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Stroke due to Left Atrial Appendage Thrombus after Pulmonary Vein Isolation despite Novel Oral Anticoagulant: A Case Report

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Novel oral anticoagulation · Stroke · Catheter ablation · Drug activity · Plasma concentration

Abstract
In patients with atrial fibrillation, catheter ablation is suggested to reduce the mortality rate and is thus frequently performed. However, peri- and postprocedural thromboembolic complications as well as high recurrence rates of atrial fibrillation limit its advantages and require concomitant anticoagulation. With the advent of novel oral anticoagulants (NOACs), fixed dosing without routine laboratory monitoring became feasible. Nevertheless, several factors are associated with either an overdose or an insufficient drug activity of NOACs. We report on a patient with atrial fibrillation undergoing catheter ablation and cardioversion suffering from ischemic stroke despite being under oral anticoagulation. It turned out that the drug activity of the NOACs used was repeatedly insufficient in spite of regular intake and adequate dosing. In sum, drug activity controls should be taken into consideration in patients with thrombotic events despite oral anticoagulation with NOACs.

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Introduction

Catheter ablation is shown to reduce recurrence rates of atrial fibrillation compared to treatment with antiarrhythmic drugs only [1–3]. In addition, ablation reduces all-cause mortality among patients with heart failure and atrial fibrillation [4]. However, studies regarding the risk of thromboembolic events after cardiac intervention are controversial. While some studies suggest a reduced risk of stroke [5–7], others show no significant decrease in the risk of cerebrovascular events after cardiac intervention in patients with atrial fibrillation [8–10]. Furthermore, there is a marked incidence of thromboembolic complications associated with ablation procedures and cardioversion [11]. Consequently, pharmacological prevention with oral anticoagulation is of great importance. According to current guidelines, oral anticoagulation for patients with atrial fibrillation is recommended depending on the CHA_2DS_2-VASc score [12].

Traditionally, vitamin K antagonists such as warfarin or phenprocoumon with frequent international normalized ratio (INR) controls were widely used for this purpose. However, the advent of novel oral anticoagulants (NOACs) facilitated a fixed dosing of the drug without the requirement of a routine coagulation test due to the predictable pharmacokinetic profiles of the substances [13]. Further advantages of NOACs are a rapid onset of action and fewer drug-drug interactions than with vitamin K antagonists [14, 15]. For quantitative measurement of thrombin and factor Xa inhibitors (diluted) thrombin time tests and anti-factor Xa chromogenic assays were established, respectively [13, 16–18].

Nevertheless, there have been several cases in which NOACs were found to be either below the therapeutic range or overdosed, resulting in a higher risk of thromboembolic complications or bleeding [19–21]. Therefore, administering NOACs without questioning their efficacy according to individual properties could lead to detrimental consequences. Below, we report on a patient with stroke after catheter ablation and cardioversion for symptomatic atrial fibrillation with low drug activity of apixaban and dabigatran.

Case Presentation

A 66-year-old male patient was admitted to the cardiology department for elective pulmonary vein re-isolation for the treatment of symptomatic persistent atrial fibrillation. His body mass index (BMI) was 30.4 kg/m^2 (weight: 93 kg; height: 1.75 m) and his creatinine clearance 102.8 mL/min (according to the Cockcroft-Gault equation; normal range: 80–120 mL/min). Further diseases were hypertension and asthma. Four years earlier, he had undergone pulmonary vein isolation with following electrical cardioversion, and soon after suffered from recurrence of atrial fibrillation with intermittent palpitations.

Oral anticoagulation with 2 × 5 mg apixaban was administered for prevention of thromboembolic events. Last intake was the day prior to the intervention. Preprocedural transesophageal echocardiography on the day of ablation excluded an intracardiac thrombus (Fig. 1a). Pulmonary vein isolation by radiofrequency ablation with concomitant electrical cardioversion was performed. In order to prevent thromboembolic procedural complications, heparin was administered intravenously during the intervention. Due to an insufficient activated clotting time (ACT) of 234 s 1 h and 15 min after initial application of 5,000 IE heparin, another 5,000 IE heparin were administered, achieving an ACT of 278 s 25 min later. In order

to achieve an ACT target >300 s, another 2,500 IE (cumulative dose of all administered heparin: 12,500 IE) were administered. Apixaban was re-initiated on the same day.

After ablation, the patient was free of symptoms and mobile on the ward. On the following day, 30 h after ablation, he was found with acute-onset left-sided hemiparesis, dysarthria, and neglect (National Institutes of Health Stroke Scale score 8). Emergency cranial computed tomography (CT) imaging showed no early ischemic changes or intracerebral hemorrhage. However, CT angiography revealed an occlusion of the proximal M1 segment of the right middle cerebral artery, and the patient was transferred immediately to our neurology department. Due to prior intake of oral anticoagulation, thrombolysis was contraindicated, and the patient was directly transferred to the Angio Suite. Successful mechanical thrombectomy was performed with one stent-retriever assisted vacuum-locked extraction (SAVE) with nearly complete reperfusion (Thrombolysis in Cerebral Infarction scale grade 2b) without any complications (Fig. 1d) [22].

CT imaging on the following day demonstrated a small infarct in the right basal ganglia. Although transesophageal echocardiography prior to catheter ablation revealed no pathological structure, a thrombus (approx. 1.4 × 0.6 cm) in the left atrial appendage was detected 5 days after the cardiac intervention (Fig. 1b). Calibrated drug activity as a surrogate for the plasma concentration of apixaban was proven to be insufficient despite supervised oral intake during the hospital stay: the estimated trough plasma concentration 12 h after last intake was 18 ng/mL (expected range: 34–230 ng/mL) and the estimated peak plasma concentration 3 h after last intake was 36 ng/mL (expected range: 69–321 ng/mL) [23, 24]. Thus, apixaban was replaced by 2 × 150 mg of dabigatran. However, this also resulted in low drug activity of the substance: the estimated trough plasma concentration 12 h after last intake was 26 ng/mL (expected range: 31–225 ng/mL) and the estimated peak plasma concentration 3 h after last intake was 56 ng/mL (expected range: 64–443 ng/mL) [24, 25]. External validation by a different laboratory showed no significant difference in results (<1 ng/mL). Furthermore, concomitant medication (ramipril, metoprolol retard, pantoprazole, atorvastatin, ipratropium bromide/fenoterol, and fluticasone/formoterol fumarate) had no interaction potential. Finally, phenprocoumon (INR target: 2.0–3.0) was chosen for continuation of oral anticoagulation. Five days after first intake of phenprocoumon, the patient's INR reached 2.1 and concomitant administration of dabigatran was terminated. The INR target of 2–3 was maintained thereafter. The patient was discharged with only minor neurological deficits (mild left-sided facial palsy).

Three months later, he had recovered completely from the stroke (no neurological deficits). A follow-up TEE showed no thrombus, and subsequent electrical cardioversion was performed.

Discussion

Catheter ablation and cardioversion in patients with symptomatic atrial fibrillation are widely performed to improve quality of life by restoring the sinus rhythm and thereby preventing left ventricular dysfunction and heart failure [2, 3]. However, it remains controversial whether there is a prominent effect on reduction of stroke risk due to peri- and postprocedural thromboembolic complications [26, 27].

During cardioversion, errant atrial conduction is converted to ordered conduction by application of an electric current (electrical cardioversion) or antiarrhythmic medication

(pharmacological/chemical cardioversion) [28, 29]. Although the risk of thromboembolic events is low in patients with atrial fibrillation under adequate chronic anticoagulation, ranging between 0.13 and 0.2%, cardioversion leads to a temporary 3- to 4-fold increase in risk of stroke [30]. An explanation for this observation is that the procedure leads to atrial stunning, resulting in reduced flow velocity and thereby favoring thrombus formation [31, 32]. Moreover, a considerable rate of atrial fibrillation recurrence after ablation requires continuation of anticoagulation [33, 34]. Consequently, pharmacological prevention of thromboembolic events despite cardiac intervention is crucial in patients with atrial fibrillation. For this purpose, NOACs are often preferred due to their improved safety profiles and noninferiority to vitamin K antagonists [35, 36]. A major advantage is a fixed dosing without requirement of frequent monitoring, owing to the predictable pharmacokinetic properties of NOACs [37]. Nevertheless, due to short half-lives of NOACs, noncompliance leads to insufficient drug activity and consequently to an increased risk of thromboembolic complications. Although NOACs are considered to have fewer drug-drug interactions than vitamin K antagonists, it has also been shown that the drug activity of NOACs is dependent on factors such as age, body weight, renal function, and even ethnic background [25, 38, 39].

In our case, the body weight was a probable explanation for the insufficient drug activity of the NOACs. The patient's BMI of 30.4 kg/m^2 met the WHO definition of obesity (obesity is a BMI ≥30) [40]. The volume of distribution and drug clearance can be influenced by weight, resulting in either underdosing or overdosing of the substance, with a correspondingly enhanced risk of thromboembolism or bleeding, when fixed dosing is used. Although studies have not revealed clinically significant effects of obesity on the pharmacokinetic properties of NOACs [20, 24], a correlation between nondiabetic obesity and increased glomerular filtration could be observed [41]. Furthermore, due to the altered liver weight, enzyme content, and metabolic rate along with the body size, variability in hepatic clearance is known to be correlated with obesity [42]. Hence, regarding apixaban, where renal excretion accounts for 27% of total apixaban clearance, an increased nonrenal elimination in our obese patient could be discussed [42]. In addition, a subanalysis of RE-LY data in regard to patients' characteristics revealed that due to reduced drug exposure, decreased peak concentrations, and shorter half-lives, patients with obesity showed 21% lower estimated dabigatran plasma concentrations than patients with normal weight [25, 43, 44]. Another single-center, retrospective cohort study described a higher thromboembolic event rate among obese patients on dabigatran than among those on apixaban or rivaroxaban, suggesting an avoidance of dabigatran in obese patients until further studies would be conducted [45, 46].

In the clinical setting, there are situations where drug activity tests could facilitate improved decision-making – i.e., in assessment of the bleeding risk of invasive procedures or medical interventions, such as thrombolytic therapy for acute ischemic stroke – or determining drug concentrations for patients suffering from thromboembolic events despite oral anticoagulation [47, 48]. Whereas vitamin K antagonists allow activity control by INR measurements, laboratory assessments of NOACs have appeared more challenging in the past few years. To date, diluted thrombin time and ecarin clotting time have been established for laboratory monitoring of dabigatran, as well as anti-factor Xa chromogenic assays for apixaban, edoxaban, and rivaroxaban [49]. However, these laboratory assays are accompanied by high costs and available only in select clinics.

Given the importance of oral anticoagulation for prevention of thromboembolic events, more studies regarding insufficient drug activity are required to validate the necessity of more

frequent drug activity controls for NOACs in patients with atrial fibrillation in high-risk situations.

Statement of Ethics

The paper does not include any research or study and is thus exempt from ethics committee approval. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

W.H.C., B.F., and M.K. conceptualized and drafted the manuscript. H.W., I.D., and C.D. revised the manuscript. All authors read and approved the manuscript.

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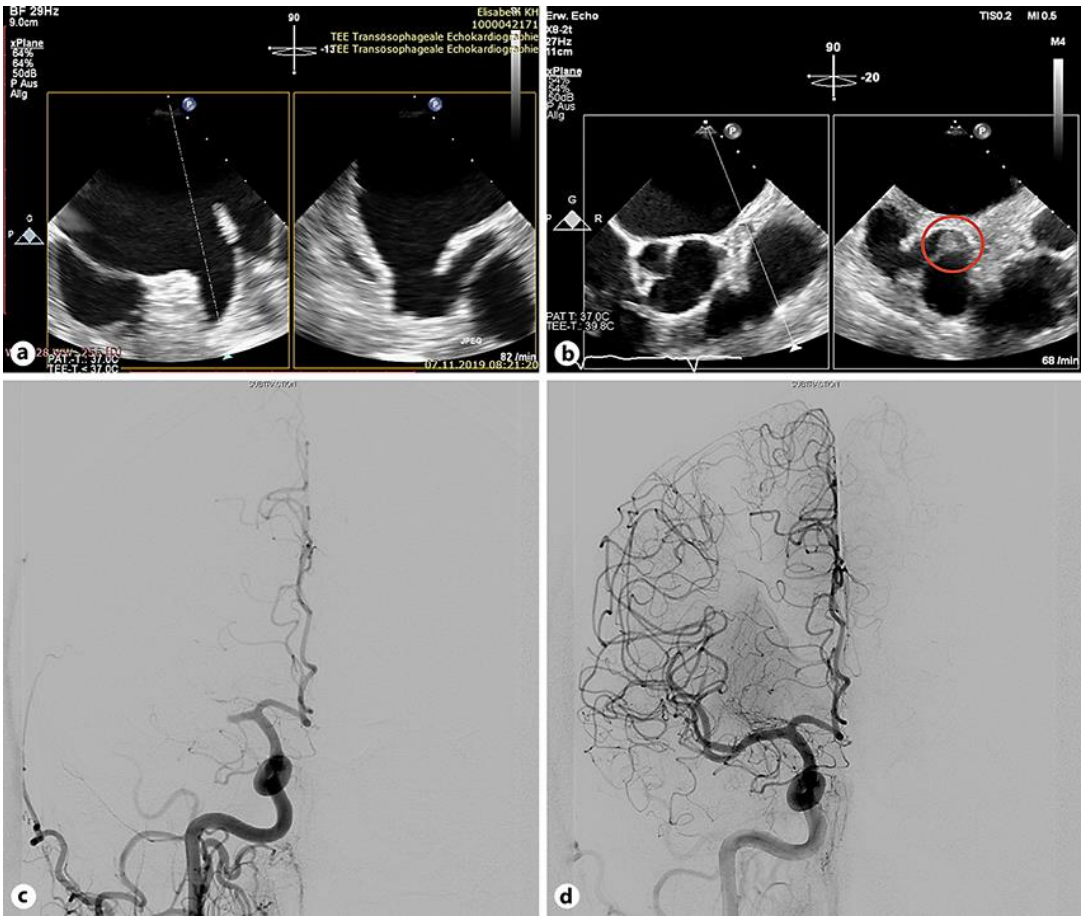

Fig. 1. Ultrasound and angiography images. **a** Images from transesophageal echocardiography directly prior to cardiac intervention depicting no pathological structure. **b** Images from transesophageal echocardiography 5 days after stroke showing a thrombus (approx. 1.4 × 0.6 cm) in the left atrial appendage. **c**, **d** Angiography images before (**c**) and after (**d**) mechanical thrombectomy of proximal M1 occlusion with one stent-retriever assisted vacuum-locked extraction (SAVE) resulted in successful reperfusion (TICI grade 2b).