

Reversal of Direct Thrombin Inhibition After Cardiopulmonary Bypass in a Patient with Heparin-Induced Thrombocytopenia

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We treated persistent hemorrhage after cardiopulmonary bypass in a heart transplant recipient who had received anticoagulation with the direct thrombin inhibitor bivalirudin by a combination therapy aimed at reducing the plasma concentration of the thrombin antagonist (hemodialysis and modified ultrafiltration), increasing the concentration of thrombin at

bleeding sites (recombinant factor VIIa), and increasing the plasma concentration of other coagulation factors (fresh frozen plasma and cryoprecipitate). The bleeding was controlled, and there was no thrombotic complication.

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When heparin-induced thrombocytopenia type II (HIT) is present, there is a high risk of development of limb- and life-threatening thromboses. All forms of heparin, including heparin flushes and heparin-coated IV catheters, should be discontinued, and an alternative anticoagulant should be used (1-4). Anticoagulation for cardiopulmonary bypass (CPB) can be achieved with direct thrombin inhibitors (DTI) such as hirudin or bivalirudin (2) but, unlike with heparin, there is no single reversal drug for DTI, which poses a risk for serious bleeding after CPB (4,5). A combined approach that included modified ultrafiltration (MUF) and hemodialysis, as well as the administration of recombinant factor VIIa (rFVIIa), fresh frozen plasma (FFP), and cryoprecipitate, controlled DTI-induced post-CPB hemorrhage in a cardiac transplant recipient with HIT.

Case Report

A 27-yr-old man with idiopathic, dilated cardiomyopathy and chronic congestive heart failure presented for cardiac

transplantation after a 4-wk period of hospitalization for acute deterioration of cardiac function. He received warfarin to prevent thromboembolic complications of atrial fibrillation and severely reduced left ventricular function. Gastrointestinal bleeding and persistent anemia prompted discontinuation of warfarin therapy. Heparin was started 3 wk before transplantation, and this caused HIT after 9 days. Lepirudin was substituted for heparin 11 days before transplantation at $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; this resulted in partial thromboplastin times (PTT) of 59 to 63 s. On the morning of transplantation, the patient was clinically stable on dobutamine ($8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and furosemide (10 mg/h) infusions. The platelet count had recovered from a nadir of 108,000/mL to 234,000/mL. The patient had not received a blood transfusion, the hematocrit (HCT) was 34%, and the lepirudin infusion had been stopped 21 h before surgery. The PTT at that time was 63 s.

After the induction of general anesthesia, the baseline kaolin-activated clotting time (ACT) was 143 s (Fig. 1); 2×10^6 kallikrein-inhibitory units of aprotinin were infused over 30 min followed by 5×10^5 kallikrein-inhibitory units per hour over 6 h.

After midline sternotomy, before aortic and right atrial cannulation and initiation of CPB, the recommendation of the hematologists at our institution was followed, and an initial loading dose of bivalirudin (1.5 mg/kg) was administered IV, followed by a continuous infusion of $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and an additional 5.0 mg/kg on initiation of CPB. In the absence of an ecarin clotting time (ECT), an ACT of 502 s was considered adequate for the initiation of CPB. The bivalirudin infusion was continued throughout the 104-min CPB period at $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Just before separation from CPB, a clot was noted in the CPB oxygenator. At this time, the bivalirudin dose was

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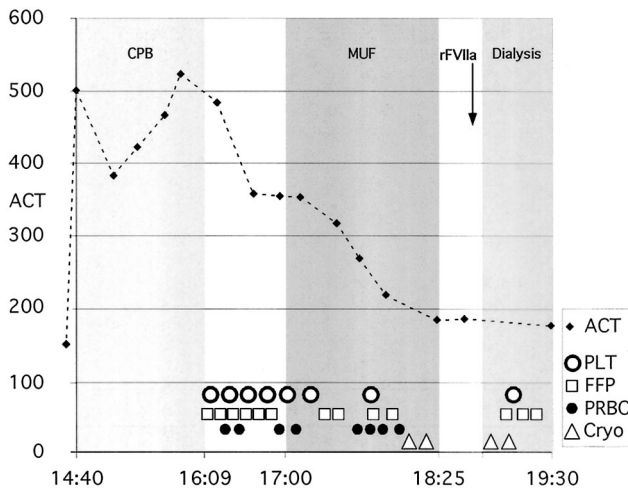


Figure 1. Transfusion events and activated clotting time relative to different stages of the procedure. The second dose of rFVIIa is not shown. ACT = activated clotting time; CPB = cardiopulmonary bypass; Cryo = cryoprecipitate; FFP = fresh frozen plasma; MUF = modified ultrafiltration; PLT = platelet concentrate; PRBC = packed red blood cells; rFVIIa = recombinant factor VIIa (90 $\mu\text{g}/\text{kg}$).

not increased because discontinuation of CPB was imminent. Separation from CPB proceeded uneventfully, and the initial Hct was 28%, the platelet count was 78,000/ mm^3 , the prothrombin time (PT) was 21 s, and the PTT was 68 s. Before chest closure, the return to the autotransfusion (cell saver) reservoir was 75 mL/min, and 4 U of packed red blood cells (PRBC), 6 U of FFP, and 5 U of platelet concentrate (30 U of platelets) had been given (Fig. 1). No visible clot was observed in the field. To facilitate removal of bivalirudin from plasma, MUF was performed for 90 min by using a Quentin dialysis catheter placed in the patient's left femoral vein. A total of 1800 mL of ultrafiltrate was collected. The patient's HCT decreased to 22%, and the bleeding continued at >1.5 L/h despite the additional transfusion of 4 U of PRBC, 4 U of FFP, 12 U of platelets, and 20 U of cryoprecipitate. Chest closure was not possible because of refractory hemorrhage with no identifiable surgical site of bleeding and an ACT of 182 s (Fig. 1).

In an additional attempt to achieve hemostasis, rFVIIa was administered at 90 $\mu\text{g}/\text{kg}$ IV. Several minutes after the administration of this medication, a clot was visualized in the surgical field, allowing chest closure to commence. Ten minutes after the administration of rFVIIa, the PT had decreased from 18 to 11 s. The administration of cryoprecipitate, FFP, and platelets continued in an attempt to provide activatable platelet and coagulation factors. Hemodialysis was instituted instead of MUF in a continued effort to remove bivalirudin without removing rFVIIa. The MUF filter (Hemacor HPH1000; Minntech) has a pore size that restricts passage of molecules larger than 65,000 D, whereas the dialysis filter (F70NR; Fresenius, Bad Homburg, Germany) has a pore size limitation of 11,800 D. We theorized that the latter would be less likely to remove rFVIIa, which has a molecular weight of approximately 50,000 D (6).

On the patient's arrival in the intensive care unit, roughly 2.5 h after the initial dose of rFVIIa had been administered, the chest tubes expressed approximately 200 mL of blood over 20 min. A second dose of rFVIIa (90 $\mu\text{g}/\text{kg}$) was therefore administered at this time, which resulted in near cessation of

Table 1. Options for Anticoagulation of Patients Undergoing Cardiopulmonary Bypass with a History of Heparin-Induced Thrombocytopenia (1-4)

Direct thrombin antagonism (bivalirudin, Argatroban, or hirudin)
 If elective, wait >3 mo, then heparin when both SRA and ELISA are negative
 Heparin plus antiplatelet agents (e.g., Pgl-2 or tirofiban) if SRA and ELISA are negative
 Heparin after plasmapheresis and negative SRA and ELISA

Heparin remains an option for cardiac surgical patients under special circumstances because alternative anticoagulants augment the bleeding tendencies after cardiopulmonary bypass. Of the alternative anticoagulants available, those with a short duration of action seem most appropriate (Table 2).

ELISA = enzyme-linked immunosorbent assay; Pgl-2 = prostacyclin; SRA = serotonin release assay.

chest tube output. Hemostasis was adequate, and the patient was discharged on hospital Day 12 after a rapid and uneventful recovery without clinical evidence of thrombotic complications.

Discussion

In this report we describe a patient with HIT who underwent cardiac transplantation with bivalirudin anticoagulation. This treatment was complicated by life-threatening nonsurgical bleeding that was successfully managed by facilitating elimination of bivalirudin with hemofiltration and hemodialysis along with the use of rFVIIa and blood products.

A similar case in which neither rFVIIa nor MUF nor dialysis was used involved a patient with HIT who underwent cardiac transplantation after anticoagulation with the DTI danaparoid. He required three inconclusive reexplorations for bleeding and experienced brain death (2).

Table 1 lists the options for anticoagulation of patients with a history of HIT. In patients with recent (less than three months) HIT, a DTI is probably the safest option (3). Bivalirudin, like other DTIs, has been used successfully for anticoagulation in patients with HIT and is being prospectively evaluated for this indication (7). The theoretical advantages of bivalirudin over other DTIs are a short plasma half-life (Table 2) and its slow conversion to a competitive DTI after administration (7), the mechanism of which is discussed below. Nevertheless, the risk of bleeding remains high. It is conceivable that not only bivalirudin, but also residual lepirudin, contributed to the absence of hemostasis after CPB in this patient (8).

Because no single antidote to DTI is clinically available, we used a triple therapeutic approach to control bleeding. It consisted of 1) MUF and hemodialysis, 2) the administration of rFVIIa, and 3) the administration of FFP and cryoprecipitate. The theoretical basis for this strategy is as follows.

Table 2. Comparison of Heparin and Direct Thrombin Inhibitors Used in Cardiac Surgery (1,8,11,28,30-36)

Variable	Bivalirudin	Lepirudin	Argatroban	Heparin
Molecular weight (D)	2,180	6,979	526	3,000-35,000 (8)
Route of elimination	Renal/proteolysis	Renal	Hepatic	Unclear (37)
Elimination half-life ($t_{1/2}$) (min)	10-24	50-120	39-51 (34)	56-152 (37)
$t_{1/2}$ when GFR is >90 mL/min (min)	25		39-51	56-152
$t_{1/2}$ when GFR is 60-89 mL/min (min)	22		39-51	
$t_{1/2}$ when GFR is 30-59 mL/min (min)	34		39-51	98 (38)
$t_{1/2}$ when GFR is 10-29 mL/min	57 min	15-41 h	39-51 min	
$t_{1/2}$ when GFR is <10 mL/min	210 min	27-316 h	39-51 min	118 min (38)
Dose (normal renal function)	1.0-1.5 mg/kg f/b 2.5-5.0 mg · kg ⁻¹ · h ⁻¹ (28)	0.1-0.4 mg/kg 0.2 mg/kg in prime- 0.15 mg · kg · h ⁻¹ (33)	0.15-0.35 mg/kg 0.05 mg/kg in prime f/b 0.3-2.4 mg · kg · h ⁻¹ (34-36)	300-400 IU/kg
Dose (impaired renal function)	5.0 mg/kg in prime Decrease infusion by 20%- 90% depending on GFR (7)	0.05-0.1 mg/kg (32)	0.35 mg/kg f/b 0.9-2.4 mg · kg · h ⁻¹ (34,35)	300-400 IU/kg
Elimination by dialysis	25%	No @ [0.2 µg/mL] Yes @ [30-50 µg/ml] (11)	No (39)	
Elimination by hemofiltration	43%-65%	15%-42% (11)	Unclear	Unclear
Elimination by plasmapheresis	69%	63%-65% (11)	Unclear	Unclear
Binding site/mechanism of action	Exosite 1, active site	Exosite 1, active site	Active site	Exosite 2, antithrombin, heparin cofactor 2
Inhibition of clot-bound thrombin	Yes	Yes	Yes	No
Reversal drug	None	None	None	Protamine, heparinase
Monitoring	ECT	ECT	ACT	ACT, Hepcon®
Target plasma concentration	2-20 µg/mL (8)	3.5-5 µg/mL (11)	0.5 µg/mL (35)	2.5 IU/mL (37)
Cost for 2-h CPB	\$1280	\$121	\$627	\$5-\$10 (28)

ACT = activated clotting time; CPB = cardiopulmonary bypass; ECT = ecarin clotting time; f/b = followed by; GFR = glomerular filtration rate; @ [] = at plasma concentrations of.

MUF eliminates 45%-69% of bivalirudin, depending on the filter type (9), whereas hemodialysis decreases the plasma concentration of bivalirudin by only 25% (7,10). Hemodialysis with a high-flux polysulfone filter eliminates lepirudin as effectively as MUF (11) and, importantly, retains native FVIIa (12-14). It seems reasonable to speculate that the dialysis membrane (with a pore size 11.9 kD, versus 65 kD of the MUF membrane) would also retain rFVIIa and that, therefore, a switch to hemodialysis after the administration of rFVIIa is prudent. This expensive hemostatic drug (approximately \$1/µg) promotes hemostasis locally at sites of tissue injury without causing systemic coagulation, which is explained by the absence of enzymatic activity of rFVIIa unless it is bound to either tissue factor (TF) (15) or activated platelets (16), both of which are usually present only at sites of tissue injury. For a review of the pharmacology of rFVIIa, the reader is referred to the work of Hedner and Erhardtson (15). Although rFVIIa is licensed only for use in hemophiliacs with antibodies to factor VIII or IX, it has been used to treat bleeding after prostatic, liver transplant, orthopedic, and cardiac surgery. During cardiac surgery, doses of 30-107 µg/kg have been reported (Table 3); hence, our dose of 90 µg/kg × 2 must be considered aggressive. Since this early experience with rFVIIa, we have been using doses of 30-50 µg/kg × 1 successfully in a variety of cardiac surgical cases.

Even though, after CPB, TF and activated platelets are present systemically (17), raising theoretical concerns of

systemic thrombosis after rFVIIa administration (18), the concentration of TF pathway inhibitor (TFPI) is also increased during and after CPB (19), mainly because of its release from endothelial cells in response to heparin. TFPI antagonizes systemic TF/FVIIa complex (20) and protects rabbits from TF-induced disseminated intravascular coagulation (21). The plasma concentration of TFPI after CPB following use of a DTI has not been compared with that after anticoagulation with heparin and reversal with protamine.

When two hemostatic drugs such as aprotinin and rFVIIa are used concomitantly, thrombotic complications are a concern (18). However, we are not aware of any case in which coadministration of an antifibrinolytic drug and rFVIIa after CPB caused a thrombotic complication (15,22-25). With one exception, all patients who received rFVIIa at our institution ($n = 22$) were also treated with aprotinin, and no clinically evident thrombosis has resulted. Aprotinin increases TFPI by preventing its cleavage by plasmin (26). We hypothesize that aprotinin confers a margin of safety from thrombotic complications via preservation of TFPI after post-CPB administration of rFVIIa.

The ECT, which was not available to us during this case, more accurately detects inadequate anticoagulation for CPB than the ACT (27). In a prior investigation, the ECT returned to baseline as the anticoagulant effect of bivalirudin diminished while the ACT remained increased (27). This is consistent with our observation of a clot in the oxygenator toward the end of CPB despite reassuring ACT values. We recommend monitoring the

Table 3. Published Experience with Recombinant Factor VIIa (rFVIIa) after Cardiopulmonary Bypass

Study	No. Patients	Type of surgery	Dose ($\mu\text{g}/\text{kg}$)	Complications	Antifibrinolytic
Al Douri (22)	5 (1 child; 4 adults)	Switch, ASD, MVR, TVR	30×1	None	Aprotinin
Hendriks (24)	1 adult	MVR + TVR	90×1	None	Aprotinin
Von Heyman (40)	1 adult	Repeat CABG	50×2 (2-h interval)	None	Aprotinin
Tobias (41)	1 infant	ASD	70×1	None	?
Naik (42)	1 adult	AVR, ARR	107×1	None	Tranexamic acid
Tanaka (43)	2 adults	MVR	45×1 ; 60×1	None	Aprotinin
Stratmann (25)	1 adult	ARR, AVR	90×2 (2-h interval)	None	Aprotinin

All cases of rFVIIa therapy in cardiac surgery have resulted in successful hemostasis with no clinically evident complications. There are two further published cases of rFVIIa therapy in patients undergoing cardiac surgery. Although the outcome was also good, those cases were not included in the table because either not enough information was available (15) or rFVIIa was not started until 7 days after surgery (23). Furthermore, both patients were hemophiliacs, whereas none of the patients listed above had a preexisting hemorrhagic diathesis.

ARR = aortic root replacement; ASD = atrial septal defect; AVR = aortic valve replacement; MVR = mitral valve repair/replacement; TVR = tricuspid valve repair/replacement; CABG = coronary artery bypass graft.

ECT to ensure adequate anticoagulation with bivalirudin during CPB.

Bivalirudin binds to both the active site and the substrate recognition site of thrombin in a noncompetitive manner. The former bond is slowly cleaved by thrombin itself, leaving a smaller molecule bound to the fibrinogen-binding site but with lower affinity than intact bivalirudin (28,29). This molecule is now subject to competitive displacement (28), which serves as a basis to administer fibrinogen in the form of FFP and cryoprecipitate. Furthermore, the administration of FFP and cryoprecipitate seems appropriate, because replacement of lost red blood cells likely caused factor dilution. Small concentrations of factor VIII and IX reduce the magnitude of the thrombin burst for a given dose of rFVIIa (16).

In conclusion, reversal of the effect of bivalirudin may be possible with a combination of MUF, dialysis, and the administration of rFVIIa, FFP, and cryoprecipitate. Prospective studies are necessary to verify the efficacy and safety of this approach and to determine the optimal doses of its individual components.

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