Electrophysiological Procedures in Patients With Coagulation Disorders
— A Systemic Review —

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Catheter ablation (CA) is considered first-line treatment for many patients with symptomatic arrhythmias. Indications for CA are constantly increasing, as is the number of procedures. Although CA is nowadays regarded a safe procedure, there is a risk of complications, including both bleeding- and thrombosis-related events. Several factors contribute to periprocedural risk; of these, patient coagulation status is of considerable clinical relevance. In this context, even a simple procedure poses a considerable challenge in a patient with coagulation disorder. However, the level of evidence regarding CA in patients with coagulation disorders is very low. Neither experts’ recommendations nor clinical guidelines have been presented so far. The aim of this article is to analyze potential procedure-related risks and provide clinicians with useful information and practical suggestions regarding optimization of procedural safety in patients with coagulation disorders.

Key Words: Bleeding; Cardiac arrhythmia; Catheter ablation; Coagulation disorders; Thrombosis

In recent decades catheter ablation (CA) has become the treatment of first choice for many patients with symptomatic arrhythmias. Aligned with constant improvements in CA techniques, indications for the procedure are constantly expanding. Thus, a further increase in the number of CA procedures is inevitable. CA is regarded as safe procedure, with low complication and high success rates that are continually improving with increased experience and new technological developments. Despite progress in the CA technique, the risk of complications remains a part of everyday practice, with bleeding and thrombosis being the most clinically relevant complications. However, the ablation procedure is associated not only with a significant bleeding risk, related to either vascular access or cardiac perforation, but also thrombus formation caused by biophysical aspects of radiofrequency energy transmission, increased tissue temperature, local endothelial damage, and the presence of catheters in the heart and vessels.

The rate of adverse events depends strongly on physician experience, the technology used, and the type of the procedure. However, patient-related risk factors also contribute. In particular, diseases that increase the tendency for bleeding or thrombosis are particular challenges, and so specific steps should be undertaken in order to safely perform CA in such patients. Unfortunately, the level of evidence regarding CA in patients with coagulation disorders is very low. The aim of this review was to systematically analyze possible procedural risks and pitfalls depending on the underlying disease and provide clinical guidance based on the available literature. Because of the number of coagulation disorders and the lack of data regarding CA in specific disorders, we focused on the most common coagulation disorders, namely heparin-induced thrombocytopenia (HIT), hemophilia, heterozygous Factor V (FV) Leiden mutation, von Willebrand Disease (vWD), light chain amyloidosis, antiphospholipid syndrome, myelodysplastic syndrome, immune-mediated disorders and hereditary hemorrhagic telangiectasia.

Methods
This systematic review was conducted in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

A systematic search was performed of the PubMed database from inception to April 2019. The search strategy focused on identifying studies and case reports that described electrophysiological procedures in patients with coagulopathies. The reference lists of the included articles and other published reviews were also examined to identify...
any additional studies relevant to this review.

**Inclusion and Exclusion Criteria**
Studies were included if they described the procedures of CA or electrophysiological study (EPS) in patients with coagulation disorders a priori, or if coagulation disorder appeared as a complication after CA. Studies and case reports were excluded if: (1) they did not precisely describe the periprocedural events; (2) they presented partial data; and (3) the manuscript was not available for review in English or was only available in abstract form. The decision to exclude conference abstracts was based on the limitations in assessing the study quality of conference abstracts alone and difficulties in extracting the required depth of information from such abstracts.

**Study Selection**
Two reviewers (B.K., J.D.-S.) independently screened the titles and abstracts of all publications identified and excluded articles that were irrelevant to the topic. The reviewers then evaluated the full text of eligible articles for suitability based on the strict inclusion and exclusion criteria. A third reviewer (J.K.) was used to resolve discrepancies.

**Results and Discussion**
The data collected from 18 studies and case reports is summarized in Table. The sections below discuss specific coagulopathies in detail.

| HIT | Description | Conclusions |
|-----|-------------|-------------|
| Case report10 | Bivalirudin use during CA (VT, PVI) in 2 patients with HIT history; no complications observed | Bivalirudin is a therapeutic option for anticoagulation during CA in patients with HIT history |
| Case report11 | Bivalirudin use during cryoballoon ablation (PVI) in a patient with HIT history | Bivalirudin in conjunction with apixaban is an option during cryoballoon ablation in patients with HIT history |
| Case report12 | Bivalirudin use during CA (PVI) in a patient with HIT history; no complications observed | Bivalirudin is a therapeutic option for anticoagulation during CA in patients with HIT history |
| Case report13 | Bivalirudin use during CA (VT) in a patient with HIT history; no complications observed | Bivalirudin is safe in patients with HIT and renal failure during CA |
| Case report17 | HIT as a complication after CA procedure (SVT) | Patients undergoing CA are at risk of HIT |
| Case report18 | Atypical HIT presentation in a patient 5 months after short exposure to LMWH; thrombus attached to ablation catheter during CA (PVI) with subsequent HIT confirmation | Rare presentation of HIT can occur during CA |
| Case report19 | Ischemic stroke 36h after CA (PVI) due to HIT-related venous thrombosis and iatrogenic right-to-left shunt | Attention should be paid to DVT in patients undergoing CA in order to reduce stroke risk |

| Hemophilia | Description | Conclusions |
|-----------|-------------|-------------|
| Case report27 | 12-year-old male with mild hemophilia A underwent successful cryoablation because of AVNRT; no complications observed | Continuous recombinant Factor VIII infusion provides sufficient coagulation status to undergo CA |
| Case series28 | Summary of 18 cardiac surgeries and catherization procedures in patients with hemophilia; one patient underwent EPS | Patients with hemophilia can safely undergo cardiac procedures |
| Case report29 | Successful CA using cryoballoon catheter in a patient with mild to moderate hemophilia | Standard factor replacement protocol can be safely used in a patient scheduled for CA Lower-intensity intraprocedural anticoagulation and avoiding postprocedural anticoagulation may allow safely PVI |

(Table continued the next page.)
been treated with heparin in the previous 30–100 days and circulating antibodies remain in the body. Even though the exact mechanism underlying the development of HIT remains unclear, there are a few hypotheses, including the release of procoagulants from activated platelets, the generation of platelet microparticles, or endothelial cell activation.

**Periprocedural Preparations for Patients With a Known History of HIT** There are no guidelines or recommendations regarding anticoagulation in patients with HIT Type II during CA. However, in analogy to the recommendations for coronary intervention, bivalirudin can be successfully used for left sided CA procedures (Figure 1). This strategy has been confirmed by case reports of patients undergoing CA due to ventricular tachycardia and atrial fibrillation (AF) in patients with normal renal function, and in patients with renal dysfunction in whom the bivalirudin dose was adjusted. One procedure has been performed in a patient receiving apixaban. In all cases, drug administration was stopped at the end of the procedure and no adverse effects were registered.

Periprocedural therapy should begin with a 0.75-mg/kg, i.e., bolus of bivalirudin, which is followed by infusion at a rate of 1.75 mL·kg⁻¹·h⁻¹ that is stopped at the end of the procedure with no need to monitor coagulation status. It should be also noted that heparin in irrigation fluids used in irrigated tip catheters and sheaths needs to be switched to bivalirudin. Furthermore, it is of clinical importance that bivalirudin has no reversal agent and should be monitored by activated clotting time (ACT) or activated partial thromboplastin time (aPTT).

Another off-label protocol describes initiation of anticoagulation using an i.v. bolus of argatroban (350 μg/kg) administered over 3–5 min, followed by continuous i.v. infusion at 25 μg·kg⁻¹·min⁻¹ to achieve a therapeutic ACT of 300–450 s. The ACT should be checked 5–10 min after administration of the bolus dose, and the rate of infusion should be adjusted accordingly (10–40 μg·kg⁻¹·min⁻¹).

**HIT Secondary to CA** HIT manifesting during or directly after CA ablation may be a serious clinical problem needing careful evaluation. It is crucial to quickly distinguish between HIT Type I and HIT Type II. HIT Type I occurs due to septic complications related to the procedure, but the only patient with MDS died due to septic complications, revealed cardiac amyloidosis; no complications observed.

Patients with accompanying diseases require multidisciplinary approach to avoid dangerous complications.

No conclusions in terms of ablation in patients with MDS.

No conclusions in terms of ablation in patients with HHT.
heparin should be switched to a different anticoagulant (argatroban, fondaparinux, danaparoid bivalirudin, lepirudin) depending on the clinical situation, and further laboratory testing of anti-PF4/heparin antibodies is needed. It is also worth keeping in mind that there is a very high prevalence of heparin/PF4 antibodies in cardiac patients, but very few have of these patients have HIT; therefore, this test should not be performed in a patient without clinical symptoms of HIT.

In case of suspected HIT, clinical observations should be made, focusing on thromboembolic complications such as neurological symptoms, swollen limbs, and shortness of breath. Standard postprocedural echocardiography is advisable in every patient with a history of HIT to rule out adverse events such as PE or pericardial effusion. In case of the need for anticoagulation after the procedure, a switch from bivalirudin to an alternative anticoagulant is recommended. Argatroban is currently the only US Food and Drug Administration (FDA)-approved drug for HIT treatment, but current guidelines recommended the use of bivalirudin for surgeries and percutaneous coronary interventions (PCIs).

Recently, Vaidya et al reported a case of the formation of a fibrin strand resembling a thrombus attached to the ablation catheter despite a target ACT of 300 s and an international normalized ratio (INR) of 2.6. Although such early manifestation is unusual, the HIT diagnosis was confirmed by laboratory testing. Another postprocedural HIT Type II presentation has been described after AF ablation: 36 h after the procedure, symptomatic cerebral embolization originating from a DVT was diagnosed despite standard anticoagulation. Rice reported a case of documented complete thrombotic vein occlusion and subsequent PE occurring 2 weeks after CA due to supraventricular tachycardia (SVT). After determination of the platelet count and laboratory testing for specific antibodies, HIT Type II was diagnosed. A direct thrombin inhibitor was administrated as initial therapy with a subsequent change to warfarin.

It is of note that due to a decrease in protein C decline, vitamin K antagonists (VKAs) are not recommended at the beginning of the therapy and can only be introduced when the platelet count has recovered. Conversely, novel oral anticoagulants (NOACs) do not decrease protein C levels and are therefore potentially an alternative treatment option. It is also worth noting that argatroban affects the INR, which complicates the monitoring of the effect of warfarin after platelet count recovery. An overlap of 5 days between a non-heparin anticoagulant and a VKA is regarded as the minimum and safe period. It is also recommended that VKAs are initially administered at low doses. Because of its limited indications, argatroban is infrequently used by clinicians, and a lack of experience may result in inaccurate dose adjustment.

Hemophilia
Hemophilia is an X-linked congenital bleeding disorder that generally affects males. Although the gene mutation is usually inherited, approximately one-third of all cases are caused by spontaneous mutations.

Hemophilia A, which accounts for 80–85% of hemophilia, is caused by Factor VIII (FVIII) deficiency, whereas hemophilia B is caused by a decrease in Factor IX (FIX). Both types are the result of respective clotting factor gene mutations. The bleeding tendency in hemophilia is directly correlated with the level of blood clotting factor.

Coincidence With Arrhythmias
Data describing the specific prevalence of arrhythmias in patients with hemophilia is very limited. In the US, Humphries et al reported trend towards a lower occurrence of ventricular arrhythmias in patients with hemophilia A compared to control group (0% vs. 4.5%; P=0.071). However, there was no difference in AF prevalence between patients with hemophilia and control group (5.4% vs. 6.3%, respectively; P=1.0). In a European trial, overall AF prevalence in patients with hemophilia reached 0.84%. Similar to trends seen in the general population, the prevalence of AF increased with age (0.42% in patients aged 40–60 years, 3.4% in patients
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The principal rule of hemophilia treatment is to prevent and treat bleeding, which is achieved by the administration of specific blood clotting factor concentrate.

There are several steps that should be followed when preparing for CA in patients with hemophilia (Figure 2). However, the timing is of greatest importance. It is advisable to schedule CA early in the week and early in the day for optimal support from the laboratory and blood bank to maintain adequate clotting factor coverage during CA and healing.

If clotting factors are not available, fresh frozen plasma (FFP) is an alternative, even though it is not recommended as first-line treatment. A 1-mL aliquot of FFP contains 1 unit of factor activity; however, it is difficult to achieve FVIII levels higher than 30% and FIX levels greater than 25%. Heparin can be administered according to standard cardiology treatment protocols if the clotting factor level is >80% during and >30% 48 h after the procedure.

Antifibrinolotic agents are not recommended and there is only very limited data regarding emacizumab, which is a bispecific antibody bridging activated Factor IX and Factor X to restore the function of activated FVIII.

In addition, inhibitors to the blood clotting factors administered should be examined before the CA procedure to ensure that factor administration will provide the expected effect. In patients with inhibitor, especially with anamnestic levels of inhibitor above 5 Bethesda units/mL, the use of bypassing agents (activated prothrombin complex concentrates and activated recombinant FVII) is recommended. Assuming that CA can be delayed, 9- to 33-month immune tolerance induction therapy should be considered in order to enable standard factor infusion.

Moreover, femoral catheterization is preferred over neck venous access because of bleeding complications connected with fibrinolysis. Taking into consideration the better care and increased life expectancy of patients with hemophilia, the number of patients with hemophilia who will need to undergo CA is estimated to increase.

Special Interventional Aspects

Hermans et al recommended that patients with hemophilia should undergo any invasive procedure, including CA, in a comprehensive hemophilia treatment center, or at least in consultation with one.

Despite the growing prevalence of CA in patients with hemophilia, the level of evidence is too low to provide guidelines regarding CA in these patients. However, there are recommendations for coronary interventions in patients with hemophilia that may be used for CA to some extent: the postulated peak factor levels should be at least 80% at the time of the procedure and adequate correction with clotting factor concentrates is required until 48 h after the procedure. Nonetheless, high factor levels may result in the development of occlusive thrombi. Therefore some authors suggest a target peak level for early PCI of ≥30%, whereas for minor surgery the recommended desired level is 40–80%.

Because blood clotting inhibitors are present in 20–30% of patients with severe hemophilia A and are rarely observed in patients with hemophilia B, reliable monitoring of clotting factor levels and inhibitor testing is required. Inhibitor presence is suspected in case of prolonged aPTT, which is not fully corrected by adding pooled normal plasma to patients’ plasma. The Nijmegen modification of the FVIII inhibitor assay offers the highest available specificity and sensitivity, and its use is therefore recommended to find an inhibitor.

Preprocedural Preparations

Patients with hemophilia scheduled for CA require an individual, multispecialist approach in order to safely undergo the procedure. Moreover, anticoagulation therapy should be reconsidered with special attention focusing on the risk of bleeding complications. The principal rule of hemophilia treatment is to prevent and treat bleeding, which is achieved by the administration of specific blood clotting factor concentrate.

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with the latter.\textsuperscript{37}  

**Previously Published Reports** Although in every described case of CA in a patient with hemophilia a different replacement protocol has been used, all protocols had a common target of peak factor level \( \geq 80\% \).\textsuperscript{37-39} DeWitt et al reported a case of a patient undergoing CA because of atrioventricular nodal re-entry tachycardia.\textsuperscript{37} Hemostasis during the procedure was achieved using continuous recombinant FVIII infusion, which was later continued after the procedure with an FVIII dosage target to maintain \( >100\% \) FVIII activity after CA.\textsuperscript{37,40} During the CA, standard heparinization was performed.\textsuperscript{37}  

An alternative strategy has been presented by MacKinlay et al, who describe experience gained during 12 cardiovascular procedures, of which 1 was an electrophysiological study.\textsuperscript{38} In that heterogeneous case series, satisfactory factor level was achieved by bolus administration or continuous infusion, with a common factor target peak level of 100%. No bleeding complications were observed.\textsuperscript{38}  

However, patients undergoing AF ablation may require more aggressive heparinization. For example, Lin et al reported a case in which maintained ACT was targeted in the lower range, between 250 and 300s, to lower bleeding risk and FVIII was replaced by bolus infusion.\textsuperscript{39} No adverse events were observed.\textsuperscript{39}  

**Patient Care After the Procedure** Subsequent anticoagulation is a challenging issue in patients with hemophilia collectively, because bleeding is the most likely complication.\textsuperscript{41} Current recommendations are that warfarin anticoagulation therapy should be considered if the clotting factor level is \( >20\% \).\textsuperscript{42} There are no data regarding the use of NOACs in patients with hemophilia; nonetheless, it seems reasonable to reflect on lower NOAC doses and with an available reversal agent. In patients with factor level \(<20\% \) and high a CHA\(_2\):D\(_2\):VASC score, the use of low-dose aspirin has been suggested,\textsuperscript{42} even though aspirin is not recommended for stroke prevention in patients with AF and without hemophilia.\textsuperscript{41}  

**vWD**  
Among all inherited bleeding disorders, vWD is considered to be the most common; according to epidemiological studies, vWD affects approximately 1% of the general population, although far fewer patients present with bleeding tendencies or require treatment.\textsuperscript{43}  

Both a quantitative lack and a qualitative defect of vWF can be the underlying cause of the disease. In addition to being involved in primary adhesion, vWF carries and stabilizes FVIII in secondary hemostasis; therefore, FVIII deficiency can also be seen. The most common and least symptomatic vWD is Type I, which is characterized by quantitative deficiency of vWF and accounts for approximately 85% of vWD cases.\textsuperscript{44} Dysfunctional vWF is the reason for coagulation disability in Type 2 vWD. The most symptomatic, Type 3 vWD, accounts for \(<5\%\) of cases and is caused by the absence of circulating vWF.\textsuperscript{45}  

Diagnosis is based on a combination of personal bleeding history and laboratory testing, including, initially, determination of total vWF protein levels via vWF antigen, vWF activity via ristocetin cofactor (vWF:RCo), and FVIII coagulant activity (FVIII:C).\textsuperscript{46} For patients with Type 1 vWD, it is generally agreed that a diagnosis is made when vWF activity is \(<0.30\text{IU/mL}\) in a patient with mucocutaneous bleeding.\textsuperscript{47}  

Treatment varies according to vWD type. Desmopressin is recommended for all patients with Type 1 vWD, as well as for most patients with Type 2 vWD.\textsuperscript{48} Desmopressin can be used either intravenously, subcutaneously (the formulation is not universally licensed), or intranasally. The typical i.v. dose is 0.3 \( \mu \text{g/kg}\) dissolved in 50–100 mL of 0.9% NaCl and infused intravenously over 30–60 min.\textsuperscript{49} Because of the risk of tachyphylaxis, desmopressin should not be given for more than 3–5 days. Antifibrinolytic therapy (i.e., tranexamic acid or epsilon-aminocaproic acid) should be considered as adjunctive treatment.\textsuperscript{49}  

**Preprocedural Preparations and Special Interventional Aspects** Available data show decreased cardiovascular risk in patients with vWD,\textsuperscript{48} as well as a lower risk of developing both venous and arterial thrombosis.\textsuperscript{50} Therefore, only very few cases of patients undergoing PCI have been reported,\textsuperscript{51} and there are no recommendations or even case reports regarding electrophysiological procedures in patients with vWD. In this context, general recommendations for patients undergoing invasive procedures should be applied when approaching CA in patients with vWD. In the case of patients who do not respond to desmopressin therapy, concentrate containing vWF should be administered. It has been postulated that, when preparing patient for minor surgery, peak levels of FVIII:C and VWF:RCo are \( \geq 80\% \) and \( \geq 50\text{IU/dL} \).\textsuperscript{49} In addition, the estimated minimum level of FVIII:C and VWF:RCo should be \( >50\text{IU/dL} \) on the day of surgery and \( >30\text{IU/dL} \) for 3–5 days after the procedure. However, it is suggested that levels \( >250\text{IU/dL} \) are avoided.\textsuperscript{48} Considering intraprocedural pharmacotherapy, thromboprophylaxis is not given routinely to patients with vWD undergoing surgery; nevertheless, heparin should not be ruled out during left-sided procedures. Finally, patients with vWD should be precisely assessed and the risk:benefit ratio should be analyzed in terms of anticoagulation after the procedure.

**Heterozygous FV Leiden Mutation**  
Heterozygous FV Leiden mutation, named after the city of Leiden in the Netherlands where this syndrome was first described,\textsuperscript{52} is one of the most common congenital causes of increased thromboembolic risk. It is triggered by a single point mutation that results in the loss of 1 of 3 activated protein C (APC) cleavage sites, leading to a 10-fold slower rate response and resistance to APC. Due to the increased thrombin generation, a hypercoagulable state is present.\textsuperscript{53}  

**Clinical Implications** The most common manifestation of FV Leiden is DVT and PE, but thrombosis also occurs in unusual locations.\textsuperscript{48} Interestingly, increased mortality or reduction in normal life expectancy has not been observed.\textsuperscript{54} Although in many individuals the mutation is asymptomatic, 10% of heterozygotes will suffer venous thromboembolism (VTE) over their lifetime.\textsuperscript{55} Clinical expression of FV Leiden becomes much more relevant when it is combined with other inherited or acquired thromboembolic risk factors, such as hormone replacement therapy, hyperhomocysteinemia, minor injury, air travel, obesity, oral contraceptives, or malignancy.\textsuperscript{54} Because the incidence of DVT after AF ablation is reported to be 0.33%, compared with 2.38% in non-AF ablation,\textsuperscript{56} CA must be considered as one of the risk factors having supra-additive thromboembolic effect.

**Preprocedural Preparations and Special Interventional Aspects** Standard screening for FV Leiden is not recommended. Nonetheless, in the case that FV Leiden is known to be present or symptoms have occurred in the past, the
patient should be accurately assessed for other risk factors. Every additional risk factor for VTE tilts the scale towards i.v. heparin use, even in the case of right-sided ablations.

The European Heart Rhythm Association recommends the use of i.v. heparin during AF and atrial flutter ablation, as well as its consideration in other right-sided ablations. Taking into consideration the multiplied VTE risk in the presence of a combination of VTE risk and other risk factors, one can consider the use of heparin in all CA, with ACT target level >300s in AF ablation. Because of a lack of evidence, no specific recommendations regarding ACT can be made when considering right-sided procedures. Therefore, the decision regarding the anticoagulation scheme should be made based on team experience.

Previously Published Reports It is unknown whether patients with VTE risk are more likely to suffer from post-procedural complications. Recently, a single center study analyzing thrombotic complications after CA for supraventricular arrhythmias reported 1 case of massive pulmonary embolization related to FV Leiden among 7 patients with thrombotic complications from a total of 400 patients. Similarly, Pesut et al reported a case of a patient suffering from symptomatic pulmonary thromboembolism following atrioventricular node ablation. The only prothrombotic conditions established in that patient were FV Leiden and methylenetetrahydrofolate reductase (MTHFR) C677T mutations, both heterozygous.

In both cases, no heparin was administrated during right-sided ablation.

Review Limitations In this review we precisely describe the most popular coagulopathies, but also draw attention to available evidence. Despite our highest efforts in studying the literature, most of the articles cited regarding CA in coagulation disorders are case reports, which have low scientific power. To the best of our knowledge, no recommendation, case reports, or expert opinions have been published regarding the long list of rare coagulopathies.

Conclusions In conclusion, careful evaluation of coagulation status and individual risk, in close collaboration with a hematologist, is advisable. There is a large spectrum of possible modifications regarding periprocedural coagulation status, which makes most CA procedures feasible, even if associated with an increased risk of adverse events.

Acknowledgments / Conflicts of Interest

None.

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