

# Recombinant Factor VIIa for Life-Threatening Bleeding in High-Risk Cardiac Surgery Despite Full-Dose Aprotinin

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We report the case of an orthotopic heart transplant in a patient with multiple previous cardiac surgeries. The case was prolonged and complicated by severe coagulopathy and bleeding despite the use of full-dose aprotinin throughout. Bleeding was not controlled after 30 U of platelets, 20 U of fresh frozen plasma, and 10 U of cryoprecipitate. However, after the administration of recombinant factor VIIa 90  $\mu\text{g}/\text{kg}$ , the rate of bleeding slowed dramatically and no further factor replacement was required. There was no evidence of unwanted clot

formation within the newly transplanted heart or around the intraaortic balloon pump that remained *in situ* for 72 h postoperatively. With the combined risks of coagulopathy and bleeding as well as acute right ventricular failure with increases in pulmonary vascular resistance, the re-do sternotomy for heart transplant seems to be an ideal situation in which to consider the use of recombinant factor VIIa.

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**B**leeding during postcardiac surgery remains a significant problem with a surgical reexploration rate of 2%–6% (1,2). A variety of mechanisms interact to create this coagulopathy, including platelet consumption, platelet dysfunction, dilution and consumption of clotting factors, hypothermia, activation of the inflammatory cascade, and fibrinolysis (3). Many of the factors that predispose to excessive bleeding after cardiac surgery have been identified (1,2), and directed therapy with drugs such as aprotinin and [epsilon]-aminocaproic acid has been used to reduce bleeding and reexploration rates (4).

Recombinant coagulation factor VIIa (rFVIIa) is a new, synthetic hemostatic drug. Currently it has approval only for the management of hemophilia A or B in the presence of inhibitors (5). However, there have been some reports of the effective use of rFVIIa in the management of severe bleeding in trauma (6), cardiac surgery (7), and major orthopedic surgery (8,9). Concerns remain that the systemic administration of rFVIIa may predispose to prothrombotic complications (10). We present a case of severe, life-threatening

bleeding in a cardiac transplant recipient despite full-dose aprotinin, in which rFVIIa seems to have been successful in controlling the bleeding.

## Case Report

A 26-yr-old man (80 kg) with a history of congenital hypoplastic left ventricle, mitral atresia, and double inlet right ventricle presented to our institution for an orthotopic heart transplant. He had previously undergone 4 cardiac surgical procedures, including pulmonary artery banding, modified Fontan procedure, and the subsequent formation of an extracardiac Fontan circulation. At the time of presentation, he had deteriorated and required home IV infusion of dobutamine. Other history was remarkable for warfarin anticoagulation in view of his severe ventricular dysfunction, and a protein-losing enteropathy. Before surgery, his international normalized ratio was 2.4 (prothrombin time 27.1 s) and serum albumin 16 g/L. His remaining coagulation profile and biochemistry data were within normal limits (Table 1). He was given vitamin K, 2 mg IV, an hour before surgery. In view of his increased risk of coagulopathy and bleeding, full-dose aprotinin ( $2 \times 10^6$  U load,  $2 \times 10^6$  U in the cardiopulmonary bypass [CPB] pump prime, 500,000 U/h infusion) was commenced at the beginning and continued for the duration of the case. Heparin 300 U/kg was administered to achieve an activated clotting time  $>480$  s. The initial bypass period was prolonged (6.5 h) and a second bypass run of an hour was also required to control surgical bleeding at the aortic anastomosis. The patient was weaned from CPB with intraaortic balloon pump support *in situ*. After the administration of protamine 300 mg, to achieve an activated clotting time of 128 s, a coagulopathy remained (see Table 1). In addition to 1200 mL of pump blood (hematocrit, 25%–30%) and 3000 mL of cell-saved blood (hematocrit, 50%–55%), 20 U of fresh frozen plasma, 30 U of platelets, 10 U of

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**Table 1.** Laboratory Coagulation Profile

	Baseline	After CPB	After 10 U platelets, 5 U FFP, 10 U cryoprecipitate	After 30 U platelets, 20 U FFP, 10 U cryoprecipitate	90 min post-rFVIIa
Hb (g/L)	132	91	69	50	106
PT (s)	27.1	35.7	25.4	20.7	12.6
INR	2.4	3.5	2.2	1.7	0.9
APTT (s)	38.1	54.1	74.6	65.1	62.3
Fibrinogen (g/L)	6.5	1.6	2.6	2.5	3
Platelets (10 <sup>9</sup> /L)	320	84	83	153	183

Hb = hemoglobin, PT = prothrombin time, INR = international normalized ratio, APTT = activated partial thromboplastin time, CPB = cardiopulmonary bypass, FFP = fresh frozen plasma.

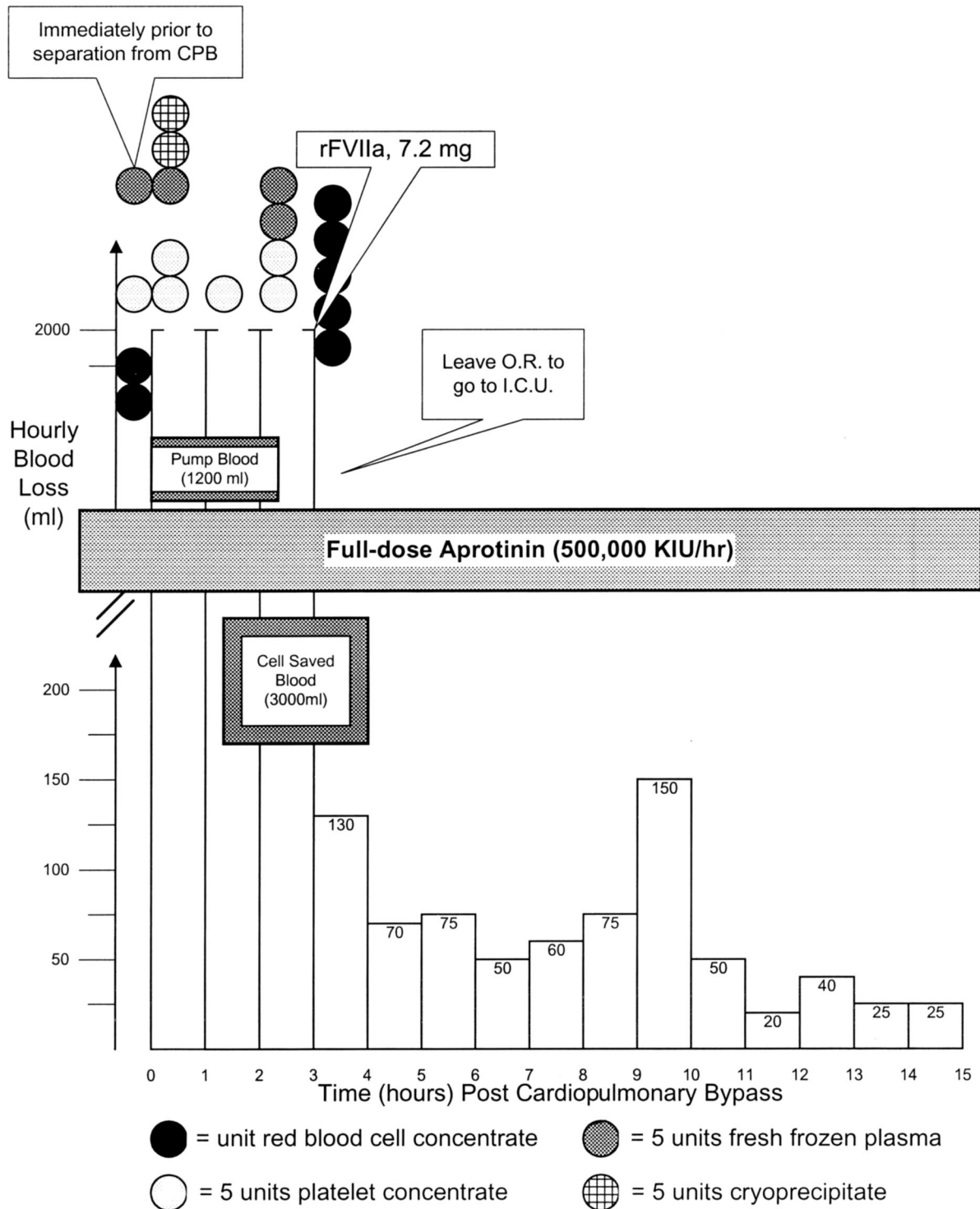
cryoprecipitate, and 7 U of packed cells were administered over the subsequent 3 h. Despite the massive transfusion, the patient remained normothermic. During the same period of time, measured blood loss was in excess of 2000 mL/h and diffuse and generalized microvascular bleeding continued at this rate despite laboratory variables of coagulation approaching normal. Without other options, the surgeons elected to close the chest with the expectation that the patient would require surgical reexploration later in the day. At the same time, in consultation with the hematology department, we administered rFVIIa, 90 µg/kg, and continued to transfuse packed cells. The patient was transported to the intensive care unit where his bleeding slowed to, and remained, <100 mL/h (see Fig. 1). Three additional units of packed cells were transfused but no other blood product was required; surgical reexploration was not necessary. He was tracheally extubated 2 days later and progressed well to discharge from hospital on day 16.

## Discussion

This patient had multiple risk factors for severe bleeding after CPB. He had had multiple previous cardiac surgeries and he underwent a very prolonged period of bypass. Previous studies indicate that preoperative anticoagulation with warfarin is not a predictor of postoperative bleeding (11) and it was thought unlikely that his protein-losing enteropathy contributed significantly, given his borderline increased activated partial thromboplastin time before surgery that was consistent with therapeutic warfarin use.

Given the predicted high risk nature of the case, he was commenced on full-dose aprotinin, which was continued throughout the procedure. Previous published reports of the use of rFVIIa in cardiac surgery have either not used an antifibrinolytic (12) or used it only as a rescue drug, by which time the fibrinolytic process may already have been in progress (7). However, despite conventional full-dose aprotinin to both prevent fibrinolysis and lessen platelet activation and consumption and the aggressive attempts to correct the coagulopathy with blood products, our patient continued to bleed. In fact, with the combination of large-volume conventional factor administration and our attempts to avoid fluid overload, we inadvertently allowed his hemoglobin level to decrease to 5 g/dL, which may itself have contributed

to the continuing coagulation disturbance. Although plasma levels of aprotinin have been shown to decrease during the first 2 hours of bypass because of a combination of metabolism and redistribution, levels have not been measured beyond this, where any continuing effect of redistribution may be reduced (13,14). A number of other trials, including a large meta-analysis, have shown the fixed-dose aprotinin regimen to be effective in reducing blood loss, transfusion requirements, and reexploration rates in complex cardiac surgery (4). We did not have access to a thromboelastograph<sup>®</sup>, which may have been able to further characterize a specific and treatable coagulation defect. In discussion with the hematology unit, we administered the rFVIIa as rescue therapy and saw a dramatic reduction in bleeding. The prolonged activated partial thromboplastin time measurement after the administration of rFVIIa is in keeping with the well documented effect of aprotinin on this measurement and does not represent a true coagulation disturbance (15). The mode of action of rFVIIa involves its interaction with tissue factor with subsequent activation of factor IX and X, in particular factor X bound to platelets or other phospholipid surfaces, with the consequent generation of thrombin. Tissue factor is exposed locally at the site of vessel wall injury, which may explain the localized prothrombotic effect of rFVIIa. There may also be a direct effect to promote platelet function, which is independent of tissue factor. The combined effect of activated platelets and activated factor IX and X provides a thrombin burst that is essential for the formation of a stable fibrin hemostatic plug. The reason(s) this may be effective in the setting of CPB-induced coagulopathy, when conventional factor replacement has failed, is not entirely clear. It may be that the rFVIIa stimulation of thrombin production via direct activation of factor X is able to activate the recently transfused platelets (16,17), whose normal function suffers in the storage process. The combination of direct and indirect effects on platelets may also overcome the effects of demargination seen with severe anemia. The minimal volume of this treatment compared with large volumes of conventional factor replacement is certainly advantageous in the setting of poor right ventricular performance and the potentially adverse effects



**Figure 1.** Hourly blood loss after separation from cardiopulmonary bypass (CPB). Red cell and conventional factor replacement are depicted. Bleeding slowed dramatically after the administration of recombinant factor VIIa (rFVIIa). O.R. = operating room, I.C.U. = intensive care unit.

of fresh frozen plasma and platelet transfusions on pulmonary vascular resistance. Re-do sternotomy for cardiac transplant may be a very strong indication to con-

sider rFVIIa in the postbypass period when there is a known risk of acute right ventricular dysfunction and marked coagulopathy.

However, at the cost of almost AUD\$1000/mg, rFVIIa is a very expensive therapeutic option. Concerns also remain that in the setting of consumptive coagulopathy, the further activation of the coagulation cascade with rFVIIa may produce prothrombotic complications. In fact, the generalized release of tissue factor into the circulation by activated monocytes after bypass may potentially increase the risk of widespread thrombus formation. A review of published cases of rFVIIa use (16) describes successful use of the product in at least 30 cases in which there was clinical concern about the possibility of a consumptive coagulopathy. There is, however, at least one case report of a patient with acquired hemophilia, treated with rFVIIa in the perioperative period, who developed significant clot around a femoral venous catheter and suffered a fatal pulmonary embolus (16). Our surgeons used a technique that attempted to produce a fully endothelialized atrial anastomosis. Continued transesophageal echocardiography monitoring in the operating room demonstrated no evidence of clot formation within the atria. Our patient also had an intraaortic balloon pump *in situ* from the cessation of CPB and for the next 3 days without evidence of unwanted clot formation. Unpublished data (G. Jankelowitz, Medical Advisor, Novo Nordisk, personal communication, 2003) indicate that thrombotic complications have been observed up to 48 hours after the administration of rFVIIa.

In summary, we present the case of severe, life-threatening bleeding after CPB in a heart transplant recipient managed with full-dose aprotinin, refractory to conventional measures, that seems to have resolved with the administration of a single dose of rFVIIa (90  $\mu\text{g}/\text{kg}$ ) and without any evidence of prothrombotic complications, despite the presence of an intraaortic balloon pump in the immediate postoperative period. With the growing body of case report literature on the successful use of rFVIIa, resternotomy for cardiac transplantation may be an appropriate setting to prospectively evaluate the drug.

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