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Acute thrombus formation in the left atrium after the termination of warfarin

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Abstract
We report a case of acute thrombosis formation in the left atrium 3 days after the discontinuation of warfarin therapy prior to mitral valve replacement in a patient with mitral stenosis and atrial fibrillation. A 58-year-old Asian female patient was scheduled for mitral valve replacement for mitral stenosis. She had received warfarin therapy every day for 2 years. Warfarin therapy was discontinued 3 days before surgery. Using transesophageal echocardiography (TEE), we confirmed that there was no thromboembolism at the left atrium 10 days before surgery. No replacement anticoagulant therapy, such as heparin, was given after the discontinuation of warfarin. After the induction of anesthesia, a TEE probe was inserted through the esophagus to monitor left ventricular function. We found two thrombi (35 mm and 40 mm in diameter) in the left atrium. This case shows that discontinuation of warfarin therapy within a few days before operation carries a risk of thromboembolism formation.

Key words Anticoagulation therapy · Warfarin · Acute thrombosis · Cardiac surgery

Introduction

Anticoagulant therapy, such as warfarin, is widely used for the prevention of throboembolic complications in patients with atrial fibrillation or a mechanical heart valve [1,2]. However, warfarin therapy must frequently be discontinued before elective surgical procedures [2]. After discontinuation of warfarin therapy, it takes about 4 days for the international normalized ratio (INR) to reach 1.5 in most patients [3]. Tinker and Tarhan [4] reported that there was a minimal risk in patients with cardiac valve prostheses receiving anticoagulants when the drug regimen was stopped for 1 to 3 days preoperatively. In addition, Goldenberg et al. [5] reported that temporary discontinuation of oral anticoagulation in patients with St. Jude mechanical prostheses did not appear to be accompanied by an increased risk of thromboembolic events. We report a case of acute thrombus formation in the left atrium 3 days following the discontinuation of warfarin therapy prior to mitral valve replacement in a patient with mitral stenosis and atrial fibrillation.

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Case report

A 58-year-old Asian female patient, weighting 50 kg, was scheduled for mitral valve replacement for mitral stenosis. She had a history of transient cerebral ischemic attacks 2 and 30 years previously. The area of the mitral valve was 0.61 cm^2, and the left ventricular ejection fraction was 71%. The electrocardiogram demonstrated atrial fibrillation. She was medicated with warfarin at a dosage of 5.0 mg a day for 2 years from the last transient ischemic attack to prevent thromboembolic complications. At that time, the prothrombin time was 15% and the international normalized ratio (INR) was 3.65 (Table 1). The INR range for the previous month was between 2.0 and 2.4. Because she had a complication of massive subcutaneous bleeding on day −18 (Table 1), the warfarin dose was adjusted to a range of 4.5 and 5.0 mg to keep the INR between 1.5 and 2.0. When the INR ratio was 1.89 on day −10, transesophageal echocardiography (TEE) (Hewlett Packard SONOS 5500, 5.0 MHz transducer, Andover, MA, USA) was performed, and we confirmed that there were no thromboemboli at the left atrium (Fig. 1a and b). The cardiac index measured by echocardiography was 3.0 $l \cdot min^{-1} \cdot m^{-2}$. The left ventricular ejection fraction was 75%. There was no left atrial spontaneous echo contrast or mitral regurgitation in this patient at the time.

Table 1. Time course of changes in coagulation variables and warfarin dosage

	Day						
Measurement	−18	−15	−10	−8	−6	−3	0
PT (s)	38.0	20.2	19.7	20.1	20.4	20.5	Operation
PT (%)	15	36	38	37	36	37	
INR	3.65	1.94	1.89	1.93	1.96	1.95	
APTT (s)	42.5	32.3	32.9	28.7			
Warfarin	5.0 mg	4.5 mg/5.0 mg				Discontinuation	
TEE			○				○

PT, prothrombin time; APTT, activated partial thrombin time; INR, international normalized ratio; TEE, transesophageal echocardiography

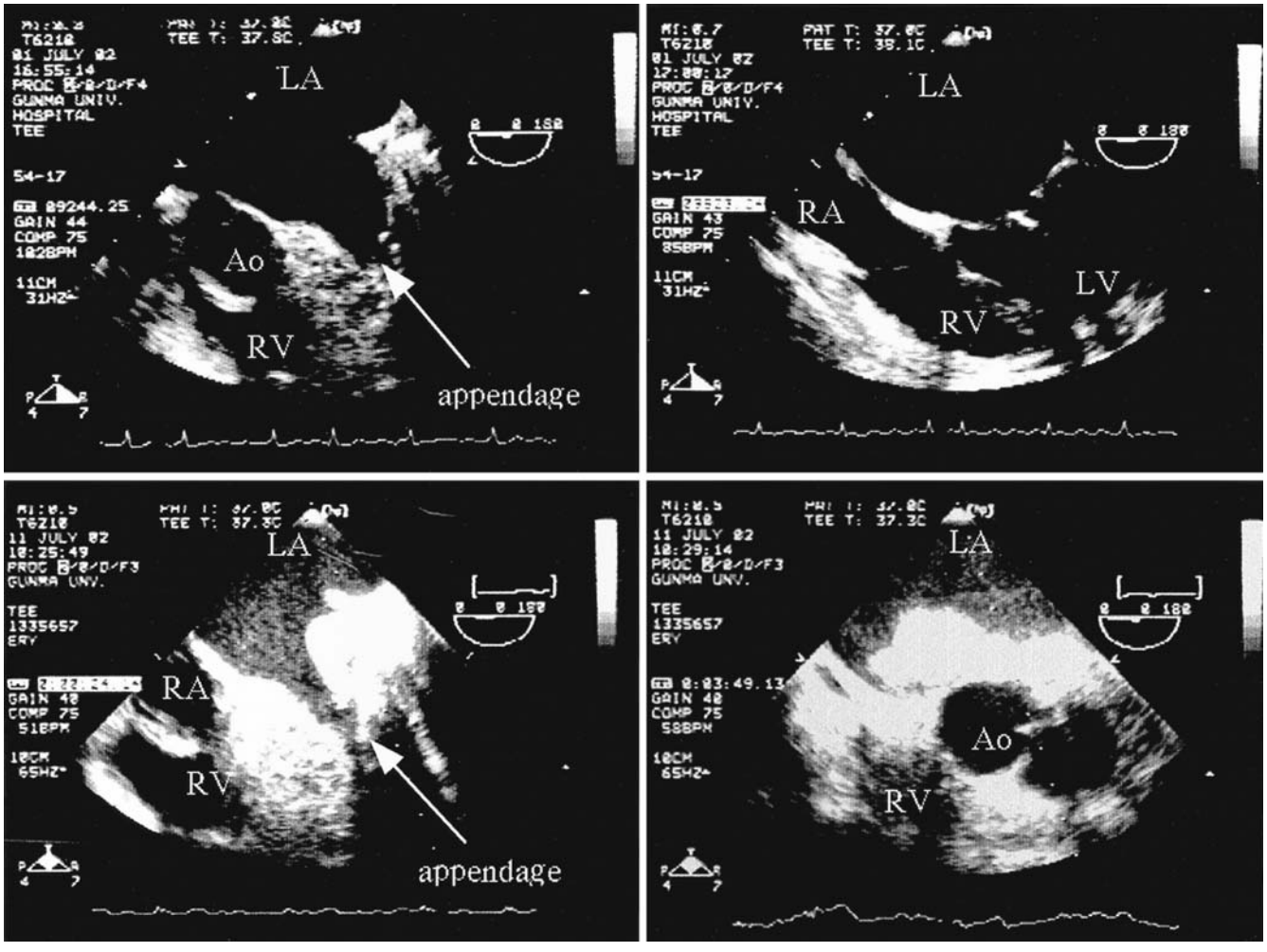

Fig. 1. a,**b** Images from transesophageal echocardiography during the preoperative period. There was no thrombus formation in the left atrial appendage (**a**) and the left atrium (**b**). **c**,**d** Images from transesophageal echocardiography during the operative period. There were two thrombi in the left atrial appendage (**c**) and the left atrium (**d**). *LA*, left atrium; *RA*, right atrium; *LV*, left ventricle; *RV*, right ventricle; *Ao*, ascending aorta

The warfarin therapy was discontinued 3 days before surgery (Table 1). Heparin was not administered. Anesthesia was induced by 0.2 mg·kg^{-1} of midazolam, 10 μg·kg^{-1} of fentanyl, and 0.2 mg·kg^{-1} of vecuronium, and the trachea was intubated. After the induction of anesthesia, a TEE probe was inserted through the esophagus. We found two thrombi in the left atrium (Fig. 1c and d). The diameter of the thrombus in the appendage was approximately 35 mm, and the diameter of the other one was approximately 40 mm. After the

start of cardiopulmonary bypass, the surgeons directly confirmed the presence of thrombi in the left atrium. The operation was performed uneventfully, and the patient was transferred to the intensive care unit. A neurological examination and brain computed tomography were performed 3 days after surgery. No new neurological dysfunction was found in the patient.

Discussion

It is generally recognized that since warfarin has a half-life of 36 to 42 hours, it takes about 4 days for the INR to reach 1.5 in most patients after warfarin therapy is stopped [1,3]. Once the INR reaches 1.5, surgery can be performed safely [2]. Tinker et al. [4] reviewed a total of 159 patients with cardiac valve prostheses undergoing 180 subsequent noncardiac operations after discontinuation of anticoagulants. They found that the overall incidence of documentable thromboembolic complications was approximately 10% and that none of the postoperative complications occurred while the patients were in the hospital. They concluded that the discontinuation of oral anticoagulants 1 to 3 days prior to the day of surgery, allowing the prothrombin time to return to within 20% of the normal range, was not accompanied by an increased risk of thromboemboli in patients with prosthetic heart valves. Subsequently, Goldenberg et al. [5] evaluated 160 patients with St. Jude mechanical bileaflet valves who had stopped their warfarin and found that only one patient experienced a thromboembolic event within 4 months. They concluded that temporary discontinuation of oral anticoagulation for an average of 5 days (range, 1–33 days) in patients with St. Jude mechanical prostheses did not appear to be accompanied by an increased risk of thromboembolic events. Kearon and Hirsh [2] reviewed the management of anticoagulation before and after elective surgery. In their review article, they suggest that although there is justification for the perioperative use of intravenous heparin in patients who have had an acute episode of venous thromboembolism in the 3 months prior to surgery, it is not indicated for most patients who are being given long-term oral anticoagulant therapy. In addition, they reported that the absolute risk of thromboembolism associated with a few days of perioperative subtherapeutic anticoagulation is generally very low, and the risk of bleeding associated with postoperative intravenous heparin therapy is often relatively high. In our case, the patient had a history of transient ischemic attack 2 and 30 years previously, in which the event might have been attributable to the thromboembolism. Before surgery, the warfarin dose was adjusted to keep the INR between 1.5 and 2.0 because of the patient's complication of massive subcutaneous bleeding. While keeping the INR between 1.5 and 2.0, we confirmed by TEE that there were no thromboembol at the left atrium (Fig. 1a and b). Therefore, we thought that the patient had a low risk of thromboembolism if warfarin therapy was discontinued temporarily. Therefore, no anticoagulant therapy, such as heparin, was administered after the discontinuation of warfarin. We thought that the risk of bleeding associated with heparin therapy was relatively high for this patient, because she had a complication of massive subcutaneous bleeding at INR 3.65. Since no thrombi were found in the left atrium by TEE during the preoperative period when the INR was stable between 1.5 to 2.0, we speculated that acute formation of thrombi in the left atrium occurred after the discontinuation of warfarin therapy. Schanbacher and Bennett [6] reported that two patients who had been taking warfarin for the prevention of thromboembolism and who stopped taking warfarin 3 to 7 days prior to cutaneous surgery had thromboembolic strokes within 1 week after surgery. They emphasized that warfarin should not be discontinued prior to surgery, because of the risk of thromboembolic strokes. Wahl [7] reported that among 493 patients undergoing dental surgery who had discontinued their warfarin temporarily, 5 patients (1%) had significant embolic complications, including death. Iorio et al. [8] reported that low-molecular-weight heparin is an effective and safe therapy without a risk of bleeding. Thus, we thought that low-molecular-weight heparin should be administered after the discontinuation of warfarin in this case.

Genewein et al. [9] investigated a rebound phenomenon after cessation of oral anticoagulant therapy in 19 patients, and found that the levels of thrombin-antithrombin III complex (TAT) increased transiently 4 days after the cessation of oral anticoagulant therapy. They concluded that the increased TAT demonstrated the existence of a significant rebound in thrombin generation in most patients. Although we did not measure the TAT level on the day of operation, a rebound phenomenon might exist at that time. Brummel et al. [10] suggested that control of anticoagulation in patients at the therapeutic range of INR may be less secure than anticipated. Therefore, the reduction in the warfarin dose and INR 16 days prior to the surgery may have contributed to thrombus formation in our patient.

The natural history of left atrial thrombus formation and the effect of anticoagulation in patients with mitral stenosis remain incompletely understood. It is possible that there may be regional hypercoagulability at the left atrium in mitral stenosis. Rebound hypercoagulability, which may be more active in an enlarged left atrium, is another possible factor. The safety and appropriate protocol of stopping warfarin in patients with mitral stenosis and atrial fibrillation remain untested. One should

keep in mind the danger of rapid thrombus formation immediately after the termination of warfarin therapy in patients with mitral stenosis. Anticoagulant therapy should be continued during the perioperative period in patients with combined risks for thromboembolism, such as atrial fibrillation and mitral stenosis.

In conclusion, our patient experienced acute thrombus formation in the left atrium 3 days after the termination of warfarin. This case teaches us that discontinuation of warfarin therapy a few days before the operation can cause thromboembolism.

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