Patients with hemophilia: Unique challenges for atrial fibrillation management

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Introduction

Patients with hemophilia present several unique challenges in the management of atrial fibrillation (AF), particularly with regard to the use of anticoagulation and procedural risks of thrombotic events. Here we describe a case of successful AF ablation performed in a patient with hemophilia A.

Case report

A 54-year-old man with mild to moderate hemophilia A, obstructive sleep apnea on continuous positive airway pressure, and paroxysmal AF was referred for AF catheter ablation. Four years prior, he was evaluated for palpitations and dyspnea. AF was confirmed on ambulatory monitoring. His CHA_2DS_2-VASc score was 0. He was trialed on a series of antiarrhythmic medications including flecainide, propafenone, dronedarone, dofetilide, and sotalol. In spite of these medications, he continued to remain highly symptomatic with paroxysms of AF initially lasting 6–9 hours at a time, 3–5 times a month but later increasing in frequency and duration. He never required cardioversion.

Because of the unique comorbidity of hemophilia A, options for management of his AF were carefully considered. This included treatment with amiodarone, surgical ablation with left atrial appendage ligation, and AF catheter ablation. In conjunction with his hematologist, the decision was made to pursue an AF catheter ablation using the Arctic Front Advance Cryoballoon catheter (Medtronic Inc, Minneapolis, MN) with a standard infusion protocol of a third-generation recombinant factor VIII.

He was well established with a primary hematologist for his hemophilia with a baseline 5% factor activity level (mild-moderate disease severity). With the use of standard factor VIII replacement protocols, he had previously undergone other procedures including an appendectomy. He had a

history of experiencing spontaneous hemarthroses of peripheral joints, for which he received infusions of recombinant factor VIII as needed.

On the morning of the ablation, a factor VIII assay showed a baseline 13% activity level. He received 40 U/kg of recombinant factor VIII per the protocol, which increased the activity level to 131%. He was then brought to the electrophysiology lab, where a transesophageal echocardiogram was performed demonstrating no left atrial thrombus. The presenting rhythm was AF that spontaneously oscillated between sinus rhythm and AF. Left and right femoral vein access was obtained in the usual fashion using a modified Seldinger technique. The left atrium was accessed with 2 separate transseptal punctures using Preface sheaths (Biosense Webster, Diamond Bar, CA) with a BRK-1 transseptal needle under intracardiac echocardiographic guidance. Immediately after the first transseptal, a heparin bolus was administered followed by a heparin infusion with a goal activated clotting time (ACT) in a lower target range between 250 and 300 seconds for this case (usual target range 300–350 seconds at our institution). During the procedure, serial ACTs were obtained to guide intraprocedural heparinization to this goal. Actual ACTs varied between 190 and 283. The first Preface sheath was exchanged over a long J wire for a 12F FlexCath Steerable Sheath (Medtronic, Minneapolis, MN), and a 28-mm Arctic Front Cryoablation balloon catheter (Medtronic, Minneapolis, MN) was advanced into the left atrium. Through the second Preface sheath, a fixed 20 mm Lasso catheter (Biosense Webster, Diamond Bar, CA) was used. Heparin was infused for a total of 1000 U/h through both transseptal sheaths. A total of 3 4-minute freezes in each of the left superior and left inferior pulmonary vein antrums resulted in pulmonary vein isolation. Two 4-minute freezes in the right superior pulmonary vein antrum resulted in isolation. Phrenic nerve function was monitored by palpating the abdomen during phrenic nerve pacing from the superior vena cava. The right inferior pulmonary vein could not be isolated using the cryoballoon owing to inability to achieve adequate occlusion and poor contact. Therefore, the cryoballoon was exchanged for an externally irrigated radiofrequency (RF) ablation catheter (3.5 mm Thermocool Navistar, Biosense Webster). Antral isolation of the right inferior vein was

KEY TEACHING POINTS

- The guideline recommendation for routine anticoagulation around the time of catheter ablation for atrial fibrillation eliminates this therapeutic option for many patients with bleeding disorders. However, the evidence demonstrating the need for such anticoagulation is based on expert opinion and small observational studies and lacks high-quality evidence to support its necessity.

- Because standard factor replacement protocols allow transient correction of the coagulation cascade, patients with hemophilia may be able to safely undergo catheter ablation for atrial fibrillation using intraprocedural heparin. However, prolonged postprocedural anticoagulation is contraindicated.

successful with the RF catheter using multiple 25- to 30-watt lesions. Entry and exit block was confirmed in all 4 pulmonary veins using the Lasso catheter. Isoproterenol challenge up to 20 microgram/min at the end of the case did not induce further arrhythmias during the infusion and washout periods. At the completion of the case, the patient was in sinus rhythm. The catheters were removed and long sheaths exchanged for short sheaths, which were then sutured in place and removed later in recovery. Protamine was not administered.

The evening of and morning after completion of the case, the patient received an additional 40 U/kg recombinant factor VIII. Another factor VIII activity level was drawn the morning after ablation that confirmed continued deficiency reversal with a measured activity level of 112%. No postprocedural anticoagulation was used. He was observed

as an inpatient for 48 hours with no procedural complications. On discharge, he received 30 U/kg of recombinant factor VIII daily for 7 days. No long-term antithrombotic therapy was given. He was continued on sotalol for 2 months, at which point it was discontinued. In follow-up, no late bleeding or thromboembolic complications had occurred, including no hemarthroses. At 2 years of follow-up, he had no clinical or documented recurrences of AF.

Discussion

Hemophilia represents a related group of inherited and acquired bleeding disorders, most commonly represented by the X-linked recessive disorders hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency). No guidelines or randomized trials exist to guide the management of patients with hemophilia and cardiovascular comorbidities. Rather, expert consensus based on case reports and observational data serve as the primary references for clinicians.[1,2] As the development and use of recombinant factors has increased the life expectancy of patients with hemophilia beyond 60–70 years of age, the population at risk for developing AF has increased.[2,3] Considerations must be made in the management of AF in patients with hemophilia, including strategies for long-term stroke reduction and procedural considerations.

Long-term stroke reduction in AF involves weighing the stroke risk profile (eg, CHA_2DS_2-VASc) vs the bleeding risk. In the case of a patient with hemophilia, the bleeding risk is dominant and warfarin is not recommended in patients other than perhaps those with very mild hemophilia (native factor activity level ≥ 30%). Algorithms have been proposed to determine whether antithrombotic therapy is advisable (Figure 1).[2] If oral anticoagulation is prescribed, co-treatment with factor infusion to an activity level goal of 30% could be considered, though has not been studied
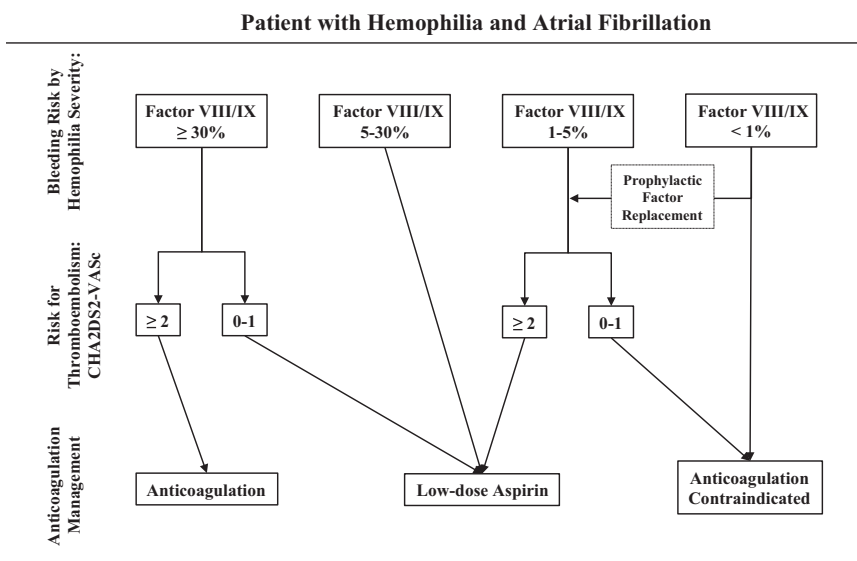

Patient with Hemophilia and Atrial Fibrillation

Figure 1 Proposed algorithm for management of antithrombotic therapy in patients with hemophilia and atrial fibrillation. Note that anticoagulation is not recommended unless the basal factor level is ≥ 30%. Adapted from Mannucci et al (2009).[2]
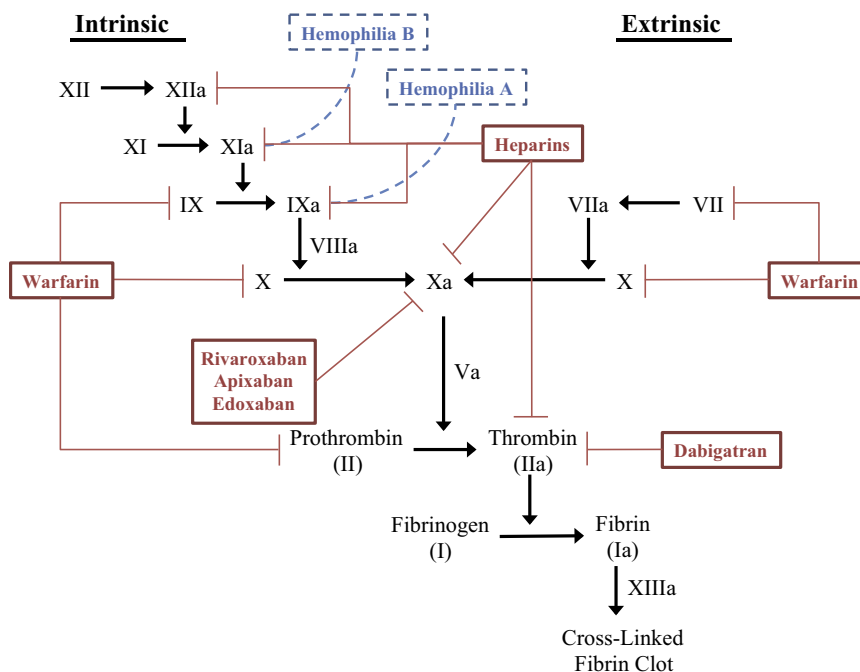
Figure 2   The coagulation cascade and primary targets of commonly used anticoagulants in the management of atrial fibrillation and sites of deficiency in patients with hemophilia A and B.

extensively.[3] Alternatives may become more widespread in the future, including the use left atrial appendage occlusion devices.[4] It is unknown what role the direct oral anticoagulants will have, if any, in patients with hemophilia and AF. Figure 2 summarizes the main targets for commonly used anticoagulants within the coagulation cascade.

For symptomatic patients, AF catheter ablation has become an accepted option for maintenance of sinus rhythm, particularly in patients who have failed an antiarrhythmic medication.[5,6] Both intraprocedural and postprocedural anticoagulation is felt to be critical to safe delivery of the procedure. The *2014 ACC/AHA Guideline for the Management of Patients With AF* issued a class III recommendation that "AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure" based on consensus opinion (level of evidence C).[7] Similarly, the 2012 *HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation* states that "systemic anticoagulation should be continued for at least 2 months following an AF ablation procedure," again based primarily on expert opinion.[5]

In approaching AF ablation, anticoagulation is first required intraprocedurally. This requirement is based on the risk of thrombus formation directly on the transseptal sheaths, on the catheters in the left atrium, or at sites of ablation. The latter is due to activation of the clotting cascade at sites of endothelial disruption or due to char formation. Expert consensus recommends intraprocedural anticoagulation with heparin to ACT goals of 300–400 seconds.[5] These are largely based on studies performed before the introduction of the open-irrigated tip RF ablation catheter or

cryoablation.[7,8] More recently, published data have shown that lower ACT goals of 225–250 seconds may be safe and effective in the setting of externally irrigated ablation catheters, single transseptal access, and relatively short duration of left atrial ablation time.[9,10] The optimal ACT target range remains unknown and most centers continue to have a goal of 300–350 seconds. The ACT relies on the presence of a normal coagulation cascade, which is inherently abnormal in the presence of a factor deficiency.[11] In the case of conditions such as hemophilia, exogenous factor replacement can at least temporarily restore normal coagulation. Therefore, the usual intraprocedural approach may not need to be significantly divergent and standard heparin administration can be utilized. We chose to deliver heparin and accepted a lower ACT target range in this patient knowing that these variances were likely to be observed. Desmopressin is an alternative to factor replacement, but it can have less predictable effects on the coagulation cascade and may have prothrombotic effects through platelet activation.

The second phase of care requiring anticoagulation is in the postprocedural period. In addition to the likelihood of early recurrence of atrial arrhythmias, other theoretical concerns include thrombus formation due to atrial stunning or at sites of endocardial ablation and endothelial disruption. Data supporting an early increased thromboembolic risk after AF catheter ablation is based on observational data. Oral et al published their experience with 7 thromboembolic events out of 755 consecutive AF catheter ablations. All of the early thromboembolic events after AF catheter ablation occurred within the first 2 weeks after ablation.[12] The international normalized ratio was documented to be subtherapeutic in 4 of 7 patients who had an early thromboembolic event (57%).

Because the early thromboembolic events were unrelated to the presenting rhythm or to baseline clinical variables, the proposed mechanism was char and/or thrombus at sites of left atrial endocardial ablation. However, all procedures in this study utilized a solid-tip 8-mm-tip ablation catheter, which is not commonly used with in modern AF ablation procedures. It is likely that cryoablation or open irrigated ablation catheters used most commonly today are less likely to cause char and thrombus formation at endocardial ablation sites than traditional RF catheters and reduce the risk of stroke. The cryoballoon in particular was chosen in this case because cryoablation has been shown to have diminished risk of thrombosis owing to decreased activation of platelets and the coagulation cascade and less vascular and endothelial disruption.[13]

Only 1 study to date has been performed to explore omitting anticoagulation after RF ablation for AF. Bunch et al shared their center's experience using aspirin alone (rather than oral anticoagulation) following AF ablation.[14] These 123 patients had a low baseline stroke risk (CHADS$_2$ scores of 0–1) and an open irrigated RF ablation catheter was used. There were no strokes or transient ischemic attacks in patients treated with aspirin alone, raising the possibility that warfarin is not needed in low-risk patients following AF ablation procedures. We chose not to use any postprocedure anticoagulation in our patient with hemophilia, given his bleeding risk and low CHA$_2$DS$_2$-VASc score.

An alternative approach for patients with relative or absolute contraindications to postprocedure anticoagulation is surgical AF ablation. Consensus opinion is that anticoagulation should also be continued after surgical ablation of AF for several months owing to the relatively high incidence of early atrial arrhythmias following the procedure.[5] However, there is a paucity of evidence regarding the optimal approach to periprocedural anticoagulation with surgical AF ablation. Surgical ablation for AF offers the theoretical advantage of surgical exclusion of the left atrial appendage, although controversy exists regarding the true benefit of this for stroke reduction. Another advantage is that the surgical approach, which is epicardial, avoids the need to place catheters inside the left atrium and therefore perhaps lowers the risk of thrombus formation.

We present a patient with hemophilia who successfully underwent AF catheter ablation by using a standard factor replacement protocol. To our knowledge, this is the first reported case of AF catheter ablation in a patient with hemophilia. Other successful catheter-based procedures have been reported in patients with hemophilia, though only 1 has involved catheter ablation of an arrhythmia.[15] In that case, a child with hemophilia A underwent successful ablation of atrioventricular nodal reentrant tachycardia with cryoablation. However, transseptal access was not required and no long-term anticoagulation was recommended.

Though our patient's baseline factor VIII level stratified him into a lower severity of disease, his particular bleeding risk was thought to be slightly higher in practice, as evidenced by his history of peripheral hemarthroses.

Moreover, his stroke risk was low, as estimated by a CHA$_2$DS$_2$-VASc of 0. Because this is a single case report, we cannot draw any conclusions as to the general safety of this approach, including for those patients with a more severe form of hemophilia or those with a higher CHA$_2$DS$_2$-VASc score.

Conclusion

AF catheter ablation involves both intraprocedural and postprocedural anticoagulation, limiting this as a therapeutic option for many patients with bleeding disorders such as hemophilia who have symptomatic AF. In patients with a low CHA$_2$DS$_2$-VASc score, an approach using a lower intensity of intraprocedural anticoagulation and avoidance of postprocedural anticoagulation may allow such patients to safely undergo AF catheter ablation.

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