Usefulness of Oral Xa Inhibitor for Management of Ischemic Stroke Associated with Thrombosis in the Pulmonary Vein Stump after Lung Resection

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Objectives: Brain infarction is a critical complication after lung resection using video-assisted thoracoscopic surgery. Recent reports have described its association with thrombosis in the pulmonary vein (PV) stump. However, the optimal management of this complication remains controversial. We describe serial 3 cases of brain infarctions associated with thrombosis in the PV stumps, which were successfully treated with the oral Xa inhibitor rivaroxaban. *Methods and Results*: We retrospectively reviewed medical records of 3 patients. The first case was a 72-year-old man who underwent left upper lobectomy for treatment of lung adenocarcinoma. The second case was a 55-year-old man who underwent right lower segmentectomy for treatment of metastatic tumor from Barrett's esophageal carcinoma. The third case was a 73-year-old man who underwent left upper lobectomy for treatment of metastatic tumor from colon adenocarcinoma. In the first case, a large cerebellar infarction was developed and a decompressive craniotomy was performed on postoperative day 4. In the second and the third case, cerebral infarctions in the territories of right middle cerebral arteries occurred on postoperative day 2. In all cases, contrast-enhanced computed tomography demonstrated the thrombi in the stumps of the PVs. They were treated with oral administration of rivaroxaban without adverse effect, and the thrombi in the PVs disappeared within 1 month. *Discussion*: Blood flow stasis in the long PV stump after lung resection might contribute to thrombosis development. Oral Xa inhibitor rivaroxaban appeared to be safe and useful for the management of ischemic stroke associated with PV thrombosis after lung resection.

Key Words: Anticoagulation therapy—cerebral infarction—lung resection—pulmonary-vein thrombosis—rivaroxaban

Introduction

Brain infarction is a rare but critical complication after lung resection.[1] The pathogenesis of this complication had not been elucidated; however, recent reports indicated its association with thrombus in the pulmonary vein (PV) stump.[1-5] The thrombus in the PV can easily enter the systemic circulation and cause embolism to vital organs such as the brain. Nevertheless, the optimal managements of this complication are still controversial. We herein describe serial 3 cases of brain infarction associated with a thrombus in the PV stump that was successfully treated with the oral Xa inhibitor rivaroxaban. We discuss the mechanisms of PV thrombosis after lung resection and usefulness of Xa inhibitor for its management.

Materials and Methods

Between January 2014 and December 2017, 93 patients underwent lung resection using video-assisted thoracoscopic surgery (VATS) for treatment of malignant tumors

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of the lungs in our hospital. Among them, 3 patients presented with brain infarction within 30 days after the surgery. All of them were transferred to our department and treated with oral Xa inhibitor rivaroxaban. We retrospectively reviewed their medical records. The study was approved by the Local Ethic Committee.

Results

Case 1

A 72-year-old man underwent left upper lobectomy using VATS for treatment of a Stage IA lung adenocarcinoma. The left superior PV (LSPV) was divided using a stapler. On postoperative day (POD) 3, he presented with symptoms of elevated intracranial pressure (hypertension, nausea, and vomiting). The next day, he fell into a comatose state and head CT revealed a large brain infarction in the right cerebellum associated with obstructive hydrocephalus (Fig 1D). A decompressive craniotomy of the posterior fossa was performed, and his neurological condition recovered. Because atrial fibrillation (AF) was not documented by continuous electrocardiogram monitoring, contrast-enhanced CT (CECT) of the body was performed on POD 19, and a thrombus in the LSPV stump was detected (Fig 1A). The patient began anticoagulation therapy with intravenous infusion of heparin (15,000 units/day) followed by oral administration of warfarin (3 mg/day). Four days later, he presented with left leg weakness, back pain, and anemia. CT revealed a left retroperitoneal hematoma (Fig 1F) and hemorrhagic changes in the right cerebellar infarction (Fig 1E), although the prothrombin time (prothrombin time-international normalized ratio, 1.98) and activated partial thrombin time (75.5 seconds) were within the therapeutic ranges. The anticoagulation therapy with heparin and warfarin was discontinued, but CECT showed persistence of the thrombus in the LSPV stump on POD 46 (Fig 1B). Thus, anticoagulation therapy with oral administration of the Xa inhibitor rivaroxaban (15 mg/day) was begun. The patient's clinical course was thereafter uncomplicated. On POD 76, CECT revealed disappearance of the residual thrombus in the LSPV stump (Fig 1C). Slight ataxia remained, but the patient fully recovered from the left leg weakness and was able to walk without assistance. He was transferred to a rehabilitation hospital on POD 109.

Case 2

A 55-year-old man, who had a medical history of surgery for Barrett's esophageal carcinoma (Stage I) and thyroid cancer (Stage IVa) at 51 years of age, underwent right lower pulmonary segmentectomy (RLPS) using VATS for treatment of 2 cm tumor in the right lower lobe (Fig 2A). The tumor was removed en bloc with the basal segment of the right lung and S6 segment was preserved. The right inferior PV (RIPV) was divided in the peripheral side using a stapler. Postoperative histological examinations confirmed the tumor of the lung as a metastatic tumor from the Barrett's esophageal carcinoma. On POD 2, he

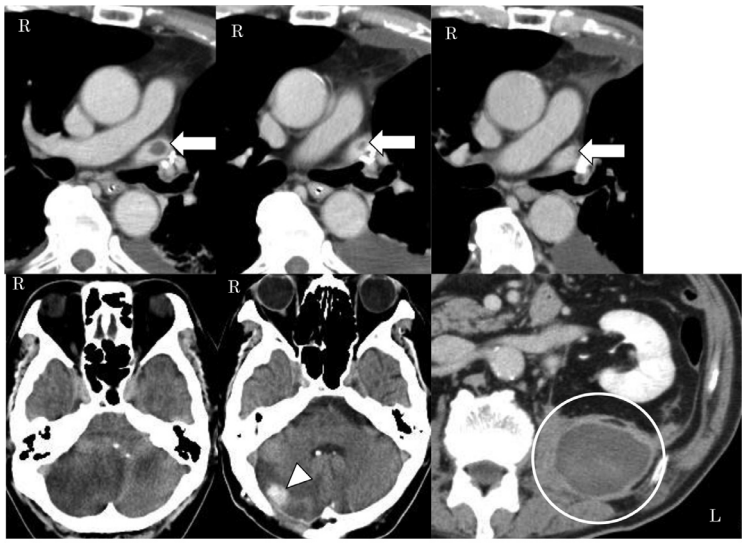

Figure 1. *In case 1, the thrombus (arrow) in the left superior pulmonary vein stump after lobectomy was evident on contrast-enhanced thoracic computed tomography (CECT) on postoperative day (POD) 19 (A) and 46 (B), but not on POD 76 (C). CT revealed a right cerebellar infarction on postoperative day 4 (D) as well as hemorrhagic changes in the cerebellar infarction (E, arrowhead) and a left retroperitoneal hematoma (F, circle) on POD 23.*

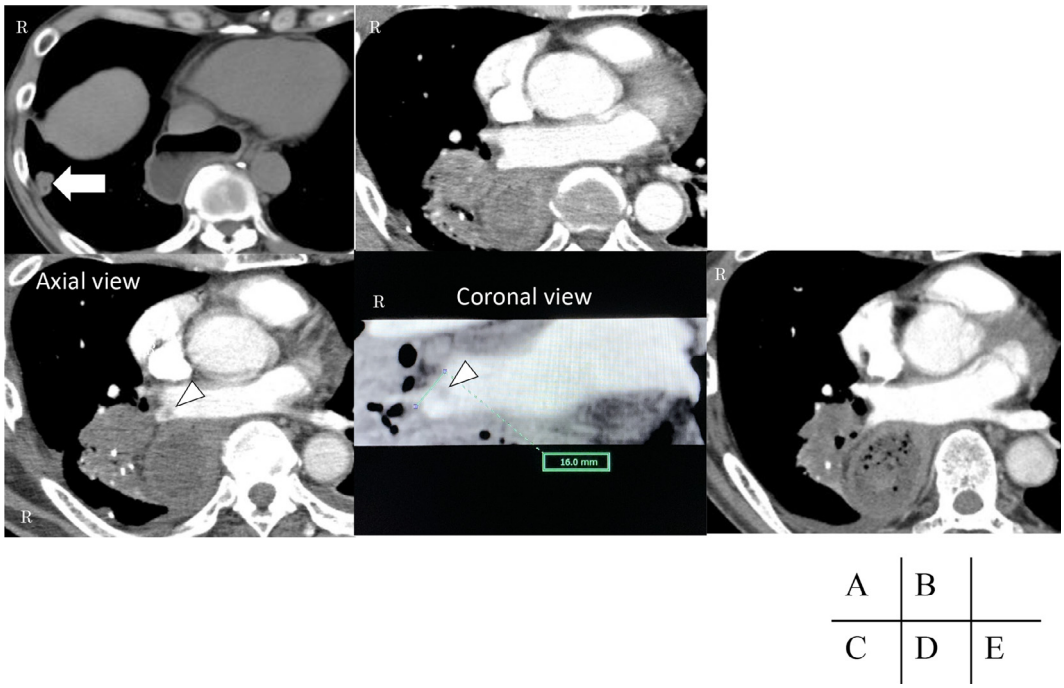

Figure 2. *In case 2, preoperative CT demonstrated the mass lesion in the in the right lower lobe (A, arrow). The thrombus in the right inferior pulmonary vein (RIPV) stump after segmentectomy was not evident on POD 3 (B) but was evident on POD 6 (C, D arrowhead) in the postoperative CECT. After the anticoagulation therapy with rivaroxaban, the thrombus was disappeared on POD 24 (E).*

presented with sudden onset left hemiparesis (manual muscle testing; MMT 2). Magnetic resonance (MR) imaging with diffusion-weighted images (DWI) detected areas of hyperintensity in the territory of right middle cerebral artery (MCA) (Fig 3A). MR angiography demonstrated an occlusion of M1 portion of right MCA (Fig 3D). On POD 3, CECT of the body was performed and acute infarction of the left kidney was detected; however, any embolic source was not detected in the cardiopulmonary area (Fig 2B). On POD 5, MR angiography confirmed recanalization of the right MCA (Fig 3D), but DWI detected new hyperintensity lesions in the posterior part of right MCA territory (Fig 3B). CECT was performed again on POD 6 and a thrombus in the stump of the RIPV was detected (Fig 2C and D). Anticoagulation therapy with oral administration of Xa inhibitor rivaroxaban (30 mg/day) was started. His left hemiparesis was gradually improved and no additional neurological deficit was recognized, although DWI detected a new small hyperintensity lesion in the left MCA territory on POD 11 (Fig 3C). The thrombus in the stump of the RIPV was disappeared in the CECT on POD 24 (Fig 2E). Thereafter, the dose of rivaroxaban was reduced to 15 mg/day and no additional cerebral infarction has been detected in the MR images. His left hemiparesis was completely recovered and he was discharged from our hospital on POD 41.

Case 3

A 73-year-old man, who had a medical history of surgery for colon cancer (Stage IIIa) at 71 years of age, underwent left upper lobectomy using VATS for treatment of tumor in the left upper lobe. The LSPV was divided using a stapler. On POD 2, he presented with sudden onset left hemiparesis (MMT 2). MR imaging with DWI detected areas of hyperintensity in the territory of right MCA (Fig 4C). CECT of the body was performed on POD 4 and a thrombus in the LSPV stump was detected (Fig 4A). Anticoagulation therapy with oral administration of the Xa inhibitor rivaroxaban (15 mg/day) was begun. The patient's symptoms were gradually improved and CECT revealed disappearance of the thrombus in the LSPV stump on POD 18 (Fig 4B). The patient gradually recovered from the left hemiparesis and was able to walk without assistance. He was transferred to a rehabilitation hospital on POD 32.

Discussion

Brain infarction is reported to occur in .08%-.7 % of general surgery and .6%-1.1 % of thoracic surgery patients. Yamamoto et al reviewed 562 patients who underwent lung resection and reported that 6 patients (1.1%) experienced brain infarction within 30 days postoperatively.[1] The patients with brain infarction accounted for 4.2% (5 of 117) of all patients who underwent left upper lobectomy.[1] Brain infarction occurred at a mean of 3.3 days (range, 1-9 days) postoperatively in their series. Consistent with the previous report, 2 patients underwent left upper lobectomy and presented with brain infarctions on POD 2 and 3 in our series. Another patient underwent RLPS and presented with brain infarction on POD 2.

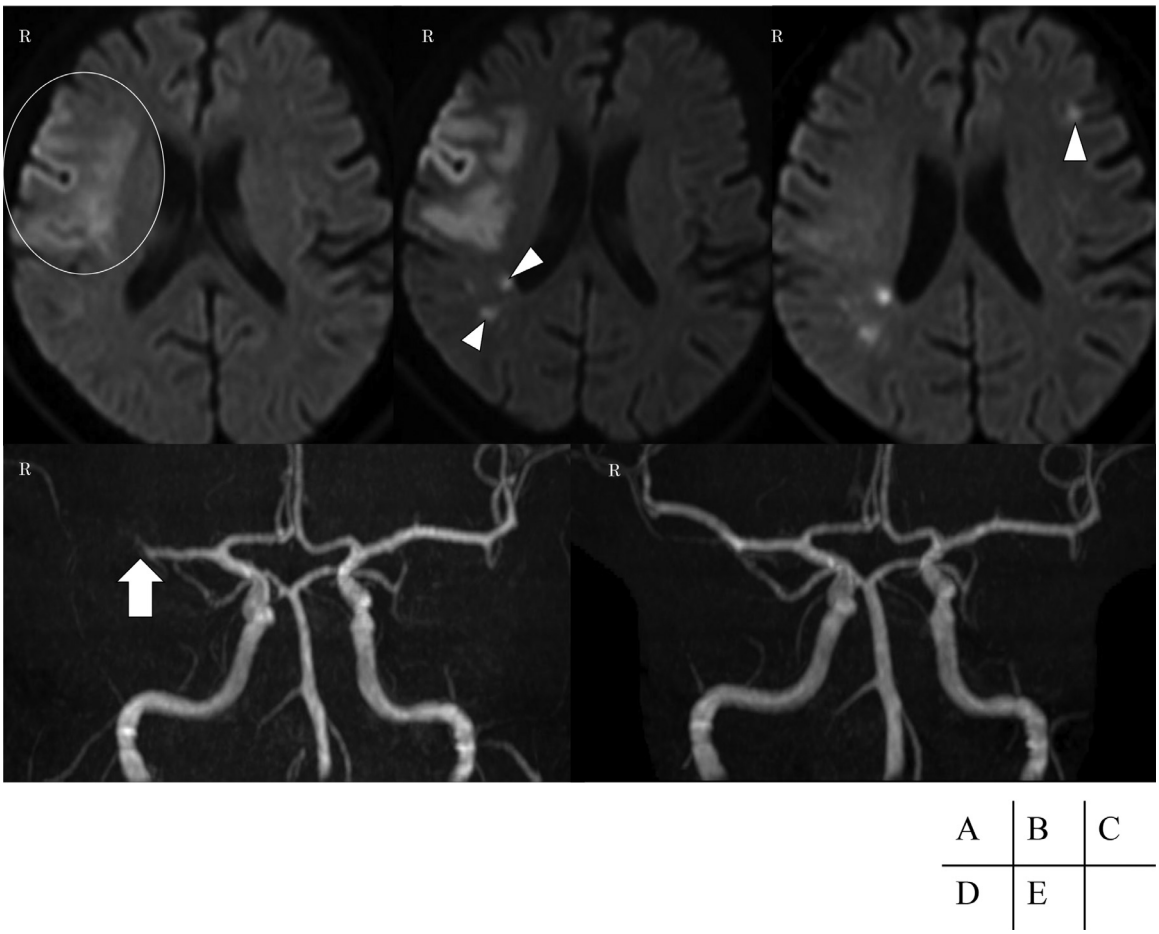

Figure 3. *In case 2, magnetic resonance (MR) imaging with diffusion-weighted images detected areas of hyperintensity in the territory of right middle cerebral artery (MCA) on POD 2 (A), new hyperintensity lesions in the posterior part of right MCA territory (B, arrow head) on POD 5, and a small recurrent hyperintensity lesion in the left MCA territory on POD 11 (C, arrow head). MR angiography demonstrated an occlusion of M1 portion of right MCA on POD 2 (D, arrow) and recanalization on POD 5 (E).*

Ohtaka et al reported that thrombosis developed in the PV stump in 3.3%-3.6% of patients who underwent lobectomy and in 13.5%-17.9% of patients who underwent left upper lobectomy as determined by CECT.[2,3] They also reported that the length of the LSPV stump (mean, 1.71 cm) after left upper lobectomy was significantly longer than that of the other PV stumps (mean, .50-.56 cm).[2,3] In our case 1 and 3, the lengths of the LSPV stumps determined by CECT were 1.69 cm and 2.83 cm, respectively. In case 2, the patient underwent RLPS preserving S6 segment. The RIPV resected in the peripheral side and the PV stump became longer than typical right lower lobectomy. The length of the RIPV stump was 1.60 cm in the CECT (Fig 2D). Blood flow stasis in the long stump might contribute to thrombosis development in the PV after lung resection.

If the patient presented with brain infarction after lung resection, CECT should be performed to detect a possible thrombus in the PV stump as soon as possible. Ohtaka et al strongly recommended CECT, because it was difficult to detect the thrombus in the PV stump by conventional transthoracic echocardiography.[2-5] In our case 1, we could not detect the thrombus in the PV stump by transthoracic echocardiography. In case 2, we performed CECT on POD 3 and 6 to investigate the thrombus. The thrombus in the RIPV stump was detected on POD 6 but not on POD 3. It is possible that the thrombus in the RIPV was released once on POD 2 and formed again before POD 6.

When a thrombus in the PV stump is detected, anticoagulation therapy should be started. In previous reports, heparin and warfarin were used for the treatment of thrombosis in the PV stump.[1-6] In our case 1, the anticoagulation therapy with heparin and warfarin resulted in hemorrhagic complications. It also contains the risk of bleeding from the surgical wound and drainage in the early postoperative period. We used rivaroxaban to treat the thrombus in the PV, because oral factor Xa inhibitors, including rivaroxaban, apixaban, and edoxaban, are approved for the treatment of venous thrombosis and pulmonary thromboembolism as well as nonvalvular AF.[7] In the clinical trials, it was proved to be as effective as warfarin for treating venous thrombosis and associated with

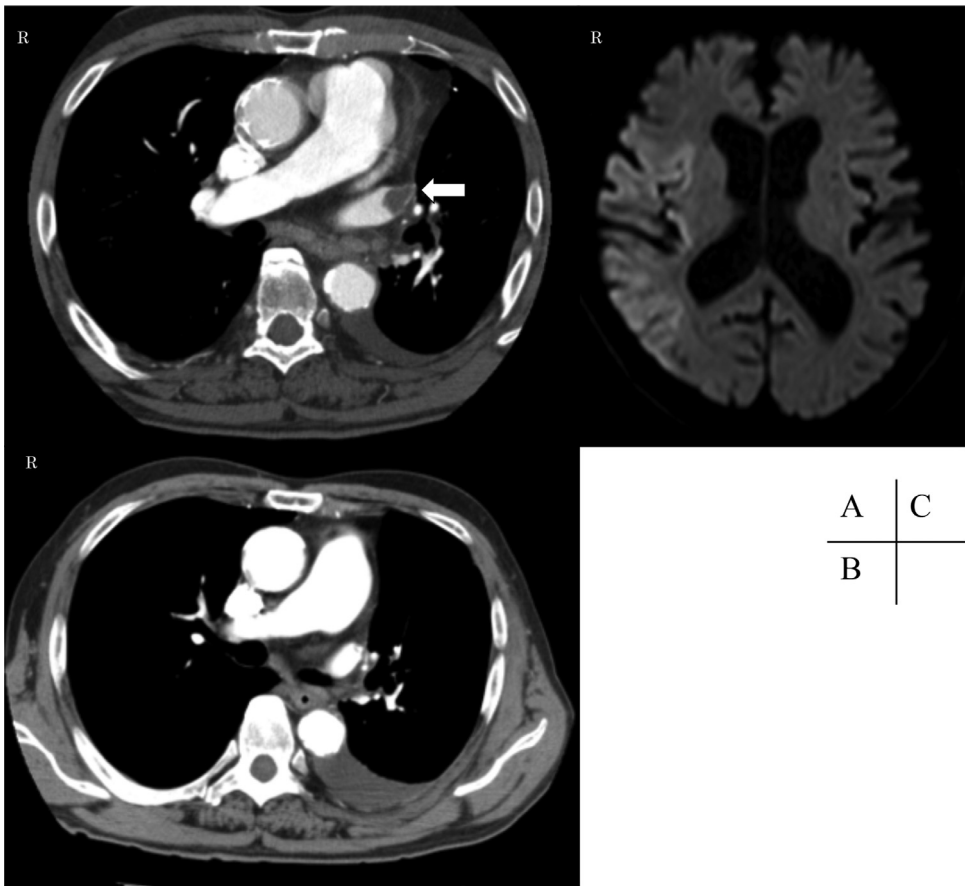

Figure 4. *In case 3, the thrombus in the left superior pulmonary vein stump after lobectomy was evident on CECT on POD 4 (A, arrow), but not on POD 18 (B). MR imaging with diffusion-weighted images detected areas of hyperintensity in the territory of right MCA on POD 2 (C).*

lower rates of serious and fatal bleeding events than warfarin.[8] Rivaroxaban is an off-label treatment for thrombi formed at the stump of the PV. This study was approved by the ethical committee in Harasanshin Hospital.

In Japan, the dose of rivaroxaban indicated for treatment of venous thrombosis and pulmonary thromboembolism is 15 mg twice daily for 3 weeks followed by 15 mg once daily.[9] In our case 2, we started anticoagulation therapy with rivaroxaban 15 mg twice daily (30 mg/day) as indicated. On the other hand, we reduced the initial dose of rivaroxaban to 15 mg once daily in the other 2 cases to avoid the hemorrhagic complications. In case 1, we anticipated the enlargement of a left retroperitoneal hematoma with high doses of rivaroxaban. In case 3, the patient still had a thoracic drainage when we started the anticoagulation therapy. In all 3 cases, we confirmed the disappearance of the thrombi in the PV stumps within 1 month without adverse effect.

Direct thrombin inhibitor davigatran is another oral anticoagulant, which is approved for the treatment of nonvalvular AF. It might be useful for the treatment of venous thrombosis; however, Kishida et al described a case of embolic ICA occlusion associated with LSPV thrombosis after left upper lobectomy even under anticoagulation with the direct thrombin inhibitor dabigatran for chronic AF.[6] In addition, dabigatran has not yet been approved for the treatment of venous thrombosis and pulmonary thromboembolism in Japan. It is not currently recommended for the management of PV thrombosis after lobectomy.

In conclusion, we successfully treated 3 patients with cerebral infarction associated with thrombus in the PV stump after lung resection using oral administration of Xa inhibitor rivaroxaban. CECT was useful for detecting a thrombus in the PV stumps and Xa inhibitors could be an important option for treating the thrombus in PV, especially when the hemorrhagic complications are anticipated by the use of conventional anticoagulation therapy with heparin and warfarin.

Declaration of Competing Interest

All authors have no conflict of interest.

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