postoperative complications.

   Ans) Thanks for your kind comments.

2. Case 1, how long did the patient take warfarin orally? Any complications?

   Ans) Thanks for your important comments. The patient had no previous history of atrial fibrillation (AF) and did not know that she had AF. At this time of admission due to cerebral infarction, the presence of AF was identified. Therefore, the patient did not took any anticoagulant before this time of admission. Because the patient presented with cerebral infarction and pulmonary vein stump thrombosis associated with AF, anticoagulation with warfarin was initiated and continued during 3 months of follow up at neurology department of our institution without any complications. After then, the patient was transferred to other hospital which is located near the house of the patient. Therefore, the clinical course after transfer cannot be described.

3. How do you prevent pulmonary embolism after thoracic surgery in your hospital? In our hospital, we emphasize early post-operative activity (within 12 hours), which is very effective.
The incidence of pulmonary embolism is limited to less than 1%. Do you think this method is useful for very late thrombosis?

Ans) Thanks for important comments. As commented by the comment of the reviewer, the prevention of pulmonary embolism (PE) after thoracic surgery would be very important. In our hospital, prophylactic anticoagulation for PE is not used before and after thoracic surgery. We also emphasize early post-operative active ambulation. In some cases, elastic pressure stocking after surgery is applied, and intermittent pneumatic compression device is applied in some patients who require prolonged immobilization. We added this comment from the reviewer in the discussion section. Thanks.

4. The incidence of PAT after pneumonectomy was 12% [14], and the incidence of PVT after lobectomy was 3.3% [15], what do you think it?

Ans) Thanks for very important comments. The reason why the incidence of PAT is higher than PVT is unclear. Larger size of dead space of the remnant PA stump after pneumonectomy than the remnant PV stump after lobectomy would be one of possible explanations. Also, more vascular injury after pneumonectomy than lobectomy would be another possible explanation. We described this issue in the discussion section.

Reviewer #2:

I have a question about the discussion.

If the stump length is confirmed by contrast-enhanced CT after surgery, is it necessary to introduce anticoagulant therapy?

I think that it is better to put into consideration the continuous intravenous injection of unfractionated heparin and intermittent pneumatic compression to prevent the development of thrombus in the pulmonary vein stump after surgery.

Ans) Thanks for your comment. Because unexpected PVST can be found sporadically and there is no randomized controlled trial for the use of anticoagulation after lung surgery to prevent PVST, routine anticoagulation after lung resection is not used in clinical practice. Therefore, the minimization of the dead space of the remnant vascular structures or vascular injury during lung resection surgery would be best option so far. However, the authors also agreed the opinion of the reviewer regarding the use of anticoagulation (IV heparinization) after lung resection in patients with long and large remnant vascular stump, at least in early postoperative period. The use of intermittent pneumatic compression also would be useful in the prevention of PAT, especially in patients who require prolonged immobilization. We added this issue in the discussion section. Thanks.
Reviewer #3:

I would like to thank the editors for the privilege to review this manuscript.

In this article, Yoon et al. report on two patients with late thrombosis of the remnant of pulmonary vascular structures and subsequent embolic complications, following major pulmonary resections. Although, early postoperative thrombosis of long pulmonary vascular stumps following lobectomy/pneumonectomy is relatively well studied. Few anecdotal studies reported on late thrombosis with associated embolic events.

I have few comments that I hope the authors find constructive.

- Please mention patients comorbidities and smoking status.

Ans) Thanks for your comments. Both patients are non-smoker and had no previous medical comorbidities except for lung surgery. We described this issue within the text of each case. Thanks.

- Did the patients have any known risk factors for thrombosis?

Ans) Thanks for important comments. As mentioned by the reviewer, the authors routinely evaluate the hypercoagulable status because hypercoagulability is an important predisposing condition of unusual thrombosis or venous thromboembolism. There were no abnormalities in laboratory studies regarding hypercoagulability in both cases. Atrial fibrillation was the only risk factor for thrombosis in case 1. We describe this issue within the text of each case. Thanks.

- I encourage the authors to provide more details on the operative technique used for pulmonary resection (i.e. surgical approach [open or VATS], instruments and technique used for vascular dissection, stapler used, etc.).

Ans) Thanks for your comments. We described operative procedure in case presentation parts.

- Did the patients have any postoperative complications (please give details on postoperative course).

Ans) Thanks for your comments. Post-operative courses were good, and there were no postoperative complications in both patients. Please accept that we did not describe this issue within the text. Thanks.

- Did the patients have any postoperative scans before the thrombosis/embolic event? If so please provide details if long vascular stumps were noted and if there were any anatomic variations.
Thanks for your comments. Both patients had postoperative CT scans before thrombosis/embolic events. There were no thrombi in the remnant vascular stumps and no anatomic variations in both cases. Because the sizes of the remnant vascular stumps are not different in the CT images which were shown in Figure 2 and Figure 4, we did not describe this issue within the text. Please allow it. Thanks.

- What is the long term plan for the management of those patients? How long will they continue anticoagulation for? Please expand on the management of early and late vascular remnants thrombosis in the discussion section.

Thanks for very important comments. Because case 1 presented with cerebral infarction and atrial fibrillation, indefinite lifelong anticoagulation was planned. However, as you know, the exact duration of anticoagulation for PVST after lung surgery without identifiable risk factors is not known as in case 2. We planned lifelong anticoagulation with warfarin in case 2 because the anatomic substrate (the dead space of the remnant vascular stump) for thrombosis will be remained and the recurrence of pulmonary embolism may be fatal in the setting of single lung. Further larger studies should be conducted to define the exact duration of anticoagulation in PVST. We described this issue in the discussion. Thanks.