Successful use of bivalirudin in place of heparin infusion for pulmonary vein isolation using a cryoballoon catheter in a patient with heparin allergy

Ethan R. Ellis, MD

From the University of Colorado Health, Fort Collins, Colorado.

Introduction
Current guidelines recommend using bivalirudin as an alternative to unfractionated heparin in patients with heparin-induced thrombocytopenia undergoing percutaneous coronary intervention (PCI).1 Pulmonary vein isolation (PVI) is a well-established treatment strategy for patients with drug-refractory atrial fibrillation (AF) and requires systemic anticoagulation to avoid thromboembolic events, generally achieved with intravenous unfractionated heparin. There are several reports in the literature of bivalirudin use in place of unfractionated heparin during PVI with radiofrequency (RF) energy in patients with heparin-induced thrombocytopenia.2,3 To our knowledge, this is the first report of the safe use of bivalirudin for PVI using a cryoballoon catheter.

Case report
A 77-year-old woman presented with recurrent episodes of highly symptomatic paroxysmal AF despite therapy with flecainide 100 mg twice daily (BID) and diltiazem controlled release 120 mg daily. In addition to her AF, she had a history of hypertension, obstructive sleep apnea, multiple sclerosis, and remote breast cancer status post mastectomy and chemotherapy. She had a port placed for her chemotherapy and while receiving heparin flushes through her port, she developed anaphylaxis and was given a diagnosis of severe heparin allergy. After reviewing her treatment options, she elected to proceed with PVI. She was on apixaban 5 mg BID for thromboembolic prophylaxis for her AF. She ultimately underwent successful PVI using a cryoballoon catheter and intravenous bivalirudin infusion in place of unfractionated heparin.

The patient was continued on her oral apixaban therapy in the month leading up to her ablation. She held her apixaban dose the morning of her procedure. The patient was given a 325-mg dose of oral aspirin therapy prior to the start of her procedure based on the recommendation that bivalirudin be used in conjunction with aspirin 300–325 mg daily, as bivalirudin has only been studied in patients on concomitant aspirin therapy. After bilateral femoral vein access was obtained, intravenous bivalirudin was administered as a 0.75-mg/kg bolus followed by a continuous infusion at 1.75 mg/kg/h. The activated clotting time (ACT) was confirmed to be greater than 300 seconds before proceeding with transseptal puncture. A 28-mm cryoballoon was used to isolate her 4 pulmonary veins. Two 180-second freezes were delivered to each pulmonary vein. Pulmonary vein occlusion was assessed using pressure monitoring and color Doppler on intracardiac echocardiography. No contrast was utilized during the procedure. Detailed 3-dimensional mapping using the St Jude Medical Ensite NavX system was performed at the start of the procedure and after PVI (Figure 1). Bivalirudin infusion was discontinued after catheters and sheaths were removed from the left atrium. The left atrial dwell time for the procedure was 58 minutes. Intracardiac echocardiography was utilized throughout the procedure and there was no evidence of intracardiac thrombus formation during the case or pericardial effusion at case end. ACT was repeated 45 minutes after bivalirudin discontinuation to ensure an ACT < 200 seconds before sheaths were removed. Hemostasis was obtained with manual compression. No bleeding or thrombotic events were noted intraprocedurally or postoperatively. The patient received a dose of apixaban 5 mg 6 hours after hemostasis and was continued on her regular BID dosing thereafter. She was seen in follow-up 1 month postprocedure without recurrent atrial fibrillation, bleeding events, or thromboembolic symptoms.

Discussion
Bivalirudin is a direct thrombin inhibitor that is frequently used in place of the indirect thrombin inhibitor heparin during
interventional coronary procedures.\cite{4,5,6,7} It is the preferred alternative to unfractionated heparin in patients with heparin-induced thrombocytopenia for percutaneous coronary intervention.\cite{1} PVI is a well-established treatment strategy for patients with drug-refractory atrial fibrillation and requires systemic anticoagulation to avoid thromboembolic events. Anticoagulation is generally achieved with intravenous unfractionated heparin with ACT monitoring. Bivalirudin’s use in the electrophysiology laboratory at the time of ablation procedures is limited. RF energy has been the most widely used source of ablation for achieving PVI. Bivalirudin has been shown to be a safe alternative to heparin for RF PVI.\cite{2,3} PVI using a cryoballoon catheter has become an increasingly popular alternative to radiofrequency ablation and has been shown to be noninferior to RF ablation.\cite{9} To our knowledge, this is the first published report of bivalirudin use in patients undergoing PVI with a cryoballoon catheter.

Bivalirudin reversibly inhibits thrombin with a rapid onset of action and a short plasma half-life. Intravenous administration produces an immediate anticoagulant effect. The half-life of bivalirudin is approximately 25 minutes and prolonged coagulation times return to normal approximately 1 hour after discontinuation. Bivalirudin inhibits circulating and clot-bound thrombin while also inhibiting thrombin-mediated platelet activation and aggregation. Because it does not bind to plasma proteins (with the exception of thrombin), it has a more predictable antithrombotic response than heparin.\cite{10} Given this, dosing of bivalirudin is weight based and does not require adjustment based on ACT results, although ACTs are generally checked to confirm administration of the medication. The dosing strategies utilized in the studies evaluating bivalirudin use in PCI were standardized doses without dose adjustment based on ACTs assessed.\cite{4,5,6,7} Current Food and Drug Administration approval for bivalirudin use in PCI suggests that bivalirudin be administered with a 0.75-mg/kg bolus followed by a continuous infusion at 1.75 mg/kg/h. Patients with renal failure do not require a change in the bolus dose, as bivalirudin is only partially excreted by the kidneys, with hepatic metabolism and proteolysis at other sites also contributing to its metabolism. A lower infusion rate may be used for patients with a CrCl < 30 mL/min (ie, 1 mg/kg per hour).\cite{10} It is recommended that an ACT be performed 5 minutes after the 0.75 mg/kg bolus dose and a 0.3 mg/kg additional bolus dose be administered if needed. However, there is no guidance regarding what value of ACT warrants an additional bolus. Limitations of ACT monitoring of bivalirudin therapy have been demonstrated previously, where the correlation between bivalirudin plasma concentration and activity were not accurately reflected by the ACT value.\cite{11} A study of PCI patients treated with bivalirudin studied whether bleeding complications were more common in bivalirudin hyperresponders (ACT > 800 seconds) and thrombotic complications were more common in bivalirudin hyporesponders (ACT < 300 seconds). ACT responses greater than 800 seconds were not found to increase the risk of clinically significant bleeding. One of 20 patients classified as a hyporesponder had a thrombotic complication, suggesting that ACT responses less than 300 seconds may be associated with increased thrombotic risk.\cite{12}

In the current case, ACT values were measured to ensure administration of the drug prior to proceeding with transseptal puncture. As the initial ACT was > 300 seconds, no additional bivalirudin bolus was administered. No adjustments were made to the infusion rate despite some ACTs > 400 seconds. Bellmann et al\cite{2} reported high ACT values during RF PVI (ACT range 463–607 seconds) on bivalirudin. They did not adjust infusion rate based on ACT value and did not report any procedural complications. Baetz et al\cite{3} only reported 2 ACT values obtained during RF PVI, 379 and 394 seconds. They also did not adjust infusion rates based on ACT values and reported no significant hemorrhagic or thrombotic complications.

**Table 1** Activated clotting time and bivalirudin infusion rate during pulmonary vein isolation.

| Time (min) | Activated clotting time (s) | Bivalirudin infusion rate |
|-----------|----------------------------|--------------------------|
| 0         | n/a                        | 0.75 mg/kg bolus         |
| 10        | 331                        | 1.75 mg/kg/h             |
| 25        | 389                        | 1.75 mg/kg/h             |
| 40        | 405                        | 1.75 mg/kg/h             |
| 55        | 399                        | 1.75 mg/kg/h             |
| 100       | 189                        | 0                        |

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Conclusions
This case report demonstrates that bivalirudin can be safely used as an alternative to intravenous heparin to perform PVI with a cryoballoon catheter in patients with heparin allergy. Our case also demonstrates that bivalirudin can be used safely in conjunction with oral apixaban therapy in patients undergoing PVI. In our case, ACT values were measured to confirm administration of bivalirudin but no adjustments were made to the infusion rate based on results. This is in keeping with interventional cardiology practice for PCI as well as previously reported bivalirudin use in RF PVI.\textsuperscript{2,3}

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