

CASE REPORT

Bivalirudin Use During Radiofrequency Catheter Ablation Procedures in Two Patients with a History of Heparin-Induced Thrombocytopenia

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Current guidelines recommend using bivalirudin, a direct thrombin inhibitor, as a preferred alternative to unfractionated heparin in patients with heparin-induced thrombocytopenia (HIT) for percutaneous coronary intervention, as well as for cardiac and vascular surgery. Anticoagulation during radiofrequency catheter ablation (RFA) procedures may be another potential use for bivalirudin in the setting of HIT. Radiofrequency catheter ablation procedures involving left atrial or left ventricular access are increasingly employed as a method to treat cardiac arrhythmias. Because stroke risk is a serious complication of RFA, anticoagulation is required during this procedure. We describe the first report, to our knowledge, of successful use of bivalirudin anticoagulation during RFA procedures in two patients with a history of clinically diagnosed HIT that precluded the use of unfractionated heparin or low-molecular-weight heparin. One of the patients underwent RFA for ventricular tachycardia, the other for pulmonary vein isolation for the treatment of atrial fibrillation. In both patients, bivalirudin was administered as a 0.75-mg/kg intravenous bolus, followed by a 1.75-mg/kg/hour infusion. Activated clotting time (ACT) was measured after the initial bolus in each patient. However, no dosage adjustment was made based on the ACT, and the infusion rate of bivalirudin remained fixed during the procedures. Both procedures were completed without any embolic events. No bleeding or clotting events were noted; one patient experienced minor access site oozing that was not felt to be clinically important. Bivalirudin is a therapeutic option for anticoagulation during left-sided catheter RFA procedures in patients with a history of HIT.

Key Words: bivalirudin, heparin-induced thrombocytopenia, HIT, electrophysiology, ventricular ablation, atrial fibrillation, ventricular tachycardia, unfractionated heparin, argatroban, pulmonary vein isolation, PVI, radiofrequency ablation.

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Heparin-induced thrombocytopenia (HIT) is an immune-mediated (type 2) adverse reaction that may occur with exposure to unfractionated heparin (UFH) or, less commonly, low-molecular-weight heparin (LMWH).^{1,2} The reported frequency of HIT ranges from 0.1–5%. The risk of developing HIT depends on several factors including duration of heparin exposure, route of administration, history of heparin

exposure, and sex of the patient.^{2–8} Thromboembolic complications of HIT may present as deep vein thrombosis, pulmonary embolism, myocardial infarction, or stroke.^{1,2} Therefore, HIT requires both the discontinuation of heparin products as well as therapy with an alternative anticoagulant.^{1,3}

Bivalirudin, a direct thrombin inhibitor, is used in the presence of HIT for intraoperative

anti-coagulation during cardiopulmonary bypass or off-pump cardiac surgery, and during percutaneous coronary intervention (PCI).^{3,9} The drug has several features that make it a desirable option for anticoagulation during short-term procedures. It has a short half-life of 27 minutes in patients with normal renal function, 60 minutes in patients with renal insufficiency, and 3.5 hours in patients receiving dialysis. As a result, the duration of anticoagulation effect is short after discontinuation of bivalirudin. Its anticoagulation effects are directly proportional to the dose administered, which necessitates fewer dosage changes to achieve consistent anticoagulation compared with UFH.^{2,10} For its approved use in PCI, bivalirudin is administered as a bolus and a fixed infusion rate, without the need for coagulation monitoring.¹¹

Anticoagulation during radiofrequency catheter ablation (RFA) may be another potential use for bivalirudin in the setting of HIT. Radiofrequency catheter ablation procedures involving left atrial or left ventricular access are increasingly employed as a method to treat cardiac arrhythmias. This procedure utilizes several catheters to record and pace the heart, and an ablation catheter to deliver thermal energy directly to the myocardium to ablate the tissue causing the cardiac arrhythmia. Procedures requiring atrial transseptal puncture or retrograde aortic left ventricular access are becoming more commonplace. Embolic stroke is one of the most serious complications of these procedures. The thromboembolic risk after RFA for pulmonary vein isolation (PVI) for the treatment of atrial fibrillation is estimated to be 0–7%, and this risk remains elevated for 2 weeks after the procedure.^{12–14} The risk of thromboembolism after RFA for ventricular tachycardia varies based on the type of procedure. It is estimated to be 0–2.7% for the commonly employed endocardial RFA procedures.¹⁵

This increased stroke risk necessitates administration of systemic anticoagulation during the RFA procedure to prevent thrombi from forming

on the catheters or newly denuded endothelium, as well careful intra- and postprocedure monitoring for signs and symptoms of stroke.^{12,16,17} Anticoagulation with UFH is typically employed before, during, and in some cases, after the procedures.^{12,16} However, we found no published reports that utilized bivalirudin in RFA. We describe two patients with previously clinically diagnosed HIT who received bivalirudin during RFA procedures with successful outcomes.

Case Reports

Patient No. 1

A 64-year-old, 95-kg man was admitted to our hospital for elective RFA of recurrent ventricular tachycardia. His medical history included placement of a Contak Renewal model H170 biventricular implantable cardioverter-defibrillator (ICD) (Boston Scientific, Minneapolis, MN) for ventricular tachycardia 3 years earlier, coronary artery disease with coronary artery bypass graft surgery 22 years earlier, carotid endarterectomy, ischemic cardiomyopathy, paroxysmal atrial fibrillation, dyslipidemia, diabetes mellitus, and severe peripheral arterial disease. The patient's left ventricular ejection fraction was estimated at 15% by transthoracic echocardiography on the day of the procedure. His documented allergies and drug intolerances included amiodarone (hyperthyroidism), angiotensin-converting enzyme inhibitor (cough), and intravenous contrast dye (rash). In addition, the patient had a history of clinically diagnosed HIT.

Before this hospitalization, the patient underwent two previous RFA attempts, 1.5 years and 3 months earlier, at a local community hospital. During the hospitalization for the first RFA procedure, the patient developed thrombocytopenia after receiving UFH, which resolved after its discontinuation. The hematology-oncology service at the hospital documented a clinical course consistent with HIT, with the patient's baseline platelet count of $240 \times 10^3/\text{mm}^3$ (normal range $150\text{--}400 \times 10^3/\text{mm}^3$) decreasing to $110 \times 10^3/\text{mm}^3$. After treatment with argatroban, his platelet count stabilized at $151 \times 10^3/\text{mm}^3$ at discharge. Confirmatory blood tests were performed at the time of clinical suspicion of HIT. However, heparin-platelet factor 4 antibody and serotonin release assay were negative. Given the high clinical suspicion, an allergy was documented in the patient's medical

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record, and bivalirudin was administered (dose and duration not reported) in place of UFH during both previous RFA procedures.

On the day of this admission for elective RFA, as well as the day before admission, the patient noted multiple ICD shocks. He denied any precipitating chest pain, shortness of breath, orthopnea, lower extremity edema, palpitations, dizziness, or near-syncope. His cardiac drug therapy consisted of oral spironolactone 12.5 mg/day; valsartan 80 mg/day; furosemide 40 mg/day; aspirin 325 mg/day; digoxin 0.125 mg on Monday, Wednesday, and Friday; extended-release metoprolol 25 mg/day; and simvastatin 20 mg at bedtime; his procainamide 750 mg every 6 hours was discontinued 2 days before the RFA was scheduled. Additional antiarrhythmic agents taken in the past included amiodarone, sotalol, mexiletine, and quinidine.

On the morning of the RFA, the patient developed asymptomatic ventricular tachycardia at a rate ranging from 90–140 beats/minute (bpm). Two doses of oral prednisone 40 mg were administered the day before the procedure because of the patient's contrast dye allergy. Aspirin 325 mg was administered 5 hours before the RFA procedure. Baseline laboratory values included hemoglobin 14.2 g/dl (normal range 13.5–17.5 g/dl), hematocrit 42% (40–52%), platelet count $185 \times 10^3/\text{mm}^3$, activated partial thromboplastin time (aPTT) 25.2 seconds (21.0–33.5 sec), and serum creatinine concentration 1.4 mg/dl (0.6–1.2 mg/dl) (estimated creatinine clearance 71.6 ml/min). No heparin–platelet factor 4–dependent enzyme immunoassays or functional assays for HIT were performed.

Femoral, arterial, and venous access was obtained by the modified Seldinger technique. The patient received intravenous midazolam 2.5 mg and fentanyl 25 μg immediately before the procedure. Because of the patients' history of severe peripheral vascular disease, left ventricular access was obtained by using transseptal puncture. Intracardiac echocardiography (ACUNAV; Biosense Webster, Inc., Diamond Bar, CA) was used to guide the transseptal puncture and monitor for procedural complications.

Bivalirudin was initiated after a neurologic assessment. A bolus dose of 0.75 mg/kg was administered before obtaining left ventricular access, followed by an infusion of 1.75 mg/kg/hour. An activated clotting time (ACT) of 125 seconds was documented immediately before initiation of the infusion, which increased to 237 seconds 20 minutes later; however, no target range was

designated. A 3.5-mm tip THERMOCOOL irrigated RFA catheter (Biosense Webster, Inc.) was advanced through the septum and mitral valve to the left ventricle by using an Agilis NxT Steerable Introducer (St. Jude Medical, St. Paul, MN).

An activation map was acquired using an electroanatomic mapping system (CARTO RMT, Biosense Webster, Inc.). The ventricular tachycardia was mapped to the posterior lateral wall near the neck of a posterobasal calcified aneurysm, and successful RFA was performed. An electroanatomic voltage map was acquired in normal sinus rhythm. Programmed stimulation induced three additional poorly tolerated ventricular tachycardias that were ablated using a substrate-based approach. At the conclusion of the procedure, programmed electrical stimulation was performed from the right ventricular apex and lateral left ventricular wall without any inducible arrhythmias.

Bivalirudin was stopped at the end of the procedure; the total duration of administration was 3 hours. The absence of pericardial effusion was confirmed with intracardiac echocardiography. Midazolam and fentanyl were administered periodically, in small divided doses, as needed throughout the procedure (total doses were 5 mg and 225 μg , respectively). Intravenous arterial catheters were removed 6 hours after and venous catheters 6.5 hours after the procedure with no hematoma or oozing at groin sites. Extended-release metoprolol 25 mg was administered that evening, and the following drugs were restarted after the procedure: oral aspirin 325 mg/day, furosemide 40 mg/day, simvastatin 20 mg at bedtime, valsartan 40 mg/day (reduced from 80 mg/day), and spironolactone 12.5 mg/day, and subcutaneous insulin (NPH/regular 70/30).

On hospital day 3, the patient remained in normal sinus rhythm and was hemodynamically stable, with a blood pressure of 120/82 mm Hg and heart rate 70 bpm (100% biventricularly paced). Rare premature ventricular contractions were noted, with no ventricular tachycardia recurrence. No significant changes in laboratory values were noted (hemoglobin 12.2 g/dl, hematocrit 36%, platelet count $139 \times 10^3/\text{mm}^3$, and serum creatinine concentration 1.5 mg/dl). The patient was ambulating without difficulty, and his drug therapy was continued. Bilateral groin sites had minimal ecchymosis with no hematoma or bruits. A noninvasive programmed stimulation was unable to induce ventricular tachycardia using singles, doubles, and triple

extrastimuli. The patient was discharged after defibrillator threshold testing was performed. No changes were made in his discharge drug therapy except for the addition of extended-release metoprolol 50 mg/day.

The patient was examined at our institution 6 months after his RFA procedure. The ICD interrogation revealed rare episodes of ventricular tachycardia, which were terminated with antitachycardia pacing. However, no shocks were received during these 6 months.

Patient No. 2

A 49-year-old, 115-kg man was admitted to our hospital for a transesophageal echocardiography (TEE) and PVI for the treatment of atrial fibrillation. The patient had a medical history of persistent atrial fibrillation, chronic obstructive pulmonary disease, and bilateral deep vein thrombosis and pulmonary embolism treated with UFH at a local hospital 1 year before this admission. During treatment of the venous thromboemboli, he was clinically diagnosed as having HIT, and a Greenfield inferior vena cava filter was placed. Allergies and drug intolerances documented in the medical record were heparin (rash and HIT), intravenous contrast dye (rash), and pantoprazole (rash). His drug therapy before this admission consisted of oral controlled-release diltiazem 180 mg/day, extended-release metoprolol 50 mg/day, digoxin 0.125 mg/day, and warfarin, albuterol, formoterol, and tiotropium (doses not specified).

On hospital day 1, the patient was in persistent atrial fibrillation with a ventricular rate of approximately 120 bpm. Baseline laboratory values included hemoglobin 14.6 g/dl, hematocrit 43%, platelet count $304 \times 10^3/\text{mm}^3$, aPTT 28 seconds, INR 1.7, and serum creatinine concentration 1.3 mg/dl (estimated creatinine clearance of 111.8 ml/min). A TEE was performed, revealing no evidence of left atrial appendage thrombi. Warfarin 4 mg was given the evening before and argatroban 2 $\mu\text{g}/\text{kg}/\text{minute}$ started 13 hours before the procedure. An aPTT 2 hours after infusion initiation was 58 seconds, followed by 56.4 seconds 2 hours later. The argatroban infusion dose was increased 8 hours later to 2.5 $\mu\text{g}/\text{kg}/\text{minute}$ to achieve a goal aPTT of 60–100 seconds. No heparin–platelet factor 4–dependent enzyme immunoassays or functional assays for HIT were performed.

On hospital day 2, the patient was taken to the electrophysiology laboratory. The argatroban

infusion was discontinued 4 hours before the procedure. The patient remained in atrial fibrillation with ventricular rates ranging from 90–110 bpm. Femoral, arterial, and venous access was obtained by the modified Seldinger technique. The patient was given intravenous midazolam 1 mg and fentanyl 50 μg . A bolus dose of bivalirudin 0.75 mg/kg was administered, followed by an infusion at 1.75 mg/kg/hour; no ACT was recorded before bivalirudin administration. An ACT of 379 seconds was documented 40 minutes after the start of the infusion (no target range was designated). Catheters were advanced to the coronary sinus and high right atrium under fluoroscopic guidance. Two transseptal punctures were performed. A 3.5-mm tip THERMOCOOL irrigated RFA catheter was inserted into the left atrium, along with a circular mapping catheter (Lasso; Biosense Webster, Inc.).

After stimulation with intravenous isoproterenol to document left atrial triggers for atrial fibrillation, circumferential isolation of all four pulmonary veins was performed. An ACT of 394 seconds was noted 1.5 hours after the infusion began. Bivalirudin was administered from the start to the end of the procedure, for a total of 5.5 hours. Venous sheaths were removed 4 hours after the conclusion of the procedure, and manual pressure was applied for 15 minutes. Recurrent bleeding after sheath removal required reapplication of pressure for 30 minutes. No hematoma or bleeding was noted after the additional pressure. Minimal oozing occurred at the site, and a pressure dressing was applied. Argatroban 2.5 $\mu\text{g}/\text{kg}/\text{minute}$ was started 6 hours after sheath removal. Three hours after the start of the infusion, an aPTT was 55.3 seconds (goal aPTT 60–100 sec). The argatroban infusion was then increased to 3 $\mu\text{g}/\text{kg}/\text{minute}$ and continued for 3 hours. An aPTT at that time was 75.3 seconds. Drug therapy started after the procedure consisted of oral flecainide 100 mg every 12 hours and metoprolol 50 mg every 12 hours; one dose of oxycodone 5 mg–acetaminophen 325 mg was given. Warfarin 10 mg was also given the evening before the procedure.

Aspirin 325 mg was given the morning after the procedure; flecainide and metoprolol were continued. Follow-up laboratory values included hemoglobin 12.6 g/dl, hematocrit 36%, platelet count $253 \times 10^3/\text{mm}^3$, and serum creatinine concentration 1.2 mg/dl. The patient's INR was elevated at 4.8 (normal range 0.8–1.2) because of the argatroban infusion, and the aPTT was 76.6

seconds. A repeat INR of 3 was noted 1 hour after argatroban was discontinued. The patient began to ambulate without difficulty.

On hospital day 3, the patient was hemodynamically stable, with a heart rate of 60–70 bpm, normal sinus rhythm, and blood pressure 112/63 mm Hg. The patient was discharged from the hospital; his drug therapy consisted of flecainide and metoprolol (dosages unchanged), along with aspirin 325 mg/day and warfarin 7.5 mg every evening.

The patient was seen for follow-up at our institution 6 months after his PVI procedure. His drug therapy remained unchanged. His transtelephonic monitor demonstrated normal sinus rhythm with an episode of atrial fibrillation that occurred 28 days after the PVI procedure, with no associated symptoms.

Discussion

We report the first cases, to our knowledge, of successful use of bivalirudin during RFA for ventricular tachycardia and for PVI of atrial fibrillation in the setting of previously clinically diagnosed HIT. Systemic anticoagulation is required before, during, and after these procedures to minimize thromboembolic risk. The type of anticoagulation before and after the procedure varies based on the underlying arrhythmia and presence of ischemic stroke risk factors.¹⁸ Typical anticoagulation would consist of short-term UFH or LMWH while transitioning from and to a long-term oral vitamin K antagonist, typically warfarin.^{12, 13, 18, 19} However, patients with a history of HIT require alternative anticoagulation during the RFA procedure and during subsequent transition back to warfarin anticoagulation. Bivalirudin offers the advantage of predictable anticoagulation with a short duration of action after cessation of the infusion¹¹ which makes it a desirable alternative to heparin for use in procedures necessitating anticoagulation in patients with a history of HIT.

Bivalirudin has been used in other invasive cardiac procedures including both PCI as well as cardiopulmonary bypass.^{3, 20–29} The product has a labeled indication for PCI in the setting of HIT.¹¹ In PCI studies, patients receiving bivalirudin had a lower frequency of bleeding compared with those receiving UFH or LMWH.^{30–33} Additional case reports describe successful anticoagulation with bivalirudin in patients with confirmed or suspected HIT for cardiac transplantation and valve repair.^{31–33} Although argatroban is also

indicated in PCI for patients with HIT and has been used during cardiopulmonary bypass in cases of HIT, reports are more limited in terms of the number of patients studied.^{34–38} We chose to administer the same dose of bivalirudin as that approved for PCI (bolus 0.75 mg/kg, infusion rate 1.75 mg/kg/hr). Although an ACT was measured, no dosage adjustment was made based on the ACT, and no target ACT was set for the patient before the RFA procedure. We did not delay the procedures by performing HIT antibody testing. Although this practice has been recommended in patients undergoing cardiopulmonary bypass surgery, with subsequent UFH administration in patients who are antibody negative,³ we did not feel this would be practical in our patient population. Results of antibody tests are not known immediately, which would thus delay the procedures. In addition, repeat RFA procedures are often necessary for both atrial and ventricular arrhythmias, which would require repeated short-term exposure to heparin (unlike cardiopulmonary bypass surgery), making the development HIT more likely.

Use of bivalirudin for RFA procedures is not without some risk. Potential complications of RFA procedures with the use of UFH include groin bleeding, retroperitoneal bleeding, or cardiac perforation and tamponade. When such bleeding events occur while a patient is receiving UFH, the infusion is stopped, and protamine is administered to reverse the effects of UFH. However, there is no reversal agent for bivalirudin, and therefore such events could lead to life-threatening complications. Therefore, the use of bivalirudin during RFA procedures at our institution is reserved for patients with a history of HIT. Although access site oozing was reported in one patient, this was felt to be no different than that observed in a typical patient who had received UFH for a RFA ablation procedure.

Conclusion

As a direct thrombin inhibitor with a short half-life, bivalirudin offers a similar or more rapid offset of anticoagulation compared with UFH while maintaining consistent anticoagulation, making it a desirable option during procedures necessitating anticoagulation in patients with a history of HIT. We successfully used bivalirudin (bolus 0.75 mg/kg, infusion rate 1.75 mg/kg/hr) anticoagulation in two patients with HIT who underwent RFA procedures. Although the ACT was measured, no dosage adjustment was made

based on the ACT; thus the dose of bivalirudin remained fixed during the procedures. Both procedures were completed without embolic events. One patient experienced minor access site oozing that was not felt to be clinically important. Bivalirudin is a therapeutic option for anticoagulation during left-sided catheter RFA procedures in patients with a history of HIT.

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