

terized by a prolonged PT and normal APTT as factor VII affects only the extrinsic pathway of the coagulation cascade. Most reports recommended replacement therapy for patients with factor VII deficiency who undergo major surgery, especially open heart surgery with CPB [4]. It is reported that factor VII activity should be maintained minimally at 15% to 25% for major surgical procedures during the first three postoperative days [1, 2]. A review of the literature revealed only three reported cases of open heart surgery in factor VII deficiency [1-3]. In all cases, factor VII activity was less than 10% and replacement therapy was carried out to maintain the plasma factor VII concentration at approximately 15% to 40%. Either continuous infusion or intermittent administration was used at every 3.5 to 4 hours during surgery and up to 48 hours postoperatively, based on the short half-life of factor VIIa as 3.5 hours *in vivo*. The doses for each administration were between 20 and 35 $\mu\text{g}/\text{kg}$.

In the present case, it is unclear whether the deficiency was inherited or induced by hepatic congestion. Although not a severe factor VII deficiency and PT was 30%, which is usually enough to secure hemostasis at least in minor surgery, we prepared the strategy for managing possible perioperative bleeding problems in this infant. Our dosing schedule (30 $\mu\text{g}/\text{kg}$ at every 2 to 3 hours during surgery) was based on the previous reports and the half-life of factor VIIa. There is no evidence which demonstrates that factor VII was the only missing element at the bleeding problem after CPB, however, the additional factor VIIa administration was certainly effective to secure the hemostasis. At least, the replacement of functioning platelets alone could not stop the bleeding. We are not convinced that our regimen was adequate, since the fourth dose was needed immediately after the third administration. We may also need to change the dose for more complex repairs with longer CPB durations.

Bleeding problems after CPB are generally related to heparin, fibrinolysis, or platelets. Usually, a deficiency of soluble coagulation factors is a rare cause of postoperative bleeding. In the present case, it is possible that a bleeding tendency with a mild factor VII deficiency was aggravated by the blood-artificial surface interaction initiated by CPB and hemodilution. A recent report confirmed that tissue factor is the main activator of the coagulation system during CPB [5]. Factor VII, as well as other extrinsic factors, could be greatly consumed by blood activation via tissue factor, especially when highly activated aspirated blood from nonvascular structures is reinfused during CPB. Therefore, in surgery under CPB, factor VII replacement therapy should be readily available even if there is only a mild deficiency. It is also presented that thrombotic complications occurred after aggressive factor VII replacement [6]. We monitored and kept PT at about 40% with the administration of fresh frozen plasma once hemostasis was secured to prevent the excessive administration of factor VII.

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Use of Recombinant Factor VIIa as a Rescue Treatment for Intractable Bleeding Following Repeat Aortic Arch Repair

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Hemorrhage, refractory to aggressive conventional therapy, at a rate of 16 L/hr following separation from cardiopulmonary bypass for aortic arch repair, was controlled with a dose of 90 $\mu\text{g}/\text{kg}$ of recombinant factor VIIa, repeated once after 2 hours.

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Recombinant factor VIIa (rFVIIa) is a synthetic hemostatic drug that is approved for use in hemophiliacs with antibodies to factor VIII or factor IX. Recent reports of the use of rFVIIa in cases of severe bleeding after trauma and following cardiac surgery [1-6] have suggested its efficacy in patients without preexisting hemorrhagic diatheses and illustrated its potential as a promising new clinical anticoagulant. We present the first case of successful use of rFVIIa in the treatment of life-threatening refractory hemorrhage at a rate of 16 L/h after prolonged cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA).

The major theoretical concern regarding the use of this

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drug, particularly after CPB, is the occurrence of thrombotic complications. rFVIIa requires tissue factor (TF) to develop its procoagulant activity and CPB induces a surge of blood-borne tissue factor (TF) on blood cells [7, 8]. CPB also employs reinfusion of shed blood which has high quantities of TF [9]. Interestingly, complications after the use of rFVIIa following CPB have not been reported [1, 2, 4, 6]. Possible explanations for this fact are proposed.

A 60-year-old male, who had undergone a Bentall aortic root replacement 19 years previously using a porcine-valved conduit for acute type A aortic dissection, was now scheduled for elective aortic valve replacement for severe prosthetic valve insufficiency and aneurysmal enlargement of the remaining ascending aorta. His past medical history was remarkable only for hypertension, which was well controlled by metoprolol and enalapril. The patient was recovering from a lobar pneumonia for which he was taking ciprofloxacin by mouth. He was not receiving any anticoagulants.

Induction of general anesthesia was accomplished with intravenous (IV) midazolam (0.1 mg/kg) and fentanyl (10 μ g/kg). After paralysis with IV pancuronium (0.1 mg/kg), endotracheal intubation, and institution of mechanical ventilation, venous and arterial cannulas were placed. Aprotinin, 2×10^6 kallikrein inhibitory units (KIU), was infused over 30 minutes, followed by 5×10^5 KIU/h for 6 hours. Bleeding from an accidental aortotomy upon sternotomy required rapid transfusion of 8 U of packed red blood cells (PRBC) and reinfusion of 550 ml of shed blood while cardiopulmonary bypass (CPB) was being instituted emergently. Sufficient anticoagulation with heparin 400 iU/kg was demonstrated by an activated clotting time of more than 600 seconds and a heparin concentration of 4.5 mg/kg (Hepcon HMS plus; Medtronic, Minneapolis, MN).

The patient's core temperature was reduced to 20°C. A vertical laceration was found in the native, dissected ascending aorta. The previous Bentall aortic root replacement covered only a 3-cm segment of the proximal ascending aorta. The remainder of the aneurysmal ascending aorta and proximal aortic arch was mobilized during the cooling period. At onset of ventricular fibrillation, an aortic cross-clamp was applied. The Dacron valved conduit was then opened and cardioplegia administered directly into the coronary ostia. A degenerated porcine valve was then removed from the base of the Dacron conduit and a St. Jude aortic prosthesis reinserted. At this point, circulation was arrested and the aortic cross clamp was removed. The dissected ascending aorta and proximal arch were removed and the remaining dissection flap was fenestrated. A new Dacron graft was interposed between the arch and original proximal graft. No bioglu or Teflon felt was used, as the residual distal aorta and proximal aortic arch were very fibrotic from chronic dissection. Total circulatory arrest time was 20 minutes. Separation from CPB was complicated by profuse bleeding from the multiple suture sites, which was difficult to control. It was necessary to reinitiate

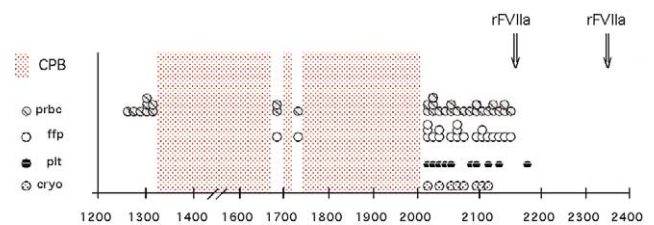


Fig 1. Transfusion timeline: Transfusion events during aortic arch replacement. The initial transfusion event occurred during an episode of torrential bleeding from the aorta during thoracotomy. The following events occurred during initial attempts of separation from CPB and the subsequent CPB period. The final event occurred after administration of protamine. Importantly, although not illustrated in this figure, the infusion of 11,000 mL of "cell saver blood" over the 90 minutes following separation from CPB contributed significantly to meeting this patient's transfusion requirements. (CPB = cardiopulmonary bypass; cryo = cryoprecipitate; ffp = fresh frozen plasma; plt = platelets; prbc = packed red blood cells.)

cardiopulmonary bypass three times in order to facilitate exposure of bleeding sites on the pulmonary artery and posterior aortic suture line. Final separation from CPB (total CPB time of almost 6 hours) was accompanied by diffuse bleeding and coagulopathy (Table 1). Inotropic/vasoactive support with dopamine ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), norepinephrine ($0.05 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and phenylephrine at varying doses and vigorous replacement of rapid blood loss prevented the imminent cardiovascular collapse. After protamine was administered, blood loss persisted at a rate of 270 mL/min despite complete reversal of heparin, as evident by a heparin concentration of zero mg/kg (Hepcon HMS plus, Medtronic). Over the next 90 minutes, 25 U of PRBC (6,250 mL), 22 U of fresh frozen plasma (FFP) (4,400 mL), 10 six-packs of platelets (Plt) (2,000 mL), and 8 ten-packs of cryoprecipitate (800 mL), in addition to 11,000 mL of shed mediastinal blood, were administered with no apparent therapeutic effect. We surmised that the replacement of the patient's blood volume 4 to 6 times likely reduced the concentrations of some critical coagulation factors including activated factor VII to levels too low to support thrombin formation.

It was then decided to administer a dose of 90 μ g/kg of recombinant factor VIIa (rFVIIa) intravenously. Three minutes later the bleeding had slowed down, so that rapid resuscitation with blood products was no longer necessary. The patient received no more blood products except for six units of platelet concentrate. The timeline of transfusion events is shown in Figure 1. Table 1 illustrates the rapid improvement of coagulation test results from 30 minutes before administration of rFVIIa to 10 minutes after. An empiric second dose of rFVIIa was administered 2 hours after the initial dose had been given. This had been suggested in previous reports [3, 6] and is in keeping with the plasma half-life of rFVIIa of 2.3 to 2.9 hours [10]. Hemostasis was permanent. The patient recovered slowly, was extubated on the third postoperative day, and left the hospital six days later without any symptoms or signs of systemic thromboses.

Table 1. Coagulation Test Results Before and After Administration of rFVIIa

	30 Minutes Before	10 Minutes After
PT (sec)	24	12
PTT (sec)	> 100	51
Fibrinogen (mg/dL)	214	206
INR	2.0	0.9
Platelets (10 ³ /mL)	152	120

INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time.

Comment

Diffuse bleeding and coagulopathy following long or repeated periods of cardiopulmonary bypass can be a difficult and morbid complication [11]. DHCA requires long periods of CPB because cooling to 20°C and subsequent rewarming is required. This can add more than one hour to the CPB period. We present a report of successful treatment of bleeding following a procedure requiring DHCA in adults. Instantaneous hemostasis following administration of rFVIIa in a patient bleeding this rapidly has not been reported in a patient undergoing a surgical procedure. Only one case with a greater rate of blood loss (18 L/h) than that reported herein has been successfully treated with rFVIIa. The patient was a soldier who had been shot in the lower abdomen [5].

Although rFVIIa is licensed only for the treatment of hemophiliacs with inhibitors [3], it has been documented in case reports to control refractory hemorrhage after various types of surgery, including cardiac surgery and transplant surgery [3]. A powerful feature of rFVIIa is the ability to promote localized hemostasis without systemic thromboses [3]. This is because TF [3] or activated platelets [12], which are usually only present at sites of tissue injury, are required for rFVIIa to develop its procoagulant activity.

After CPB, however, TF and activated platelets may be present systemically, raising concerns of systemic thrombosis or disseminated intravascular coagulation (DIC) when rFVIIa is administered in this setting. Interestingly, in the eight reported cases of rFVIIa use after CPB (Table 2), no thrombotic complication or DIC occurred [1, 2, 4, 6].

Indeed, blood cells like neutrophils and monocytes have the ability to express TF [8], which is augmented by CPB [7]. Most of the blood-borne TF is encrypted, that is, bound to FVII and tissue factor pathway inhibitor (TFPI). TFPI is a strong inhibitor of the enzymatic activity of the TF-FVIIa complex and at normal plasma concentrations probably inhibits any blood borne TF-FVIIa activity [8]. The fact that localized hemostasis is nonetheless possible is presumably due to the fact that TF is present at injury sites to a much greater degree than in blood, overwhelming the concentrations of TFPI and allowing coagulation to occur locally [8]. After administration of heparin and again during CPB, the plasma concentration of TFPI increases significantly above baseline, continues to rise

as a function of CPB time, and then, although quickly diminishing in response to administration of protamine, remains elevated above baseline [13, 14]. It therefore seems reasonable to speculate that even if CPB had resulted in additional blood borne TF, more TFPI would have been available for its neutralization.

CPB induces a hyperfibrinolytic state. Plasmin cleaves TFPI at 5 different sites, leading to reduced anticoagulant activity of TFPI in vivo [15]. This could potentially result in intravascular coagulation when rFVIIa is administered after CPB because the amount of naturally occurring TFPI may no longer be sufficient to antagonize the amount of blood borne TF. However, this patient had received aprotinin, which prevents the cleavage of TFPI by plasmin [15], and thus may have introduced a margin of safety. Interestingly, in most cases in which rFVIIa was used after CPB, antifibrinolytics were used concomitantly [1, 2, 4, 6].

Endothelial cells express TF in response to activated platelets [16] and cytokines [17]. Cytokine release and platelet activation do occur in response to CPB [18] but it is not known whether endothelial cells express TF after CPB in humans. Hypothermia, as used during this patient's DHCA-CPB period, has been shown to reversibly inhibit the expression of TF on endothelial cells [19] and help prevent thrombotic complications when rFVIIa is used.

Another source of TF is reinfused, shed blood ("cell saver blood"). During the final episode of massive hemorrhage, the majority of this patient's transfusion requirements were met by reinfusion of unwashed, shed blood. There is evidence to suggest that, although the TF antigen concentration is very high in unwashed, shed blood, it is devoid of procoagulant activity, possibly because of inactivation by TFPI or because of proteolysis of TF [9]. Likewise, platelet activation does not occur when blood is collected by an autotransfusion device, and although platelet function after bypass is impaired, the autotransfusion device does not add further to this impairment [20].

In summary, a set of circumstances exists following CPB, which may have protected patients receiving rFVIIa from thrombotic complications.

The more liberal use of rFVIIa in cardiac surgical patients is limited by at least 4 shortcomings. (1) No randomized controlled trial has proven its efficacy and safety in cardiac surgical patients. (2) No dose finding study has been performed in this patient population. (3) The threshold for its administration is not defined. (4) The drug is prohibitively expensive. The acquisition cost of a 4.8-mg vial of rFVIIa is \$4,080.

It is, therefore, our opinion that rFVIIa should currently only be used if all reasonable surgical attempts have been made to control bleeding and if a coagulopathy is uncorrected despite aggressive administration of standard blood products.

However, despite all concerns, the lifesaving potential of rFVIIa must not be underestimated.

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Cavernous Hemangioma of the Tricuspid Valve: Minimally Invasive Surgical Resection

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Cardiac hemangioma is a rare, benign vascular tumor, occurring with an incidence of 1% to 2% of all detected benign heart neoplasms. Hemangioma of the tricuspid valve has never been previously reported. We describe the successful excision of this tumor through a right anterolateral mini-thoracotomy in a 49-year-old woman. Competency of the valve was confirmed intraoperatively and at discharge by transesophageal echocardiography.

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Cardiac hemangiomas are rare, benign neoplasms, with only 37 reported cases involving surgical treatment and none primarily arising from the tricuspid valve. A variety of clinical presentations may be seen, depending on the size and location of the tumor. These tumors can be completely asymptomatic, but they can also precipitate conductive and hemodynamic abnormalities resulting in sudden death. Because of the natural, unpredictable history of these tumors, surgical intervention is mandatory for resectable lesions. We report the case of a cavernous hemangioma of the septal leaflet of the tricuspid valve successfully resected using a minimally invasive surgical approach.

A healthy 49-year-old white woman was referred to our department with a history of syncopal episodes and an echocardiographic diagnosis of cardiac tumor localized on the tricuspid valve. No apparent abnormality was found on electrocardiogram and chest roentgenogram. A transesophageal echocardiogram demonstrated a 3 × 2 cm large mass with a thin capsule and an echo-free content, which was attached to the base of the septal leaflet of the tricuspid valve or possibly to the annulus (Fig 1A). The mass appeared peduncolated, mobile, and prolapsing into the right ventricle (Fig. 1B). A mild tricuspid regurgitation was documented. Coronary angiogram showed normal coronary arteries. We did not perform computed tomography or magnetic resonance imaging, because we believed that these would not

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