

# Recombinant Factor VIIa for Refractory Bleeding Following Orthotopic Heart Transplantation

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**OBJECTIVE:** To report a case of successful use of recombinant factor VIIa (rFVIIa) for the treatment of refractory bleeding in a patient undergoing orthotopic heart transplantation.

**CASE SUMMARY:** A 57-year-old white male with idiopathic cardiomyopathy was taken to the operating room for explantation of his left-ventricular assist device and orthotopic heart transplantation. He experienced excessive generalized oozing that required transfusions of multiple units of blood products and significant amounts of Cellsaver (washed red blood cells via autotransfusion) without achieving adequate hemostasis. After ruling out any obvious surgical sources of bleeding and attempting to correct all coagulation deficiencies, the clinicians administered rFVIIa 90 µg/kg. The oozing rapidly declined to a negligible level, chest tubes and sternal wires were placed, and the chest was closed. The patient was on minimal inotropic support and was transferred to the intensive care unit in stable condition.

**DISCUSSION:** Cardiac surgery is often associated with significant disruption of the coagulation system, particularly in high-risk patients, such as those undergoing removal of a ventricular assist device and subsequent orthotopic heart transplantation. This can lead to life-threatening bleeding that can require multiple hemostatic agents and significant transfusions to restore hemostasis. Recently, rFVIIa has been utilized as an alternative to massive transfusion for treatment of refractory bleeding in several patient populations, including some cardiac surgery patients.

**CONCLUSIONS:** rFVIIa appears to be a viable option as rescue therapy for treatment of refractory bleeding following orthotopic heart transplantation. Despite the anecdotal success of rFVIIa in this setting, further clinical research is needed.

**KEY WORDS:** bleeding, factor VIIa, heart transplantation, ventricular assist device.

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The reported incidence of clinically significant postoperative bleeding and coagulopathies following cardiac surgery ranges between 4% and 32% and leads to increased morbidity and mortality.<sup>1,2</sup> Various physiologic factors contribute to excessive bleeding in this patient population, much of which is often attributed to the effects of the cardiopulmonary bypass (CPB) machine.<sup>3</sup> CPB can result in severe platelet dysfunction, thrombocytopenia, and deficiencies in coagulation factors. This is further complicated by the need for anticoagulation with full-dose heparin to prevent clotting in the CPB circuit and oxygenator. Bleeding during surgery can typically be controlled via the ad-

ministration of hemostatic agents, antifibrinolytics, and various blood products. Postoperative surgical bleeding is also problematic, as large amounts of chest tube drainage (>200 mL/h) following primary closure can necessitate surgical reexploration, which also leads to a significant increase in morbidity and mortality. Certain subsets of patients, including those undergoing a reoperation or heart transplantation, are at high risk of experiencing significant surgical bleeding that is difficult to control with conventional interventions.

A possible alternative to massive transfusions for the control of refractory and life-threatening bleeding following cardiac surgery is the coordinated use of recombinant factor VIIa (rFVIIa). Although there is considerable experience utilizing this agent for bleeding in patients with

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hemophilia, there is little information concerning the safety and efficacy of rFVIIa in patients undergoing cardiac surgery. Recently, there has been increasing use in several other populations with severe bleeding refractory to standard treatments including liver transplantation, intracranial hemorrhage, trauma, and surgery.<sup>3-5</sup> To date, there is minimal experience limited to case reports/series with the use of this agent in cardiac surgical patients, and there have been no reports in heart transplant recipients.<sup>1,2,6-10</sup>

We describe the use of rFVIIa in a patient undergoing explantation of a left-ventricular assist device (LVAD) and subsequent orthotopic heart transplantation. The patient experienced life-threatening bleeding that failed to respond to conventional therapy and massive blood product transfusions, and rFVIIa was administered successfully as a salvage therapy.

### Case Report

A 57-year-old white man with a history of idiopathic cardiomyopathy and New York Heart Association class IV heart failure requiring continuous inotropic therapy was admitted to our institution in cardiogenic shock. He continued to deteriorate over the next several days, and the decision was made to place an LVAD. The patient did well postoperatively and was able to be weaned from all inotropic support. His hospital course was complicated with methicillin-resistant *Staphylococcus aureus* bacteremia and subsequent seeding of the LVAD and driveline. The patient's transplant status was elevated to 1A after failure to clear the infection with antibiotics, although he remained hemodynamically stable. A suitable organ became available, and the patient was taken to the operating room for explantation of the LVAD and orthotopic heart transplantation.

The patient's heart was extremely large, with a dilated left ventricle and atrium. A cross clamp was applied to the ascending aorta and the heart was removed. The atrial cuffs were then prepared and the remnants of the left and right atria were approximated to the donor's atria. After assurance that all anastomoses were completed, the cross clamp was removed and there was return of spontaneous function of the implanted heart. The patient received high-dose aprotinin via protocol throughout the procedure, and the heparin activity was fully reversed with protamine

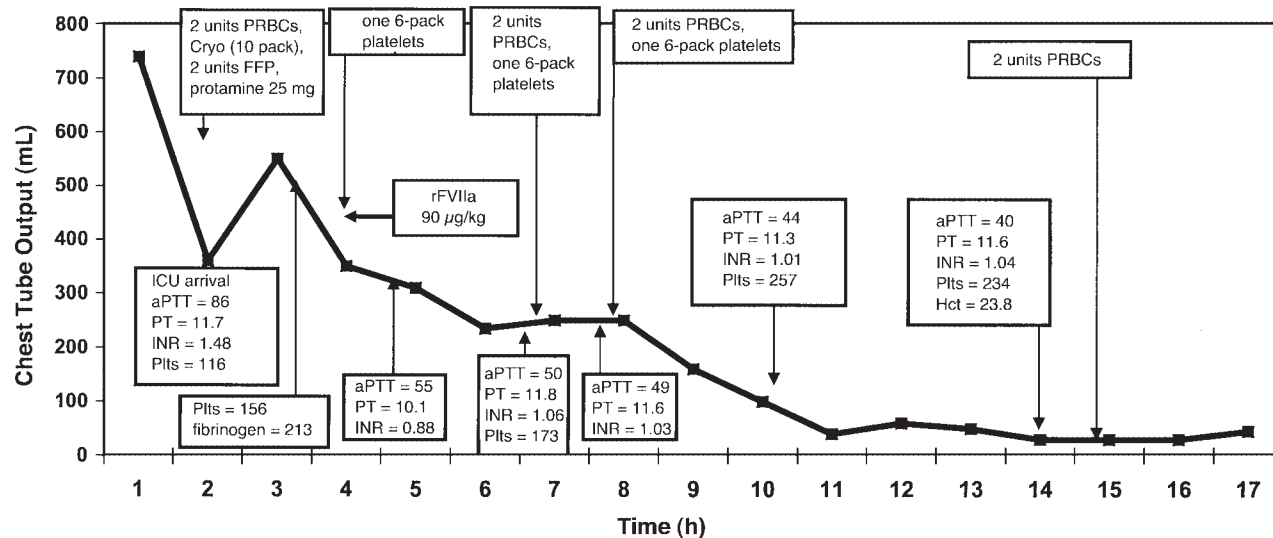
at the conclusion of the procedure. The patient was successfully weaned from CPB, and the heart functioned well with adequate cardiac output. However, he experienced excessive generalized oozing (chest tube output >200 mL/h) and drops in hematocrit (<22%) that required transfusions of multiple units of blood products, including 12 units of fresh-frozen plasma (FFP), one 10-pack of cryoprecipitate, one 6-pack of platelets, 6 units of packed red blood cells, and 1.9 L of Cellsaver (washed red blood cells via autotransfusion) without achieving adequate hemostasis. After ruling out any obvious surgical sources of bleeding and correcting all coagulation deficiencies, the decision was made to give the patient a single intravenous bolus dose of rFVIIa 90 µg/kg administered slowly, which is the approved dose for patients with hemophilia and the most commonly used dose for off-label indications.<sup>11</sup> The oozing rapidly declined to a negligible level, chest tubes and sternal wires were placed, and the chest was closed. The patient was on minimal inotropic support and was transferred to the intensive care unit (ICU) in stable condition.

Over the first few hours in the ICU, the patient again experienced significant chest tube output (>200 mL/h) despite further administration of blood products and intravenous desmopressin (0.3 µg/kg) in an attempt to correct the coagulopathy (Figure 1). Surgical reexploration was not attempted at this time because the excessive oozing was felt to be a result of the large area of unopposed chest wall that resulted from the significant size difference in the excised heart and the newly transplanted heart, along with the excision of a chronically deflated left lower lobe of the lung. As a result of his continued chest tube output of >200 mL/h despite aggressive treatment with conventional therapies and correction of coagulation factors, the patient received rFVIIa 90 µg/kg 4 hours after the first dose.

Following this administration of rFVIIa, the patient's chest tube drainage again declined to negligible levels and his hematologic values stabilized. The drainage continued to decline over the next several hours to a satisfactory level (<50 mL/h), and surgical reexploration was deemed unnecessary. There were no signs of postoperative myocardial infarction or other clinically significant thrombosis, and the patient continued to improve. He recovered from complications following his transplant and was eventually discharged from the hospital.

### Discussion

There is currently a lack of experience with the use of rFVIIa in postoperative cardiac surgery and heart transplantation. There have been a few case reports in patients



**Figure 1.** Time course of chest tube output from ICU admission through 18 postoperative hours. Laboratory values, blood products administered, and the administration of rFVIIa are denoted in the boxes along the time continuum. aPTT = activated partial thromboplastin time; Cryo = cryoprecipitate; FFP = fresh-frozen plasma; Hct = hematocrit (%); ICU = intensive care unit; INR = international normalized ratio; Plts = platelets; PRBCs = packed red blood cells; PT = prothrombin time; rFVIIa = recombinant factor VIIa.

undergoing heart valve repair/replacement, after repeat coronary artery bypass graft surgery, and following the implantation of an LVAD.<sup>1,2,6-10</sup> In each of these cases, rFVIIa was used as salvage therapy when other therapies had failed to achieve adequate hemostasis. The doses of rFVIIa ranged anywhere from 20 to 107 µg/kg. We used the dose approved for use in hemophilia (90 µg/kg), as we felt there was more experience with this dose in various populations.<sup>11</sup> In some of these cases, patients received more than one dose of rFVIIa, and redosing was based upon the available literature and experience in hemophilia (every 2–4 h based upon response and presence or absence of further blood loss). The patients were thoroughly examined for any obvious sources of bleeding, anticoagulation was completely reversed, and the patients received multiple units of FFP, cryoprecipitate, and platelets to attempt to reverse any coagulopathies. Once each of these therapies had been exhausted without resolution of the bleeding event, rFVIIa was given in a desperate attempt to halt life-threatening blood loss. A second dose of rFVIIa was administered in some cases due to copious chest tube output or continued generalized oozing.

Despite the anecdotal reports of successful use of rFVIIa in cardiac surgery patients, as of August 26, 2004, there is still very little known about the safety of this agent, and there have been no controlled trials reported in the literature. The precise mechanism of action of rFVIIa has not yet been fully elucidated, but it is believed that initiation of hemostasis occurs with the formation of a complex between tissue factor (TF) and activated FVIIa. This occurs within a few minutes of administration, and the median residence time is approximately 3 hours (half-life 2.3 h).<sup>11</sup> Once exposed, TF forms a complex with FVIIa and initiates thrombin production. Exogenous rFVIIa can also bind directly to activated platelets, most likely because of the superphysiologic concentrations achieved, which creates a “burst” of thrombin generation at the site of injury.<sup>10</sup> Ultimately, this leads to rapid, targeted activation of the clotting cascade and hemostasis, leading to the formation of a stable fibrin hemostatic plug at the site of tissue injury that is resistant to premature fibrinolysis. However, the obvious concern is the potential for acute thrombosis of the surgical conduits and/or the coronary vasculature of the newly implanted heart. It would seem that there is clearly a risk of thrombin generation and thrombosis at the site of the endothelial damage/disruption and subsequent release of tissue factor that is unavoidable in procedures of this type. Importantly, there were no signs of acute thrombosis or graft failure following the administration of rFVIIa in our patient or in previously published case reports. Also of utmost concern is the potential financial impact on the already strained healthcare system that could be caused by widespread or frivolous use of rFVIIa. At a cost of approximately \$1 per µg and an estimated half-life of 2 hours, the cost of treating a single patient with a life-threatening hemorrhage can be thousands of dollars.<sup>12</sup> In our case, the hospital cost for 2 doses of 90 µg/kg in a 70-kg patient (rounded to the nearest vial size) was \$8160.

## Summary

Due to a variety of factors, cardiac surgery can be associated with clinically significant bleeding that is potentially life-threatening. The management of such bleeding has not been well described in the literature and usually consists of a combination of hemostatic agents and blood product transfusions. Recently, recombinant blood factors, specifically rFVIIa, have been employed in the treatment of postoperative bleeding in cardiac surgery patients with promising results and no reported clinically significant adverse events.

Although there are several case reports documenting the use of rFVIIa for this type of off-label indication, its place in therapy is still unclear. At this point, rFVIIa should be reserved for patients with life-threatening bleeding that is refractory to standard treatment modalities including multiple units of blood products, complete reversal of any anticoagulant activity, and mechanical repair of any obvious sources of bleeding.

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#### EXTRACTO

**OBJETIVO:** Reportar un caso de la utilización exitosa de rFVIIa para el tratamiento de sangrado en un paciente que va a recibir un trasplante cardíaco.

**RESUMEN DEL CASO:** Un hombre de 57 años con cardiomiopatía idiopática fue llevado a sala de operaciones por su disfunción ventricular izquierda y trasplante cardíaco. El paciente experimentó una excesivo exudado sanguíneo generalizado que requirió varias transfusiones de múltiples componentes de sangre y cantidades significativas de Cellsaver (células rojas de sangre lavadas via autotransfusión) sin obtener una hemostasis adecuada. Después de descartar razones quirúrgicas obvias de sangrado e intentar corregir todas las deficiencias de coagulación, el paciente recibió rFVIIa (90 µg/kg). El exudado sanguíneo disminuyó rápidamente a un nivel insignificante, y los tubos de pecho y alambreado esternal fueron colocados; al final el pecho fue cerrado. El paciente estuvo con un soporte inotrópico mínimo y posteriormente fue transferido a la Unidad de Cuidado Intensivo en condición estable.

**DISCUSIÓN:** Con frecuencia una cirugía cardíaca es asociada con una ruptura del sistema de coagulación, particularmente en pacientes de alto riesgo como aquellos de la remoción de artefacto de asistencia ventricular y subsecuentemente trasplante cardíaco. Esto podría llevar a un sangrado que amenaza contra la vida que podrían requerir múltiples agentes hemostáticos y significativas transfusiones para restaurar hemostasis. Recientemente, rFVIIa ha sido utilizado como alternativa para transfusión masiva en algunos pacientes, incluyendo cirugía cardíaca.

**CONCLUSIONES:** rFVIIa parece ser una alternativa viable como terapia de rescate para el tratamiento de sangrado refractario después de un trasplante cardíaco. A pesar de los sucesos anecdotaes de rFVIIa en este escenario, futuras investigaciones clínicas son necesarias.

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#### RÉSUMÉ

**OBJECTIF:** Rapporter un cas d'utilisation du facteur VIIa recombinant (rFVIIa) pour le traitement du saignement réfractaire chez un patient ayant subi une greffe cardiaque orthotopique.

**RÉSUMÉ:** Un homme de 57 ans ayant une cardiomyopathie idiopathique a été amené en salle d'opération pour qu'on lui retire le dispositif d'assistance ventriculaire (DAV) implanté précédemment et qu'on procède à une greffe cardiaque orthotopique. Suite à l'opération, un saignement généralisé est survenu et le patient a reçu plusieurs unités de produits sanguins ainsi qu'une quantité significative de Cellsaver (globules rouges lavés et autotransfusés) sans toutefois pouvoir obtenir une hémostase adéquate. Après avoir éliminé toute cause chirurgicale évidente de saignement et avoir corrigé tous les problèmes de coagulation, le patient a reçu du rFVIIa (90 µg/kg). Le saignement diminue rapidement à un niveau négligeable et le champ opératoire pu être refermé. Le patient demeura sous support inotrope minimal et fut transféré à l'unité des soins intensifs dans un état stable.

**DISCUSSION:** La chirurgie cardiaque entraîne fréquemment des perturbations de la coagulation, particulièrement chez les patients à risque élevé tels que ceux nécessitant le retrait d'un DAV avec greffe cardiaque orthotopique subséquente. Des hémorragies mettant la vie du patient en danger peuvent survenir et nécessiter l'utilisation d'agents hémostatiques et de plusieurs transfusions afin d'assurer l'hémostase. Récemment, le rFVIIa a été utilisé comme solution de rechange aux transfusions multiples pour le traitement du saignement réfractaire chez plusieurs types de patients, incluant quelques cas de patients ayant subi une chirurgie cardiaque.

**CONCLUSIONS:** Le rFVIIa semble être une option intéressante comme traitement de secours du saignement réfractaire survenant lors d'une greffe cardiaque orthotopique. Des études seront toutefois requises pour confirmer le rôle du rFVIIa dans cette indication.

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