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Bivalirudin for Cardiopulmonary Bypass in the Setting of Heparin-Induced Thrombocytopenia and Combined Heart and Kidney Transplantation—Diagnostic and Therapeutic Challenges

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SINCE THE PUBLICATION of the first case reports, heparin-induced thrombocytopenia (HIT) has persisted as a serious management dilemma for cardiothoracic anesthesiologists.[1–3] Nonimmune-mediated and immune-mediated forms of HIT, type I and II, respectively, both have been described in the literature.[3–6] Of these 2 HIT phenotypes, the devastating and life-threatening thrombotic complications, such as limb ischemia, pulmonary embolism, stroke, and myocardial infarction, are almost associated exclusively with type-II HIT disease.[6–9] The immunologic mechanism for type-II HIT involves immunoglobulin G (IgG) antibodies against platelet factor 4 (PF4), resulting in decreased platelet counts and a hypercoagulable state.[2,3,9,10] Although there is a strong focus in the HIT literature on this immune-mediated disease, suspected type-I disease also can result in significant management challenges in the setting of severe thrombocytopenia.

Further complicating the care of these patients are the diagnostic obstacles with respect to accurate diagnosis.[1–3,11] The lack of an ideal alternative anticoagulant, particularly in the setting of renal failure, only adds to the complexities in caring for these patients during cardiac surgery requiring cardiopulmonary bypass (CPB).[2,3,11–14] These complexities typically can be avoided by delaying elective surgery until resolution of the offending immunologic response in HIT.[3,13] There are circumstances, on the other hand, in which surgical delay is not always a management option, such as in cardiac transplantation.[13,14] Patients requiring urgent cardiac surgery with CPB in the setting of renal failure and HIT may pose major management challenges, despite the current anticoagulation strategies.[13–15] This case conference discusses a challenging case of a patient with suspected HIT and renal failure undergoing combined cardiac and renal transplantation. The abundant perioperative hurdles in this setting are highlighted.

CASE REPORT*

A 49-year-old woman presented for orthotopic heart and heterotopic kidney transplantation. Her medical history was significant for end-stage cardiomyopathy, chronic kidney disease, diabetes mellitus, hypothyroidism, obstructive sleep apnea, and gout. The cardiomyopathy likely was secondary to suspected viral myocarditis 12 years earlier. Her functional status subsequently had steadily deteriorated despite maximal medical therapy, including digoxin, diuretics, and milrinone.

Four months before transplantation, the patient presented with acute-on-chronic heart failure that resulted in further management and evaluation for transplantation as an inpatient. A transthoracic echocardiogram revealed a left ventricular ejection fraction of 10% and severe right ventricular dysfunction. Right-heart catheterization demonstrated a right atrial pressure of 20 mmHg and moderate-to-severe pulmonary hypertension. Shortly after hospital admission for this heart failure exacerbation, she developed acute-on-chronic kidney injury that required hemodialysis.

Furthermore, during this hospital admission, she also developed persistent atrial fibrillation that was managed with rate control and heparinization for thromboembolic prophylaxis. Within the first week of heparin therapy, her platelet count declined from 153,000 mm^3 to 64,000 mm^3, representing an acute decrease greater than 50%. Clinical suspicion for the diagnosis of HIT triggered consultation with hematology to

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advise about further management. Testing for PF4 antibodies with an enzyme-linked immunosorbent assay (ELISA) was positive, with an optical density of 0.96.[3,13,16] Due to this suggestive screening result, HIT was strongly suspected. Heparin therapy was stopped, and further anticoagulation was achieved with the direct thrombin inhibitor argatroban, titrated to effect. There was no clinical evidence of thrombosis. In the interim, further specific testing with the serotonin release assay (SRA) was performed and indicated a lack of platelet activation due to the detected PF4 antibodies.[3,13,16] After further consultation with hematology, heparin therapy was restarted. With the initiation of heparin therapy, the platelet count again decreased acutely over 3 days by more than 50%, from 50,000 mm^3 to 18,000 mm^3. Even though there still was no evidence of clinical thrombosis, the hematologists recommended that heparin therapy be avoided at this point due to probable severe and sustained type-I HIT. Argatroban therapy subsequently was titrated to achieve clinical anticoagulation with no adverse effects.

In the interim, the multidisciplinary transplant evaluation was completed. The patient was listed for heart and kidney transplantation. After extensive deliberation among the surgical, anesthesiology, and hematology teams, the selected anticoagulation strategy for CPB was the direct thrombin inhibitor bivalirudin. The rationale for this choice was that heparin should be avoided due to concerns about clinically significant HIT, most likely type I. At the time of suitable donor availability, the patient still had PF4 antibodies detected with careful ELISA testing. The patient thus presented for heart and kidney transplantation with bivalirudin as the planned anticoagulant for CPB.

The argatroban infusion was stopped 4 hours before presentation to the operating room. The induction of general anesthesia and placement of invasive monitoring both proceeded in an uncomplicated fashion. The baseline activated clotting time (ACT) was elevated at 194 seconds, most likely due to residual effects of argatroban. After sternotomy, the surgical team requested full anticoagulation in preparation for CPB. Anticoagulation administration was based on the institutional protocol for bivalirudin anticoagulation during CPB that was adapted from the landmark clinical trials (Table 1).[7,17,18] Bivalirudin was given as a 1.5 mg/kg (150 mg total) intravenous bolus, followed by an infusion at 2.5 mg/kg/hour. The initial ACT after the first bolus of bivalirudin was 288 seconds. After an additional bivalirudin bolus of 0.5 μg/kg (50 mg total), the repeat ACT was 594 seconds (Fig 1). Based on this elevated ACT, the anticoagulation level was deemed adequate for CPB.

After achieving an adequate ACT, CPB was initiated with an additional 50 mg of bivalirudin added to the pump prime. Cardiac transplantation proceeded during hypothermic CPB without complication. During the CPB period, the ACT peaked at 634 seconds, and the bivalirudin infusion at that time was reduced to 1.5 mg/kg/hour (Fig 1). As the final anastomoses were completed, therapy with bivalirudin was terminated per the institutional protocol in preparation to separate the patient from CPB (Table 1). As weaning from CPB ensued, the perfusion team noted thrombus formation in the CPB reservoir, despite an ACT >600 seconds. The patient was separated promptly and successfully from CPB.

Despite adherence to the institutional bivalirudin protocol for CPB, significant bleeding continued after successful separation from CPB. Despite massive transfusion, the coagulopathy persisted. In an effort to achieve hemostasis, recombinant factor VII at low dose was given (2 mg total, representing 20 μg/kg). The ongoing coagulopathy prevented chest closure. At this juncture, the transfusion totals were as follows: 26 U of packed red blood cells, 21 U of fresh frozen plasma, 30 U of cryoprecipitate, and 40 U of platelets. Although the ACT gradually declined over the next 4 hours, it nevertheless persisted above 200 seconds (Fig 1). Given the persistent and severe coagulopathy, intraoperative hemodialysis was initiated after urgent consultation with the nephrology service. After approximately 2 hours of hemodialysis, the augmented clearance of bivalirudin resulted in gradual clinical resolution, as evidenced by an ACT <200 seconds, visible hemostasis, and ultimate closure of the chest.

Secondary to massive transfusion and significant vasopressor support, renal transplantation was deferred and the patient was admitted to the intensive care unit. Within several hours after admission, significant mediastinal bleeding developed that prompted chest exploration and resumption of hemodialysis. The day after stabilization, the patient underwent successful chest closure and renal transplantation. The patient had a prolonged stay in the intensive care unit with eventual

Table 1. University of Miami Protocol for Bivalirudin Therapy to Achieve Anticoagulation for Cardiopulmonary Bypass in Patients With Suspected or Known Heparin-Induced Thrombocytopenia

Recommendations for Bivalirudin	
Recommendation for Perfusion Team	Recommendation for Anesthesiology Team
Priming dose of bivalirudin 50 mg in CPB circuit	Bivalirudin, 1-1.5 mg/kg, as an intravenous bolus
Avoid ultrafiltration-hemoconcentration during CPB because it increases elimination of bivalirudin	After bolus, bivalirudin, 2.5 mg/kg/hour, as an intravenous infusion
Consider ultrafiltration after CPB because it may facilitate bivalirudin elimination	Check ACT 5 minutes after the bolus dose of bivalirudin
Avoid stasis in CPB circuit; suggested strategies include intermittent compression of venous reservoir, processing of excess blood in circuit using cell-saver, and minimizing use of cardiotomy suction	Monitor ACT for a target of 2.5-fold increase in ACT from baseline value
Use nonheparin cell-saver anticoagulation, such as sodium citrate	If ACT falls short of target value, consider additional bivalirudin (0.1-0.5 mg/kg) as an intravenous bolus
	Discontinue bivalirudin infusion 15 minutes before termination of CPB

Abbreviations: ACT, activated clotting time; CPB, cardiopulmonary bypass.