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【 CASE REPORT 】

Atrial Fibrillation in a Patient with Heparin-induced Thrombocytopenia Successfully Treated by Radiofrequency Catheter Ablation Using a Direct Thrombin Inhibitor

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Abstract:
A 74-year-old man was admitted to our hospital to undergo radiofrequency catheter ablation (RFCA) of persistent atrial fibrillation (AF). We found that he had a history of heparin-induced thrombocytopenia (HIT). Thus, a direct thrombin inhibitor, Argatroban Hydrate (Argatroban®), was used instead of heparin as anticoagulation therapy during the RFCA procedure. Finally, the AF was successfully treated by RFCA without any complications. Given these findings, the direct thrombin inhibitor Argatroban® may be effective and feasible for anticoagulation therapy during RFCA procedures for AF in patients with HIT, such as the present case.

Key words: atrial fibrillation, direct thrombin inhibitor, heparin-induced thrombocytopenia, radiofrequency catheter ablation

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Introduction

Pulmonary vein (PV) antrum isolation (PVAI) has proven to be a useful strategy for radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF) worldwide (1). Anticoagulation therapies are necessary to avoid thromboembolic events before, during, and after RFCA of AF. Performing RFCA of AF with a target activated coagulation time (ACT) of more than 300 seconds reportedly decreases the risk of thromboembolic complications without increasing the risk of bleeding (2). Thus, it is recommended that the ACT be maintained between 300 to 400 seconds using heparin as an anticoagulant during RFCA of AF (3).

The recent guidelines of the European Society of Cardiology (4) and Japanese Circulation Society (3) recommend using a direct thrombin inhibitor as a preferred alternative to heparin in patients with heparin-induced thrombocytopenia (HIT) for percutaneous coronary intervention (PCI), as well as for cardiac and vascular surgery (5). However, no clear guidelines currently exist concerning the management of patients with HIT during RFCA.

We herein report a case of persistent AF in a patient with HIT successfully treated by RFCA using the direct thrombin inhibitor Argatroban Hydrate (Argatroban®) instead of heparin as anticoagulation therapy without any complications.

Case Report

A 74-year-old man was admitted to our hospital to undergo RFCA of persistent AF. He had a history of coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus, hypertension, dyslipidemia, sleep apnea-hypopnea syndrome, and chronic kidney disease. He had repeated episodes of CHF and was admitted to our or another hospital several times. In addition, he had been clinically diagnosed with HIT, which precluded the use of heparin, at a previous admission with CAD, and he underwent PCI and received heparin at another hospital. Two days after PCI, he suffered from subacute stent thrombosis. His 4Ts score (6) and HIT expert probability (HEP) score (7) were 8 and 14 points, respectively. Thus, although his HIT antibody test [platelet factor 4/heparin (PF4/H) antibody] (8) findings were negative on admission to our hospital, he had a very

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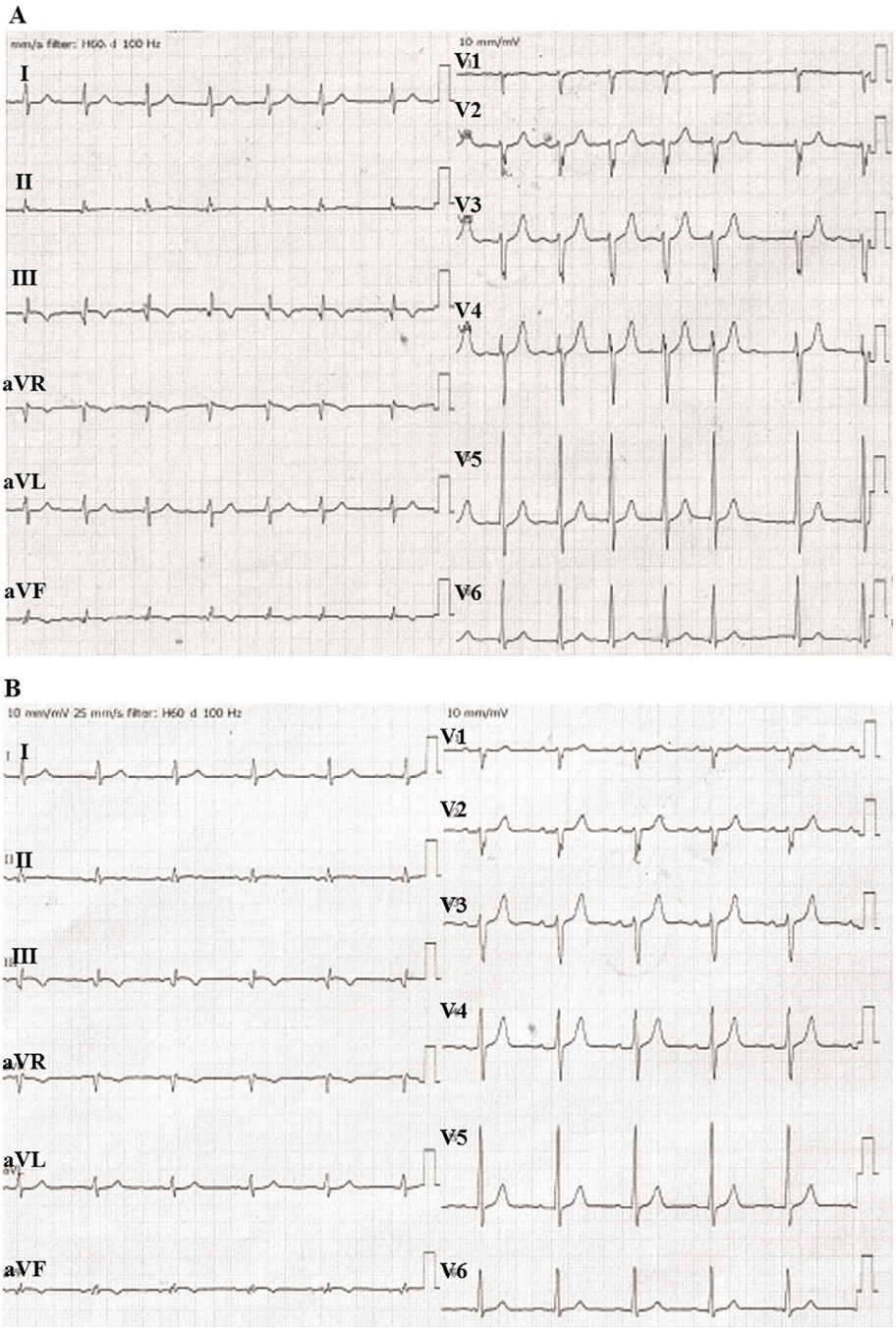

Figure 1. The 12-lead electrocardiogram findings on admission (A) and after pulmonary vein antrum isolation (B).

high probability of and was clinically diagnosed with HIT (9).

Anticoagulation therapy with Apixaban® and antiarrhythmic agent therapy with Bepridil® had already been started. He had also been taking a renin-angiotensin system inhibitor, beta-blocker, statin, diuretics, mineralocorticoid receptor antagonist, calcium channel blocker, and sodium-glucose cotransporter 2 inhibitor.

On admission, his blood pressure and heart rate were 110/68 mmHg and 87 bpm, respectively. Auscultation revealed normal cardiac sounds without any significant murmur and normal breath sounds over the bilateral lung fields. His serum creatine, brain natriuretic peptide (BNP), and hemoglobin A1c were 1.15 mg/dL, 235 pg/mL, and 7.1%, respectively.

A 12-lead electrocardiogram exhibited AF (Fig. 1A). Echocardiography yielded a decreased left ventricular ejection fraction (LVEF) of 36%, a normal valvular function, and no evidence of structural heart disease. His left atrial (LA) dimension was enlarged to 53.6 mm. His $CHADS_2$/CHA_2DS_2-VASc score was 3/5.

We explained his condition and the use of Argatroban® instead of heparin as anticoagulation therapy during the procedure to the patient and his family and obtained their in-

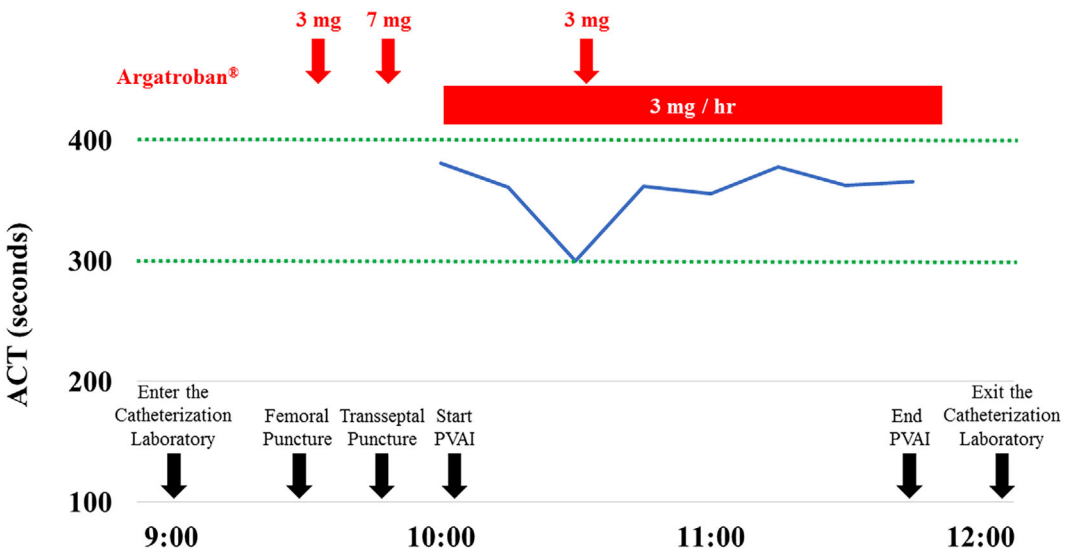

Figure 2. **The time course of activated coagulation time (ACT) during use of Argatroban®. PVAI: pulmonary vein antrum isolation**

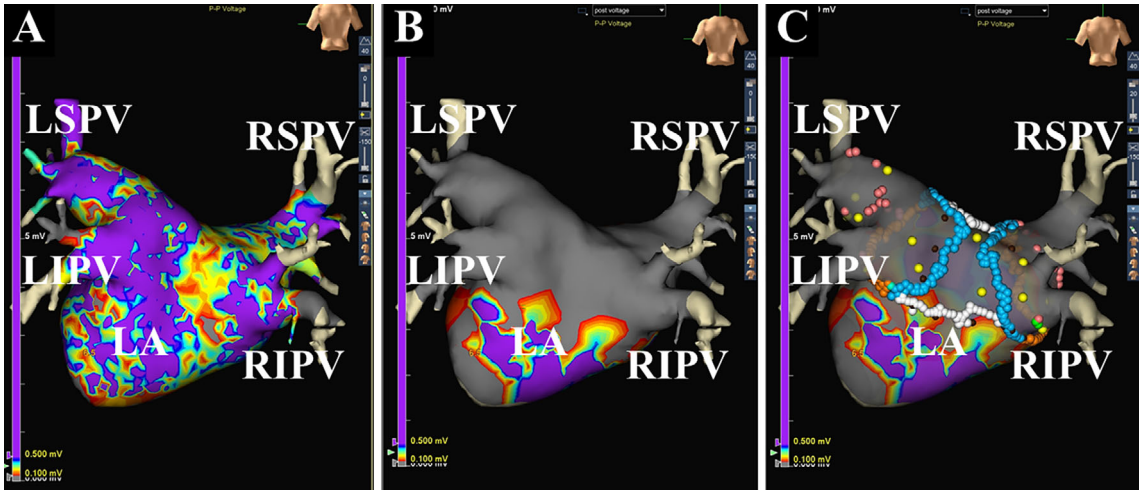

Figure 3. **The EnSite image in the posteroanterior view of the patient before (A) and after (B) ablation. The colored tags are the points of the pulmonary vein antrum and left posterior wall isolation (C). LA: left atrium, LSPV: left supra pulmonary vein, LIPV: left inferior pulmonary vein, RSPV: right supra pulmonary vein, RIPV: right inferior pulmonary vein**

formed consent to proceed. We also reported these conditions to the institutional review committee of our hospital and obtained their permission to use Argatroban® instead of heparin because Argatroban® use for RFCA of AF is uncommon.

Transesophageal echocardiography demonstrated the absence of any LA thrombus. Anticoagulation therapy with Apixaban® was continued until the day before the RFCA and then withheld on the morning of RFCA. After a bolus injection of Argatroban® at 3 mg (Fig. 2), double transseptal puncture was performed under guidance with intracardiac echocardiography (Ultra ICE catheter; EP Technologies, Boston Scientific, San Jose, USA). A 7-mg dose of Argatroban® was then additionally administered. Furthermore, 3 mg/h (0.7 μg/kg/min) was additionally and continuously infused, and a 3-mg dose of Argatroban® was also administered to maintain the ACT at 300 to 400 seconds (3). The ACT was revealed to be 381 seconds and was subsequently measured every 15 minutes during the procedure to be sure it was maintained between 300 and 400 seconds. Circumferential PVAI and LA posterior wall isolation and ablation of epicardial connection involving PVs (10) were then performed under electroanatomic guidance with a three-dimensional mapping system until the achievement of bidirectional conduction block between the LA and PVs under the administration of isoproterenol (Fig. 3A-C). Thereafter, programmed stimulation failed to induce any arrhythmias, including AF. The AF was thus successfully treated by RFCA without any complications (Fig. 1B).

Anticoagulation therapy with Apixaban® was resumed immediately after RFCA. He continued to take anticoagulation therapy and has remained well without any symptoms for

one year since RFCA.

Discussion

RFCA is an increasingly commonly utilized treatment strategy for various arrhythmias, including AF (1). Although heparin is the most widely used intraprocedural anticoagulant for the majority of patients undergoing RFCA, it may be contraindicated in patients with HIT, resistance to heparin (11), or heparin allergies (12). Previous studies have demonstrated that HIT occurs in <0.1% to 5% of heparin-exposed patients (9). The diagnosis of HIT requires clinical and laboratory evaluations, such as the 4Ts score (6), HEP score (7), and PF4/H antibody (8). Although the HIT antibody test (PF4/H antibody) (8) in this patient was negative, his 4Ts score (6) and HEP score (7) were 8 and 14 points, respectively. Furthermore, HIT antibodies (PF4/H antibody) (8) are widely available and highly sensitive (> 99%) (8). However, they are notorious for having a poor specificity (30-70%) (8). Thus, this patient had a high probability of HIT (9) and was ultimately clinically diagnosed with HIT.

The guidelines of the European Society of Cardiology (4) and Japanese Circulation Society (3) recommend the use of heparin as anticoagulation therapy during a number of procedures, including coronary angiography (CAG) and/or a PCI, RFCA of AF, as well as for cardiac and vascular surgery (5). In contrast, Argatroban® is well-known as a direct thrombin inhibitor and has dose-dependent anticoagulation effects, regardless of the concentration of the antithrombin-III. Argatroban® was previously reported to demonstrate a superior anticoagulant effect in patients undergoing elective PCI (13, 14). Thus, it is usually used for anticoagulation therapy during CAG and/or PCI as well as for cardiac and vascular surgery (5) in patients with HIT (15). However, because no clear guidelines concerning anticoagulation therapy exist at present for patients with HIT during RFCA of AF, we administered Argatroban® with reference to its use in patients with HIT during CAG and/or PCI.

Argatroban® is unique among direct thrombin inhibitors because it is predominantly hepatically metabolized, mainly by the liver microsomal cytochrome P450 enzyme CYP3A4/5, which acts rapidly and has a short elimination half-life of 52±16 minutes (16). Furthermore, Argatroban® dependently increases not only the ACT but also the activated partial thromboplastin time, prothrombin time of the international normalized ratio, and thrombin time (16). When we encounter patients with heparin-resistance, including HIT, during RFCA of AF, it may be important to use an alternative anticoagulation therapy instead of heparin. As such, during RFCA, the direct thrombin inhibitor Argatroban® may be an extremely effective and feasible candidate for anticoagulation therapy in patients with HIT, such as in the present case. While another direct thrombin inhibitor, bivalirudin (Angiomax®) (5), might also be a viable alternative, bivalirudin was not yet commercially available in Japan at that time of this procedure, despite being commonly used in Europe and the U.S.

In the present case, anticoagulation therapy with Apixaban® was withheld on the morning of RFCA. However, the current guidelines do not recommend the interruption of anticoagulation therapy during the procedure (4), particularly for such high risk cases. Thus, we should have continued anticoagulation therapy with Apixaban® on the morning of RFCA. Because his $CHADS_2/CHA_2DS_2$-VASc score was 3/5, anticoagulation therapy with Apixaban® was continued after RFCA of AF, even though he had no recurrence of AF. Furthermore, the LVEF on echocardiography and the BNP improved to 50% and 74 pg/mL, respectively, and he had suffered no episodes of CHF by 1 year later.

To our knowledge, this was the first report concerning AF in a patient with HIT successfully and safely treated by RFCA using the direct thrombin inhibitor Argatroban® in Japan.

The authors state that they have no Conflict of Interest (COI).

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