A case report of atrial fibrillation in a patient with heparin resistance associated with an antithrombin III deficiency successfully treated by radiofrequency catheter ablation using a direct thrombin inhibitor

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Background	Pulmonary vein antrum isolation has proven to be a useful strategy for radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF) worldwide. Anticoagulation therapies are necessary to avoid thromboembolic events before, during, and after RFCA of AF. During the RFCA procedure for AF, it is recommended that the activated coagulation time be maintained between 300 s and 400 s using heparin as an anticoagulation therapy.
Case summary	An 81-year-old man with symptomatic and drug-refractory paroxysmal AF underwent RFCA. We found that he had a severe heparin resistance during the RFCA procedure, and heparin had little effect on him. Thus, a direct thrombin inhibitor, Argatroban Hydrate®, was used instead of heparin for anticoagulation therapy during the procedure. Finally, the AF was successfully treated by RFCA without any complications. With a post-procedural inspection, we found that he had a Type-1 antithrombin III (AT-III) deficiency.
Discussion	Atrial fibrillation is the most common clinical arrhythmia and is associated with significant clinical morbidity and increased mortality. An AT-III deficiency is a well-known autosomal dominant hereditary disease and congenital blood coagulation abnormality occurring in about 1:500–5000 live births that may sometimes cause thrombophilia. Thus, the physicians may occasionally come across patients with an AT-III deficiency in real-world clinical practice, even though they have no history of thrombophilia. Argatroban Hydrate® may be effective and feasible for anticoagulation therapy during the RFCA procedure of AF in patients with heparin resistance such as in this present case.
Keywords	Antithrombin III deficiency • Atrial fibrillation • Case report • Direct thrombin inhibitor • Heparin resistance • 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. In our hospitals, the systemic anticoagulation therapy with uninterrupted warfarin is routinely continued routinely peri-procedurally. On the other hand, the direct oral anticoagulants are continued routinely until the day before the RFCA, withheld on the morning of the procedure, and restarted immediately after RFCA. Because it has been reported that performing RFCA of AF with a target activated coagulation time (ACT) of more than 300 s decreases the risk of thromboembolic complications without increasing the risk of bleeding,[2] it is recommended that the ACT be maintained between 300 s and 400 s using heparin as an anticoagulant during the RFCA procedure of AF.[3] Thus, we usually use an initial bolus injection of 150 units per kilogram of heparin prior to the delivery of any radiofrequency energy, and check the ACT every 15 min during the RFCA procedure. Moreover, we give an additional appropriate quantity of heparin while monitoring the ACT value. Here, we report a case of paroxysmal AF in a patient with a severe heparin resistance associated with an antithrombin III (AT-III) deficiency successfully treated by RFCA using the direct thrombin inhibitor, Argatroban Hydrate[®], instead of heparin as an anticoagulation therapy without any complications.

Timeline

Case presentation

An 81-year-old man was admitted to our hospital to undergo RFCA of paroxysmal AF. He had a history of hypertension, and suffered from cerebrovascular apoplexy at the age of 80 years. Then, AF was documented (*Figure 1A*), and anticoagulation therapy with Apixaban[®] and antiarrhythmic agents including 100 mg per day of Bepridil[®] and 40 mg per day of Aprindine[®] were started. However, he experienced several attacks of paroxysmal AF with intolerable palpitations under treatment with antiarrhythmic agents. On admission, his blood pressure and heart rate were 108/62 mmHg and 62 b.p.m., respectively. Auscultation revealed normal cardiac sounds without any significant murmur and normal breath sounds over the bilateral lung fields. His laboratory analysis was almost normal. The 12-lead electrocardiogram exhibited normal sinus rhythm (*Figure 1B*). The echocardiography yielded a normal left ventricular and valvular function and no evidence of structural heart disease. His left atrial (LA) dimension was 38 mm. His CHA_2DS_2-VASc score was 5. He had a family history of thrombophilia including his mother who suffered from deep vein thrombosis. However, this was not further investigated.

Anticoagulation therapy with Apixaban[®] was continued until the day before the RFCA, and was withheld on the morning of the RFCA. After a bolus injection of heparin at 50 units per kilogram (3300 units), a double transseptal puncture was performed under guidance with intracardiac echocardiography (Ultra ICE catheter; EP Technologies, Boston Scientific Corporation, San Jose, CA, USA). Then, a 100 unit per kilogram (6700 units) administration of heparin was additionally administered to maintain the ACT at 300–400 s.[3] However, the ACT was revealed to be only 133 s at that time. Because the retesting of the ACT level revealed it was only 135 s, a

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1 year before presentation	He suffered from cerebrovascular apoplexy. Then, atrial fibrillation (AF) was documented, and anticoagulation therapy with 10 mg per day of Apixaban[®] and antiarrhythmic agents consisting of 100 mg per day of Bepridil[®] and 40 mg per day of Aprindine[®] were started.
At presentation	He was admitted to undergo radiofrequency catheter ablation (RFCA) of drug-refractory AF.
During procedure	He had a severe heparin resistance during the RFCA procedure. Thus, a direct thrombin inhibitor, Argatroban Hydrate[®], was used instead of heparin for anticoagulation therapy. Finally, the AF was successfully treated by RFCA without any complications.
After the RFCA	Laboratory analysis after the RFCA yielded a decrease in his antithrombin III (AT-III) activity and concentration of AT-III antigen down to 47% and 22.6 ng/mL, respectively. He was diagnosed with a Type-1 AT-III deficiency.
Follow-up at 6-month	He has remained well without any arrhythmias.
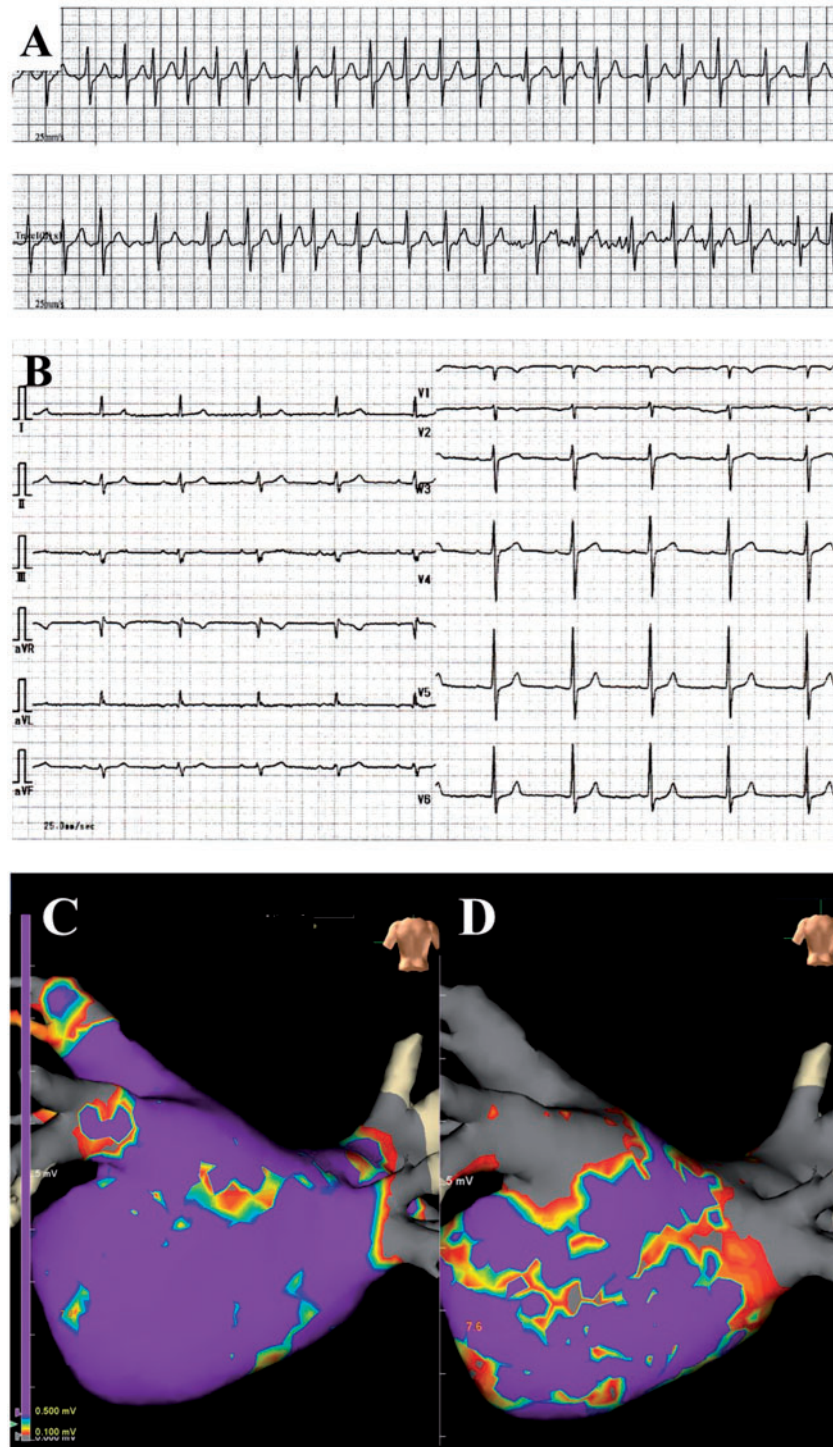
Figure I The electrocardiogram while suffering from cerebrovascular apoplexy at the age of 80-year-old (*A*) and 12-lead electrocardiogram on admission (*B*). The EnSite 3-dimensional mapping system voltage maps viewed from the back before (*C*) and after (*D*) the pulmonary vein antrum ablation.

10 000 units dose of heparin was additionally administered. However, the ACT was still low at 200 s.

Although we initially doubted he had heparin-induced thrombocytopenia (HIT), a blood test was performed revealing that the platelet level was $225 \times 10^3/\mu L$ and there was no thrombus formation in

the sheaths with no evidence of HIT. Based on the ACT results, we speculated that the patient had heparin resistance, and the direct thrombin inhibitor, Argatroban Hydrate®, was used instead of heparin as an anticoagulation therapy. At first, a 10 mg dose of Argatroban Hydrate® was administered, and then 4 mg/h (1.6 mg/kg/

Table 1　Laboratory analysis

	On admission	During RFCA	Before discharge	Normal value
Platelet level ($\times 10^3$/μL)	219	225	220	158–348
Prothrombin time (s)	—	—	13.8	9.5–12.5
Prothrombin time (%)	—	—	72	70–100
Prothrombin time (international normalized ratio)	—	—	1.20	—
Activated partial thromboplastin time (s)	—	—	39.2	27–35
D-dimer (μg/mL)	—	—	<0.5	0.1–0.9
Protein C (%)	—	—	83	70–150
Protein S (%)	—	—	65	60–150
Thrombin-AT-III complex (ng/mL)	—	—	2.3	0–3.0
Concentration of antithrombin-III antigen (ng/mL)	—	22.6	22.4	23.6–33.5
Antithrombin-III activity (%)	—	47	73	75–125

RFCA, radiofrequency catheter ablation.

min) was additionally and continuously infused to maintain the ACT at 300–400 s. After an administration of Argatroban Hydrate® for 10 min the ACT was 391 s. Then, the RFCA of AF was resumed. The ACT was measured every 15 min during the procedure and was maintained at 300–400 s.

Next, a circumferential PVAI was performed under electroanatomic guidance with the 3D mapping system, until the achievement of bidirectional conduction block between the LA and PVs under the administration of isoproterenol (*Figure 1C and D*). Thereafter, programmed stimulation could no longer induce any arrhythmias including AF. Finally, the AF was successfully treated by RFCA without any complications. Anticoagulation therapy with Apixaban® was resumed immediately after the RFCA.

His laboratory analysis during the RFCA yielded a decrease in his AT-III activity and concentration of AT-III antigen down to 47% and 22.6 ng/mL, respectively. However, the analysis demonstrated that he had negative HIT antibodies. Thus, he was diagnosed with a Type I AT-III deficiency.[4] We explained these results and the Argatroban Hydrate® use instead of heparin as an anticoagulation therapy during the procedure to the patient and his family, and obtained their informed consent. Moreover, we also reported these conditions to the institutional review committee of our hospital, because Argatroban Hydrate® use for RFCA of AF is uncommon. We recommended his family evaluate their AT-III activity and concentration of AT-III antigen. He did not want to undertake genetic testing.

His laboratory analysis before discharge yielded a further decrease in his AT-III activity and concentration of AT-III antigen down to 73% and 22.4 ng/mL, respectively. Moreover, the analysis demonstrated that normal levels of the thrombin-AT-III complex, Protein C and S, and D-dimer under anticoagulation therapy with Apixaban® (*Table 1*). He continued on the anticoagulation therapy because of his history of cerebrovascular apoplexy associated with AF and the AT-III deficiency and has remained well without any symptoms after the RFCA.

Discussion

It has been previously reported that heparin resistance can be caused by different conditions: AT-III deficiency or abnormalities, cardiopulmonary bypass, increased heparin clearance, increase of other heparin binding proteins, peri-partum period, and neoplasias.[5] In this case, a direct thrombin inhibitor was administered during the procedure without having an established diagnosis. Indeed, an AT-III deficiency was considered as a potential cause of the heparin resistance and confirmed by the efficacy of a direct thrombin inhibitor administration.

An AT-III deficiency is a well-known autosomal dominant hereditary disease and congenital blood coagulation abnormality occurring in about 1:500–5000 live births that may sometimes cause thrombophilia.[4,6] The AT protein, encoded by the SERPINC1 gene, is a potent inhibitor of multiple coagulation proteases including thrombin and factor Xa. Close to 300 mutations have been identified in the SERPINC1 gene, which result in either a quantitative (Type I) deficiency or a qualitative (Type II) defect in the protein synthesized.[7] However, it has been reported that about one-third of patients with an AT-III deficiency do not have thrombophilia during their lifetime.[4,6] Moreover, laboratory analyses, such as for markers of blood coagulation, including the prothrombin time, activated partial thromboplastin time (APTT), fibrinogen, and fibrinogen degradation products, in patients with an AT-III deficiency do not often yield abnormalities. Thus, an AT-III deficiency is often first noticed when thrombophilia occurs. The physicians may occasionally come across patients with an AT-III deficiency in real-world clinical practice despite not having a prior history of thrombophilia.

Because AT-III deficiency is an autosomal dominant hereditary disease, affected patients may have a family history of thrombophilia.[4,6] In this present case, he had no history of thrombophilia, but had a family history of thrombophilia, and both his AT-III activity and AT-III antigen concentration were low. Moreover, because his oral medications were a beta-blocker and calcium channel blocker, which had no effect on the AT-III, he was negative for a drug-induced secondary AT-III deficiency. Finally, he was diagnosed with a congenital Type I AT-III deficiency. Thus, a screening examination for AT-III may be useful if patients have a history and/or family history of thrombophilia, although a routine AT-III examination may not be necessary.

The guidelines of the European Society of Cardiology[8] and Japanese Circulation Society[3] recommend the use of heparin as an

anticoagulation therapy during procedures including coronary angiography (CAG) and/or percutaneous coronary intervention (PCI), and RFCA of AF. On the other hand, Argatroban Hydrate® is well-known as a direct thrombin inhibitor and has dose-dependent anticoagulation effects regardless of the concentration of the AT-III. It has been reported that Argatroban Hydrate® demonstrates a superior anticoagulant effect in patients undergoing an elective PCI.[9,10] Thus, it is usually used for anticoagulation therapy during a CAG and/or PCI in patients who have heparin resistance including HIT.[11] However, because it is not specified in the guidelines whether or not to use Argatroban Hydrate® during the RFCA of AF, we used it in reference to the use in patients with HIT. Argatroban Hydrate® is unique among the 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 min.[12] Moreover, Argatroban Hydrate® dependently increases the ACT, APTT, the prothrombin time of the international normalized ratio, and thrombin time.[12] When we experience patients with heparin resistance, such as an AT-III deficiency, during RFCA of AF, it may be important to use an alternative anticoagulation therapy instead of heparin. In view of these findings, the direct thrombin inhibitor, Argatroban Hydrate®, may be one of the most effective and feasible candidates for anticoagulation therapy in patients with heparin resistance, such as in this present case. Although another direct thrombin inhibitor, Bivalirudin (Angiomax®) might be used as an alternative. Bivalirudin (Angiomax®) is commonly used in Europe and the U.S., but was not yet commercially available in Japan at that time of this procedure.

Because His CHA_2DS_2-VASc score was 5 and he suffered from an AT-III deficiency, anticoagulation therapy with Apixaban® was continued after the RFCA of AF even though he had no recurrence of AF. Finally, to the best of our knowledge, this is the first report concerning AF in a patient with an AT-III deficiency successfully and safely treated by RFCA using the direct thrombin inhibitor, Argatroban Hydrate®.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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