

## Recombinant activated factor VII for treatment of refractory hemorrhage after surgery for acute aortic dissection

H. GRUBITZSCH<sup>1</sup>, O. VARGAS-HEIN<sup>2</sup>, C. VON HEYMAN<sup>2</sup>, W. KONERTZ<sup>1</sup>

**Despite appropriate treatment, surgery for aortic dissection is frequently associated with bleeding problems. In these series we report on the employment of recombinant activated factor VII (rFVIIa) for refractory hemorrhage after emergency surgery for acute type A aortic dissection, used to face the problems of postoperative blood loss and transfusion requirements. Despite the good results of the therapy, a patient presented with thrombosis of the left cavernous sinus. Although a risk of thromboembolic complications has to be considered, rFVIIa is a reasonable rescue option in life-threatening hemorrhage and enlarges our hemostatic armamentarium in surgery for acute aortic dissection.**

**KEY WORDS:** Hemorrhage - Aortic dissections - Endovascular surgical procedures.

Problematic bleeding is a common issue in surgery for aortic dissection. Coagulopathy may persist despite appropriate treatment with blood cells, plasma, factor concentrates and antifibrinolytics. The off-label use of recombinant activated factor VII (rFVIIa), originally approved for the management of bleeding related to hemophilia in patients with inhibitors, has recently been reported to be successful in reversing life-threatening bleeding in a number of clinical scenarios including cardiac surgery.<sup>1-9</sup> From January to November 2005, 10 patients undergoing emergency surgery for acute type A aortic dissection were treated in our hospital. We report two cases with refractory hemorrhage that were successfully treated intraoperatively by rFVIIa, applied according to hospital standards.<sup>10</sup> The risks and benefits of rFVIIa as rescue therapy in the described clinical setting are discussed.

<sup>1</sup>Department of Cardiovascular Surgery  
University of Clinic Charité  
Campus Charité Mitte, Berlin, Germany  
<sup>2</sup>Department of Anaesthesiology  
and Intensive Care Medicine  
University Clinic Charité  
Campus Charité Mitte, Berlin, Germany

### Clinical series

*Case 1.*—A 74-year-old woman (height 165 cm, weight 75 kg), presenting with severe and sudden onset chest pain, was referred for emergency surgery after a computed tomography (CT) scan detected acute type A aortic dissection involving the aortic valve. Preoperatively, the patient was not on platelet aggregation inhibitors or anticoagulant drugs. Coagulation laboratory tests (prothrombin time, activated partial thromboplastin time, antithrombin III activity, fibrinogen, and platelet count) were normal. The patient underwent the replacement of the ascending aorta with a tubular graft (Gelweave 28 mm, Vascutek Ltd., Inchinnan, Scotland, UK) and the aortic root replacement with a stentless bioprosthesis (Toronto Root Bioprosthesis 25 mm, St. Jude Medical, St. Paul, MN., USA). Anticoagulation for cardiopulmonary bypass (CPB) followed a standardized institutional protocol (initially heparin 400 IU/kg, ACT  $\geq$ 410 s., protamine dosage at a ratio 1:1). According to institutional standard, deep hypothermic circulatory arrest (DHCA) at 16 °C and retrograde cerebral perfusion (RCP) were applied. DHCA and CPB times were 29 and 196 minutes, respectively. During the operation a cumulative heparin dosage of 35 000 IU was given, which was reversed with protamine chloride 35 000 IU after cessation of CPB. Since hemorrhage persisted, 1 000 000 kallikrein-inhibiting units aprotinin, antithrombin III 1 000 IU, and calcium 3 g were administered, followed by 17 units of packed red blood cells (RBC), 20 units of fresh frozen plasma (FFP), 4 units of single donor platelet apheresis concentrates (PAC), and 2 000 IU prothrombin complex concentrates. Despite normothermia, diffuse oozing of blood persisted, reaching up to 50 mL/min blood loss *via* cell saver sucker. According to published standards<sup>10</sup> rFVIIa (100  $\mu$ g/kg) was used to control bleeding.

Corresponding author: H. Grubitzsch, Klinik für Kardiovaskuläre Chirurgie, Charité – Universitätsmedizin Berlin, Campus Charité Mitte, Schumannstrasse 20/21, 10117 Berlin, Germany.  
E-mail: herko.grubitzsch@charite.de

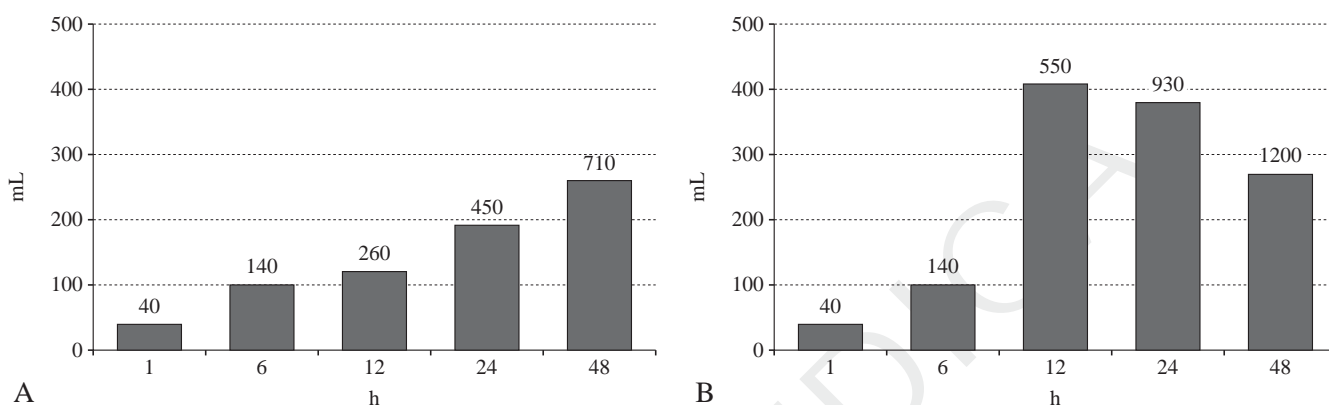


Figure 1.—Postoperative chest tube drainage volume. Successive drainage volume is represented by bars; cumulative drainage volume is given by values above bars.

TABLE I.—First postoperative coagulation laboratory tests.

	Case 1	Case 2	Normal values
Hemoglobin g/dL	14.0	10.6	12.0-15.7
Hematocrit %	0.40	0.30	0.35-0.47
Platelet count 10 <sup>9</sup> /L	107	97	150-400
Prothrombin time %	>130	>130	70-130
INR	<0.88	<0.88	0.9-1.25
aPTT s	39.1	43.4	26-40
AT III activity %	82	73	70-130
Fibrinogen mg/dL	247	251	150-450
ACT+ s	119	128	110-130

INR: international normalized ratio of prothrombin time; aPPT: activated partial thromboplastin time; AT III: antithrombin III; ACT+ = kaolin-activated clotting time (Hemochron Jr., Edison, NJ, USA).

Postoperative chest tube drainage volume and first coagulation laboratory tests are shown in Figure 1 and Table I. Within the first 24 postoperative hours, transfusion of no more than three units of FFP were required. The patient was extubated on the third postoperative day. Due to onset of a right arm palsy, a cranial CT scan was performed on the fourth postoperative day, which excluded intracerebral hemorrhage or ischemia. The scan showed thrombosis of the left cavernous sinus, which was confirmed by another CT scan on the tenth postoperative day. Heparin was temporarily administered to the patient, who was transferred to another hospital on postoperative day 16 and then transferred to rehabilitation. Neuromotor dysfunction of the right arm recovered completely. At four months postoperatively the patient lives on her own without any disability.

**Case 2.**—A 62-year-old man (height 180 cm, weight 96 kg) presenting with sudden onset severe chest pain was referred for emergency surgery after a CT scan detected an ascending aortic aneurysm with acute type A aortic dissection. Preoperative coagulation laboratory tests (prothrombin time, activated par-

tial thromboplastin time, antithrombin III activity, fibrinogen, and platelet count) were normal. However, because myocardial infarction was suspected at first, acetylsalicylic acid 500 mg were given intravenously before the CT scan. The patient underwent a replacement of the ascending aorta and hemiarch with a tubular graft (Gelweave 30 mm, Vascutek Ltd., Inchinnan, Scotland, UK), as well as a common trunk reconstruction and reinsertion. Duration of DHCA at 16 °C was 47 minutes. RCB was used for cerebral protection. CPB time was 187 minutes. During the operation a cumulative dose of heparin 50 000 IU was given. For primary hemostasis, protamine 50 000 IU, 1 000 000 kallikrein-inhibiting units aprotinin, and calcium 4 g were administered, followed by 16 units of packed RBC, 24 units of FFP, 4 units of PAC, antithrombin III 1 500 IU, prothrombin complex concentrates 2 000 IU, and 1-deamino-8-D-arginine vasopressin (DDAVP) 20 µg. Since life-threatening hemorrhage persisted, rFVIIa 100 µg/kg was given according to our protocol, leading to cessation of bleeding. Postoperative blood loss and coagulation laboratory tests are shown in Figure 1 and Table I. The patient was given 1 unit of RBC, 8 units of FFP, and 2 units of PAC within the first postoperative 24 hours. Cranial CT scan on the fourth postoperative day, performed because of inadequate vigilance after sedation cessation, excluded cerebral ischemia or hemorrhage. The perioperative course was complicated by respiratory and renal failure requiring tracheotomy and temporary hemodialysis. The patient was weaned off the respiratory machine and transferred to a community hospital on postoperative day 16. Renal function renormalized. After completing a rehabilitation program, the patient lives without any residual disability.

## Discussion

Hemostasis is a central problem in surgery for acute aortic dissection. Bleeding in these patients is an important cause of morbidity and mortality.<sup>11</sup> Hemorrhage

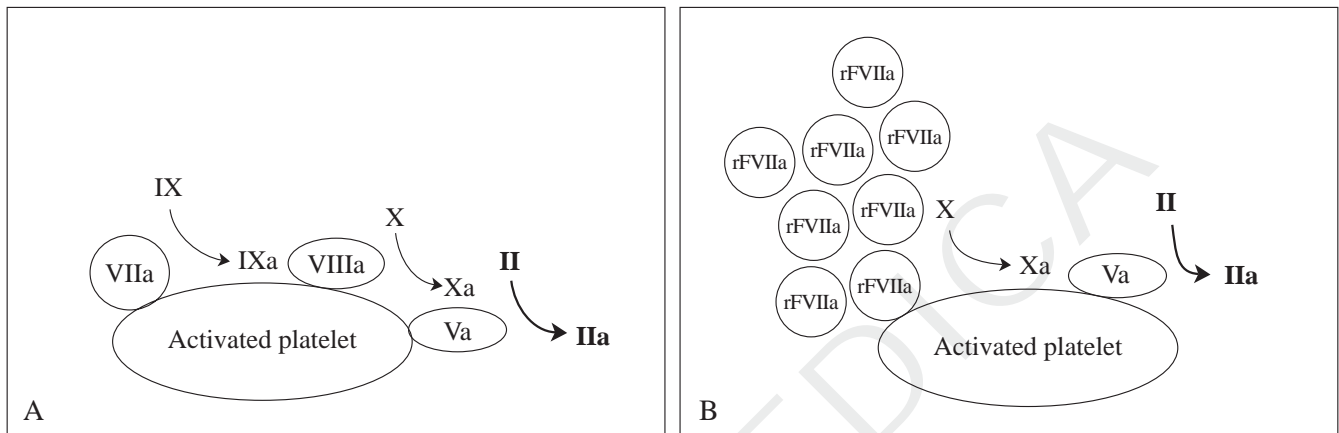


Figure 2.—Role of activated platelets and factor VII in hemostasis. Panel A shows binding of FVIIa, FIXa, FVIIIa, FXa and FVa to negatively charged phospholipids exposed after platelet activation by initially produced thrombin and subsequent activation, leading to the full thrombin formation during normal conditions.<sup>1</sup> The effect of exogenously added high-dose rFVIIa is shown in panel B. The rate of thrombin generation, referred to as “thrombin burst”, is enhanced by rFVIIa attaching to a low affinity binding site of activated platelets and direct activation of FX.<sup>1, 14</sup> That, in turn, activates more platelets and results in a stabilized thrombin plug with a tight fibrin structure, making it resistant to premature lysis.<sup>1</sup>

results from multiple interrelated factors, including the diseased aorta itself, the extent of surgical dissection, and the transient need for complete anticoagulation, hypothermia, ischemia and reperfusion, extracorporeal circulation system, systemic inflammatory response, fibrinolysis, and hemodilution.

In our patients, bleeding after aortic surgery was life-threatening and unresponsive to conventional treatment. According to hospital standards<sup>10</sup> for the escalating use of coagulation factor concentrates in perioperative bleeding, rFVIIa was administered as a last resort. The dosage of 100 µg/kg was chosen empirically on the basis of published experimental and clinical data indicating that 100-200 µg/kg rFVIIa lead to full thrombin generation.<sup>1, 4, 6, 14</sup> Bleeding ceased immediately and treatment was very effective, furthering reducing blood loss and postoperative transfusion needs. However, one patient presented with a transient neurological lesion, probably due to a thrombosis of the left cavernous sinus. While there are several potential causes that may lead to such a complication, including thrombus deposition due to stasis during DHCA,<sup>12</sup> the venous thrombosis observed in that distinct clinical setting is a highly suspicious side effect of rFVIIa use. Neurological complications are particularly critical matter in acute aortic dissection. A recent analysis of data on 550 patients of the International Registry of Acute Aortic Dissection revealed neurological deficits in 23%.<sup>13</sup>

According to current concepts, hemostasis is initiated by the formation of a complex between tissue factor (TF), exposed to the circulation after tissue injury, and FVII or FVIIa.<sup>1</sup> As a result, limited amounts of thrombin are formed, leading to platelet activation at the site of tissue injury, which is a necessary requirement for full thrombin generation and subsequently a stable fibrin plug. The hemostatic effect of exogenously added rFVIIa in supraphysiologic doses (100-200 µg/kg) seems to be mediated by enhancing the rate of thrombin generation on thrombin-activated platelet surfaces through the direct activation of FX (Figure 2). It was shown that rFVIIa binds to thrombin-activated platelets surface with a low affinity, requiring higher concentrations of rFVIIa than those normally found in circulating blood, thereby generating full thrombin formation also in the absence of FVIII or FIX, referred to as “thrombin burst”.<sup>14</sup> That, in turn, activates more platelets and results in a stabilized thrombin plug with a tight fibrin structure, making it resistant to premature lysis.<sup>1</sup> *Vice versa*, platelet activation due to other mechanisms, e.g. extracorporeal circulation circuits or arteriosclerotic plaques in cerebrovascular, coronary artery, or peripheral arterial disease, may lead to thrombosis distant from the site of injured tissue—a potential risk of rFVIIa treatment.

Several studies have reported effective treatment of severe bleeding after rFVIIa administration. A significantly reduced mortality was achieved in patients

with intracranial hemorrhage.<sup>3</sup> The beneficial effect of rFVIIa for intractable hemorrhage after cardiac surgery and reduction in blood loss and/or blood product usage was demonstrated in case reports, some small case series and 2 case-control studies.<sup>2, 4-8</sup> rFVIIa failed to establish secure hemostasis in only two cohorts: in 19% (3/16) and 25% (6/24) of patients, respectively.<sup>6, 8</sup> No thromboembolic events were observed in the majority of cases.<sup>2, 4-7</sup> By contrast, thromboembolic complications occurred in 25% (4/16 patients) in Raivio's cohort of patients.<sup>8</sup> However, 2 of these patients – one who developed multiple cerebral infarctions and another who developed thrombosis of the right iliac artery – underwent emergency surgery for acute type A aortic dissection. Although there are various diseases and surgery-related factors predisposing to thromboembolism in these patients, a causative role of rFVIIa treatment can not be excluded. Accepting that thromboembolic risk, the use of rFVIIa is justified in life-threatening bleeding nevertheless, when other means to achieve hemostasis have failed. Hemorrhage severity is strikingly evident in Raivio's report:<sup>8</sup> those patients who did not respond to rFVIIa treatment died. Undoubtedly, exhaustive surgical and conventional bleeding control needs to be an absolute prerequisite of rFVIIa use.

### Conclusions

Hospital standards for a stepwise escalating regimen of administration of blood products and coagulation factor concentrates in severe bleeding should be developed and regularly reviewed on an annual basis. In that protocol, off-label use of rFVIIa is a reasonable rescue option in life-threatening hemorrhage. Although a risk of thromboembolic complications has to be considered, rFVIIa enlarges our *armamentarium* for achieving hemostasis in surgery for acute aortic dissection. As long as data from

ongoing controlled trials are pending, rFVIIa administration has to be carefully evaluated in each of these particular situations.

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