Bleeding after cardiac surgery

The role of recombinant factor VIIa

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Summary
Cardiac surgery carries the risk of significant blood loss requiring the transfusion of blood products. In addition to such blood loss, international studies have shown that severe bleeding necessitating re-operation occurs in 3–5% of patients. Morbidity and mortality are significantly increased, so effective and safe haemostatic measures will decisively improve outcome of patients.

Recombinant activated factor VII (rFVIIa) has been approved for the treatment of patients with inhibitor haemophilia, as well as with Glanzmann’s thrombasthenia and factor VII deficiency. Many publications have appeared in the last few years which report the successful and reliable use of rFVIIa for the treatment of refractory bleeding after cardiac surgery. This review presents the pathophysiological changes in the coagulation system which occur when a heart-lung machine is used and which have been blamed for an increased risk of bleeding in patients who have undergone cardiac surgery. Published experience with rFVIIa in paediatric and adult cardiac surgery is presented and discussed critically with regard to the efficacy and safety of its use.

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More than 96 000 open-heart operations with cardiopulmonary bypass (CPB) – establishment of an extracorporeal circulation (ECC) using a heart-lung machine (HLM) – were performed in Germany during 2004 (12). CPB induces marked activation of the coagulation system as a result of the multiple interactions of the HLM with biological systems of the human body. This activation is mutually increased and perpetuated by the parallel induction of an inflammatory enzymatic cascade (24). In addition to surgical bleeding, activation of the coagulation system with reactivity increased fibrinolysis is an important determinant of postoperative blood loss and the need for transfusion in cardiac surgery. According to data from the USA, 20% of all packed red blood cells that are transfused annually are given after cardiac operations (76). Large multicentre studies have shown that postoperative bleeding is an independent risk factor for morbidity and mortality after cardiac surgery, especially when re-operation is needed to achieve haemostasis (20, 63, 87). Furthermore, the number of packed red blood cell units that are regularly infused because of severe surgically-induced bleeding is an independent risk factor for mortality in hospital (41) and in the long term (29) after a cardiac operation. The higher morbidity risk from bleeding after cardiac operations is associated with a longer postoperative hospital stay (20) and much higher treatment costs. The significantly increased mortality risk in particular requires safe and effective preventive measures, including surgical arrest of bleeding and differentiated haemostatic treatment with blood products and coagulation factors.

In the last few years, many case reports and case series have been published on the successful use of recombinant factor VIIa (rFVIIa) – approved in Germany for the treatment of haemophilia with inhibitors (51) – in bleeding refractory to other haemostatic measures after cardiac surgery. This review includes a short presentation of CPB-induced pathophysiological changes in the coagulation system after cardiac operations and also a critical discussion of the haemostatic management of postoperative bleeding with coagulation factor concentrates, especially recombinant factor VIIa.

Haemostatic changes after CPB

In addition to surgical factors such as the complexity of the operation (e.g. combined procedures on coronary arteries and heart valves), revision operations, size of the wound and patient-related factors (e.g. previous administration of platelet aggregation inhibitors or anticoagulants), the main cause of coagulation disorders after cardiac operations is foreign-body contact of the blood with the extracorporeal circuit (referred to as CPB in this review). The effects of CPB on the coagulation system are complex and closely connected to the activation of inflammatory mediator cascades. Furthermore, other factors such as CPB-induced abnormalities of platelet function, thrombocytopenia, coagulation factor consumption, residual heparin effect, hypothermia, and increased fibrinolytic activity influence the postoperative function of the coagulation system (Fig. 1). The most important of these factors are described and discussed here.

Plasma coagulation and consumption of coagulation factors

The contact of blood with the surface of a foreign body activates the coagulation pathway previously referred to as “intrinsic”. Activation of factor XII (FXII) to factor XIIa (FXIIa) is induced by the activation of factor VII (FVII) to factor VIIa (FVIIa) and in this way the polymerisation of fibrin by thrombin is initiated in the “final pathway”. Factor XIIa also catalyses the formation of kallikrein from prekallikrein (15). The significance of this step in thrombin generation...
when on CPB remains under debate, because normal thrombin generation was measured in a patient with high molecular weight kininogen (HMWK) deficiency (<1%) while on pump. Similarly thrombin generation during CPB by activation of the contact phase (FXII → FXIIa) pathway alone is still being debated (10).

These findings suggest that the activation of prothrombin by the “extrinsic” coagulation system also plays an important role in thrombin formation during CPB. This hypothesis is supported by demonstrating tissue factor (TF) expression in monocytes and high levels of FVIIa in pericardial blood after cardiac operations (34). These findings correlated significantly with the activation of thrombin, measured as prothrombin fragment (PF) 1.2 (34).

This hypothesis that activation of plasma coagulation is inhibited during and after CPB, even when blood from the pericardium and the mediastinal wound is not retransfused, is supported by the results of clinical studies (2, 22).

Activation of plasma coagulation leads to the consumption of coagulation factors, which can result in an increased loss of blood postoperatively (22). The increased activation of the plasma coagulation system with consumption of coagulation factors is attenuated by higher doses of heparin (600–700 IU/kg body weight) given before connection to the HLM (23, 46). There was no significant difference in postoperative blood loss between the groups studied, but patients in the high-dose heparin group had significantly less drainage loss in the first four hours after the operation (23), and transfusion requirements were significantly lower.

Activation of the coagulation system with thrombin formation on CPB is due to activation of the intrinsic coagulation system and re-transfusion of blood aspirated from the pericardium and mediastinum. The associated consumption of coagulation factors can probably be reduced by higher doses of heparin so that coagulation factor activity is better maintained (46) without increasing the risk of postoperative bleeding.

**Anticoagulation during CPB**

Systemic anticoagulation is traditionally achieved by giving unfractionated heparin. The minimum effective dose was determined empirically as the dosage at which no thrombin forms in the extracorporeal circulation. After activated coagulation time (ACT) had been introduced, Bull et al. established a dose/effect curve for heparin based on this parameter (13). In the meantime a dose of 300 to 400 IU heparin/kg body weight before starting CPB has been the practice in most cardiac surgery centres. The target ACT is >400 s and it is kept above this level by intermittent bolus administration during CPB. Despite the lack of diagnostic precision of ACT (resulting from aprotinin administration, haemodilution etc.) this treatment regimen in cardiac surgery has proved itself over many years.

The question of whether the dosage of heparin influences postoperative bleeding remains the subject of scientific debate. Although the previously-mentioned studies have not shown any relationship between heparin dosage and postoperative blood loss, others have described higher drainage losses with higher heparin dosages (100–400 IU/kg body weight) (33, 77). The anticoagulation management introduced by Koster and Despotis, in which the heparin concentration is measured before, during and after CPB and the corresponding dose of protamine calculated, has made it possible to achieve more effective anticoagulation during CPB and to decrease postoperative blood loss by giving a protamine dose derived from the heparin dosage and the level of ACT.

The heparin effect is usually reversed with protamine chloride or sulphate after the HLM has been disconnected. The sulphate is used more often than the chloride, so that protamine sulphate is the one that has been used in most studies. Protamine can have haemodynamic side effects (e.g. systemic hypotension, pulmonary arterial hypertension, anaphylactic reactions) (55). These effects of protamine, together with its anticoagulant properties – inhibition of platelet aggregation – are caused by the activation of platelets (54) and the GP Ib-V-Willebrand factor interaction (7) – require the determination of an “optimal” protamine dosage. Because of the short half-life of protamine sulphate (approx. 4 min) (14), heparin rebound (re-emergence of the heparin effect) after protamine administration cannot be excluded (81).

A clinical study with the additional administration of small doses of protamine sulphate (2500 IU over six hours) showed this to be effective in counteracting heparin rebound (80). The significance of this phenomenon in everyday clinical practice is unclear, but should be taken into account in any therapeutic decision if drainage loss is increased and ACT is prolonged.

**Platelet aggregation inhibitors or anticoagulants**

Inhibition of platelet aggregation with low-dose acetylsalicylic acid (ASS, aspirin) is a firmly established part of treating coronary
heart disease (CHD). It significantly reduces the risk of death from CHD in itself (3) and after coronary artery bypass grafting (CABG) (58). The additional administration of clopidogrel, an oral adenosine diphosphate (ADP) receptor inhibitor, has been shown to reduce the mortality rate in unstable angina (96) and the rate of occlusion of a coronary stent (74), so that most patients are now given single or combined platelet aggregation inhibitors before CABG.

It is a moot point whether preoperative administration of aspirin is associated with an increased risk of bleeding (20, 42, 86). But taking aspirin or clopidogrel has been reported to increase postoperative drainage loss and re-thoracotomy (depending especially on which day the drug had last been taken) (38, 92, 95). However, Saw et al. found that preoperative ingestion of clopidogrel is of particular advantage for those patients who, after an initial percutaneous coronary intervention (PCI), needed a repeat intervention (PCI or CABG) (relative risk reduction 42.4%; 95% CI 1.0–67.0%). In such cases the preoperative decision whether to discontinue aspirin and clopidogrel because of the increased risk of bleeding requiring transfusion, should be subject to careful cost/benefit analysis (4).

Effective systemic anticoagulation with unfractionated or low molecular weight heparin is a firmly established therapeutic principle in patients with unstable angina. Unfractionated heparin does not carry an increased risk of postoperative bleeding, because it can be reversed by protamine. But retrospective studies have shown that preoperative administration of enoxaparin is associated with an increased rate of repeat thoracotomy (39) and greater drainage losses (60); in this situation switching to unfractionated heparin is thought to lower the risk of postoperative bleeding.

Thrombolysis continues to have a role, especially in the treatment of acute myocardial infarction. Patients who are scheduled to undergo CABG after thrombolysis and failed PCI (i. e. as an emergency intervention) are likely to have a markedly increased risk of postoperative bleeding. A prospective study of patients who underwent emergency CABG, some of whom had been pre-treated with tirofiban, actually had a significantly lower drainage loss and need for transfusion (9). This agrees with findings that GP IIb/IIIa inhibitors have an effect on platelets, protecting them against activation during CPB (45).

From these data it cannot be assumed that the preoperative or intraoperative administration of tirofiban, a short-acting GP IIb/IIIa receptor inhibitor, increases the risk of bleeding.

Platelet dysfunction

For a long time, CPB-associated platelet dysfunction was considered to be a main factor in the inhibition of clotting after extracorporeal circulation. In addition to thrombocytopenia, presumably resulting from haemodilution, activation of platelets with subsequent loss of glycoprotein receptors –GP Ib for the von Willebrand factor, and GP IIb/IIa for fibrinogen (92) – and an increased liberation of β-thromboglobulin and platelet factor 4 from α-granules have been reported (97). But in this study the loss of GP Ib correlated with the amount of blood loss, while Chung et al. (18) demonstrated that the intraoperative administration of nitric acid (NO) significantly reduces down-regulation of GP Ib/IX and GP IIb/IIa receptors on platelet surfaces and the amount of blood loss compared with untreated patients. Another factor that influences the activation of platelets is the administration of heparin: a marked increase in platelet aggregation (49) and a reduction in the liberation of thromboxane B2 (43), but also a reduction in platelet aggregation (63) and in thrombocytoc microaggregate formation (65) has been shown. Taking all these findings together, the clinical significance of platelet dysfunction after cardiopulmonary bypass (duration, amount of blood loss and need for transfusion) has not been clarified.

However, hypothermia also induces platelet inhibition by down-regulation of the GP Ib/IX receptor (59), reduction of platelet aggregation and the formation of thromboxane B2 (61). But the clinical effect of this down-regulation is unclear because hypothermic temperature regulation during CPB is not uniformly associated with increased blood loss (11, 59) or transfusion (8) so that the effect of hypothermia on platelet function remains a matter of debate.

Fibrinolysis

Activation of the plasma coagulation system with formation of fibrin results in a “regulatory” activation of fibrinolysis (82), either via factor XIIa or via fibrin-stimulated liberation of tissue plasminogen activator (tPA). Valen et al. described a significant increase of tPA antigen, tPA/plasminogen activator inhibitor-1 (PAI-1) complex, D-dimer, thrombin-antithrombin (TAT) complexes and prothrombin fragment 1.2 (PF 1.2) in arterial blood (88), which was confirmed by Hunt et al. (38). These investigators found increased levels of activation markers (TAT, PAI-1) up to 48 hours after the cardiac operation. Lo et al. described significantly raised levels of D-dimer and PF 1.2 up to 48 hours postoperatively in patients who underwent “on-pump” CABG (with CPB), while these two markers were significantly raised for up to 96 hours in patients who had “off-pump” CABG (without CPB) (56). It can therefore be assumed that fibrinolytic activity is increased for at least 48 hours postoperatively, regardless of whether or not CPB is used.

In addition to this physiological regulation after CPB, the administration of heparin also stimulates fibrinolysis (43). The association between increased post-CBP fibrinolysis and blood loss (32) was confirmed by the results of numerous studies on the efficacy of antifibrinolytic treatment (16, 47, 52), so that antifibrinolytic therapy is now accepted standard treatment in cardiac surgery for avoiding excessive blood loss and the associated need for transfusion.

CPB: inflammation and coagulation

In the past few years more and more findings have been published which demonstrate a close interconnection of pro-inflammatory and procoagulant pathways of activation during CPB. As a presentation of the
complex pathophysiological relationships of different mediator systems would go far beyond the scope of this review, these important activation pathways will be described only briefly. Those wishing to read more detailed accounts are referred to other publications (19, 24, 68, 69, 89). The primary activation pathways comprise activation of leucocytes with liberation of pro-inflammatory mediators which stimulate tissue factor expression by monocytes (38) and the formation of thrombin (19, 24), as well as the stimulation of nuclear factor kappa B (NF-kB), during CPB, tissue factor activation occurs with subsequent liberation of thrombin (62). As a result, effective inhibition of NF-kB reduces procoagulant activation during CPB (62); a dose-dependent effect, resulting from heparin-induced liberation of tissue factor pathway inhibitor (TFPI), has been described (31, 44).

**Prophylaxis of blood loss and the need for transfusion**

**Antifibrinolytic therapy**

Given all the haemostatic changes during CPB, the following occur the entire time the patient is on pump, despite systemic anticoagulation:

- activation of plasma coagulation with consumption of coagulation factors,
- reactive fibrinolysis,
- reduced platelet aggregation caused by loss of glycoprotein receptors on the surface of platelets.

Together with factors particular to the individual patient and the surgery (area of wound surface) these processes form the pathophysiological basis for substantial blood loss after cardiac surgery. The prophylactic use of antifibrinolytic agents has been established and accepted for years in this field. Antifibrinolytic therapy is usually begun with administration of a bolus before CPB is commenced and continued for the duration or (depending on dosage) after the HLM has been disconnected.

The purpose of this early treatment is to inhibit coagulation activation due to surgical trauma and subsequent fibrinolysis. Aprotinin, tranexamic acid and e-aminocaproic acid are the antifibrinolytic drugs most frequently used in cardiac surgery. But different dosages of, in particular, aprotinin and tranexamic acid are used in German-speaking countries.

Aprotinin, which inhibits plasmin and kallikrein in particular, has proven to be effective in reducing drainage loss and the need for transfusion, especially in cardiac revision operations. Recent studies and meta-analyses have shown these effects also in primary cardiac surgery (52, 75), complex procedures of arterial revascularisation (79) and in patients on treatment with aspirin (66). This has led to the widespread use of aprotinin in cardiac surgery. In addition, in-vitro experiments demonstrated stabilisation of platelet function by inhibiting thrombin-induced activation of protease-activated receptors (PAR-1) (70) and weakening of the CPB-induced pro-inflammatory immune response (e.g. by inhibiting leucocyte elastase) (6).

While the efficacy of aprotinin is taken as proven, the safety profile of this drug has not been investigated adequately, especially regarding adverse renal effects (57). For this reason, further studies on the renal effects of aprotinin in cardiac surgery are urgently required. The incidence of myocardial infarction from acute postoperative occlusion of a coronary artery bypass graft is not significantly higher with aprotinin than with placebo (52).

Tranexamic acid is a synthetic antifibrinolytic agent that binds to the lysine binding site of plasminogen and plasmin and in this way inhibits fibrinolysis. There is no evidence that it influences activation of the plasma coagulation system (48) or platelet function. Clinical studies have found tranexamic acid to be effective in reducing blood loss (52), but aprotinin was superior to tranexamic acid in both the reduction of blood loss (52) and the need for transfusion (25). Aprotinin and tranexamic acid both reduced the incidence of re-operation and mortality after cardiac surgery: odds ratio (OR) 0.5, 95% CI 0.34–0.90 and OR 0.75, 95% CI 0.27–2.16, respectively (52). The safety profile of tranexamic acid was judged to be high, because there was no increased incidence of bypass occlusion or adverse renal effects compared with placebo (52, 57).

Aprotinin and tranexamic acid, both with established efficacy, are used in most cardiac centres as standard drug management in the prophylaxis of postoperative bleeding. However, the efficacy of antifibrinolytic agents in the treatment of postoperative bleeding requiring transfusion has to our knowledge not yet been demonstrated in controlled studies. Altogether there have been few publications of controlled studies on the treatment of postoperative bleeding, so that there is no accepted standard treatment at the present time. Doctors in cardiac units follow hospital-specific treatment algorithms and standards, which are often the result of years of experience, but in individual situations are not always based on scientific evidence.

The following forms of treatment are the most important ones available for bleeding after cardiac operations:

- **Drugs:**
  - protamine for neutralising any residual heparin effect
  - aprotinin/tranexamic acid for treating postoperative hyperfibrinolysis
  - desmopressin for liberating factor VIII and the von Willebrand factor from endothelium and for stabilising platelet function
  - recombinant factor VIIa for thrombin synthesis in bleeding (not as factor replacement)

- **Blood products:**
  - platelet concentrates for thrombocytopenia and CPB-induced platelet dysfunction,
  - fresh plasma for loss of coagulation factors,
  - coagulation factor concentrates for the selective replacement of lacking individual factors.

**rFVIIa, cell-based haemostasis**

The activated coagulation factor VII (rFVIIa), produced by gene technology (ep-tacog-alfa, NovoSeven®; NovoNordisk, Bagsvaerd, Denmark) was first successfully used preoperatively in 1988 in a patient with
haemophilia A and antibodies against factor VIII (35). Since 1996, rFVIIa has been used in Germany in the treatment of bleeding or in the prevention of bleeding before surgical or invasive procedures in patients with congenital haemophilia and inhibitors and patients with acquired haemophilia and inhibitors (51).

The model of cell-based haemostasis postulates (36) that, according to present knowledge, coagulation is initiated at the site of vascular damage by the formation of a complex with tissue factor (TF) (Fig. 2). Locally bound FV and FX are subsequently activated to generate a just-adequate amount of thrombin, which in turn activates platelets at the site of vascular damage. The propagation of coagulation takes place on the surface of the activated platelets. The supraphysiological plasma concentrations of rFVIIa achieved after intravenous administration make it possible for rFVIIa to bind directly to phospholipid structures on the surface of the activated platelets, renewing the direct activation of factor X. The thrombin generation so induced is quantitatively high (thrombin burst). It occurs while avoiding intermediate steps of haemostasis (including factors VII and IX that are lacking in haemophilia or the coagulation factors inhibited by antibodies in acquired haemophilia).

Thrombin, a procoagulant compound, acts as the key enzyme of coagulation via activation of other platelets and coagulation factors. In the presence of high concentrations of thrombin the rate of fibrin formation is increased, fibrin structure is firmied up via activation of fibrin-stabilising factor XIII, and resulting clots are protected from premature breakdown by the activation of a fibrin-inhibiting, thrombin-activating fibrinolyis inhibitor (TAFI) (5).

According to this model, uncontrolled systemic activation of plasma coagulation should be prevented: rFVIIa is proteolytically active only in a complex with TF and binds only to activated platelets which aggregate at the site of TF expression (vascular damage). An in-vitro investigation has confirmed that rFVIIa does not induce hypercoagulability in healthy people (30).

**Application in cardiac surgery**

The described localised action of rFVIIa on haemostasis and its efficacy in different congenital bleeding disorders (e.g. haemophilia A and B, with or without inhibitors, factor VII deficiency, thrombocytopenia, Glanzmann’s thrombasthenia) or acquired ones made the recombinant preparation also seem appropriate for controlling severe bleeding in patients without coagulation abnormalities. Severe bleeding requiring re-operation occurs in 3% to 5% of patients after cardiac surgery (20, 42, 63, 87). Morbidity and mortality rates are significantly increased in patients who bleed after cardiac operations. Effective and safe haemostasis will, therefore, improve prognosis.

In 2000, Al Dour et al. published the first case series on the use of rFVIIa in patients who had uncontrolled intra- or postoperative bleeding requiring transfusion after cardiac surgery but were refractory to treatment (1). In all these patients blood loss was significantly reduced after the single administration of 30 µg/kg body weight of rFVIIa. These workers did not describe any thromboembolic complications or adverse events. Since then there have been numerous publications of case reports and series describing the successful application of rFVIIa in cardiac surgery. These findings characterise the clinical importance of postoperative bleeding and also the need for effective and safe haemostatic therapy.

The comments below are based on a critical analysis of published reports on the use of rFVIIa in patients without coagulation disorders in

- paediatric cardiac surgery,
- targeted prophylaxis and treatment in adult cardiac surgery.

**rFVIIa in paediatric cardiac surgery**

There is one placebo-controlled study on the prophylactic use of rFVIIa in paediatric cardiac surgery. Moreover, a search of PubMed (key words: rFVIIa – paediatric cardiac surgery) found six case reports or series; one of these reported a case in which rFVIIa was used in gastrointestinal bleeding, unconnected to any cardiac surgery (84), so this report was not considered further. There were two additional publications that had not been listed in PubMed. Table 1 summarises the indications, dosage and thromboembolic complications listed in the case reports and series. This review presents and discusses the case reports of the therapeutic use of rFVIIa and the prospective and placebo controlled trial on the prophylactic use of rFVIIa.

Leibovitch et al. reported the first use of rFVIIa in paediatric cardiac surgery, in a child with acute diffuse pulmonary bleeding two days after cardiac surgery, which failed to be stopped with tranexamic acid, desmopressin (DDAVP), fresh frozen plasma (FFP), platelet concentrate (PC) and packed red blood cells (PRBC) (50). After four doses of rFVIIa (100 µg/kg body weight) at two, three and four hours the bleeding ceased. No thromboembolic complications
were noted during the hospital stay. The child was discharged after seven days.
Egan et al. reported on the use of rFVIIa in six children who had excessive bleeding in the wound or recurrent haemothorax (four of them with two episodes of refractory intraoperative bleeding of more than 10 ml/kg/hour for at least two hours postoperative), which could not be arrested by conventional treatment with protamine, aprotinin, FFP, PC, and PRBC or by cryoprecipitate (CP) and vitamin K (28). The children were given 180 µg/kg body weight rFVIIa. In five patients this dose was repeated after two hours. The bleeding ceased after the second dose at the latest so that no further transfusions were required. The authors did not report any thromboembolic complications and did not mention outcome.

In an open-label study, the efficacy of rFVIIa for bleeding after cardiac surgery with CPB was investigated. The criteria for re-thoracotomy had been met: FFP and PC were inadequate (71). The study comprised eight children with drainage loss of 60 to 600 ml/hour before the first administration of rFVIIa. According to the study protocol they were given one to four doses (30 µg/kg body weight or 60 µg/kg body weight if there was pre-existing coagulopathy or it was an emergency).

Blood loss was significantly reduced at latest after the second dose of rFVIIa and re-thoracotomy was avoided in seven of the eight children. Re-operation was necessary in one child because the blood loss increased again after the first dose and a further supply of the drug was not available. Thromboembolic complications or other adverse events were not observed. The outcome was not reported.

Tobias et al. investigated the haemostatic effects of rFVIIa as first-line treatment in children who had had open-heart surgery with CPB, as part of a medical developmental aid project in the Dominican Republic, which has no blood-bank facilities (83). The criterion for inclusion in the study was a blood loss of at least 24 ml/kg body weight/hour in the first three hours after the operation. Eight children were given a single dose of 90 µg/kg body weight. Three hours after administration of rFVIIa, the mean hourly blood loss had decreased from 5.8 ± 2.8 to 2.0 ± 1.3 ml/kg body weight (p = 0.002). In the control group, which had not received rFVIIa, the mean hourly blood loss was 1.6 ± 0.9 ml/kg body weight in the first three postoperative hours and 1.2 ± 0.6 ml/kg body weight in the second period of observation. They did not mention thromboembolic or any other complications, or the survival rate.

Yilmaz et al. (95) reported the prophylactic administration of rFVIIa in a child with Glanzmann’s thrombasthenia who had undergone surgical closure of a ventricular septal defect. A total of four doses of rFVIIa (90 µg/kg body weight) were administered – at the end of CPB and then every two hours. The total blood loss over four hours was 705 ml, replaced with whole blood. After the drains had been removed no further blood loss or other complication occurred. The child was discharged home on day 8 after the operation and no complications occurred in the three months after the operation.

In addition to the publications described, which were accessed from PubMed, there were two other reports on the use of rFVIIa in cardiac operations. Tokunaga et al. described its use in a child with FVII deficiency who had to undergo cardiac surgery with CPB (85). Two doses of rFVIIa were administered preoperatively (each 30 µg/kg body weight). Despite a third dose of rFVIIa after the CPB the child developed bleeding which required transfusion and the administration of FFP, PC and PRBC, but the bleeding stopped only after a fourth dose of rFVIIa. The FVII concentration was maintained at between 20% and 37% by continual infusion of FFP (20 ml/kg body weight daily). No thromboembolic complication or further bleeding was reported, and the child was discharged home.

Extracorporeal membrane oxygenation (ECMO) is a therapeutic option for patients who cannot be weaned from the HLM. Tendency towards profuse bleeding, accentuated by the necessary heparinisation, is a serious complication in such cases. Wittenstein et al. reported findings in four children who developed profuse refractory bleeding while on ECMO after cardiac operation (93). Despite re-operation and conventional haemostatic treatment [aprotinin, PRBC, FFP, platelet concentrates (PC), cryoprecipitate (CP) and vitamin K] the hourly blood loss amounted to a mean of 47 ml/kg body weight. After a single dose of rFVIIa (90–120 µg/kg body weight) blood loss was reduced to 8 ml/kg body weight (p <0.05). The amount of PRBC, PC and CP that had to be transfused was also significantly reduced (p <0.05), while the reduction in FFP did not achieve significance. Neither thromboembolism nor occlusion in the ECMO was observed, but the outcome was not reported.

Ekert et al. enrolled paediatric patients with congenital heart disease (CHD) in a placebo-controlled trial investigating the ef-

### Tab. 1 Results of the use of rFVIIa in paediatric cardiac surgery

<table>
<thead>
<tr>
<th>author</th>
<th>indication</th>
<th>dose rFVIIa (µg/kg body weight)</th>
<th>refractory bleeding massive transfusion</th>
<th>n</th>
<th>thromboembolic events</th>
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<tbody>
<tr>
<td>Egan et al. [28]</td>
<td>diffuse bleeding/repeat thoracotomy</td>
<td>4 × 100</td>
<td>yes</td>
<td>1</td>
<td>none</td>
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<tr>
<td>Leibovitch et al. [50]</td>
<td>diffuse pulmonary bleeding</td>
<td>2 × 180 (n = 5)</td>
<td>yes</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td>Pychynska-Pokorska et al. [71]</td>
<td>bleeding, requiring re-operation</td>
<td>1–4 × 30</td>
<td>yes</td>
<td>8</td>
<td>none</td>
</tr>
<tr>
<td>Tobias et al. [83]</td>
<td>blood loss &gt; 4 ml/kg bw/h for 3 hours</td>
<td>1 × 90</td>
<td>prophyaxis</td>
<td>8</td>
<td>none</td>
</tr>
<tr>
<td>Tokunaga et al. [85]</td>
<td>F VII deficiency</td>
<td>4 × 90</td>
<td>prophyaxis</td>
<td>1</td>
<td>none</td>
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<tr>
<td>Wittenstein et al. [93]</td>
<td>bleeding during ECMO</td>
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<td>none</td>
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<tr>
<td>Yilmaz et al. [95]</td>
<td>Glanzmann’s thrombasthenia</td>
<td>2 × 90–120</td>
<td>yes</td>
<td>4</td>
<td>none</td>
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</tbody>
</table>
The authors concluded that this pilot study, taking into account its inadequate statistical power, showed that rFVIIa reduces the requirement for transfusion after complex cardiac operations. As the costs of blood products in the control group (£10 000) were lower than for the study medications in the group receiving rFVIIa (£32 000), further studies with more patients are needed to prove that prophylactic administration of the drug to reduce blood loss and decrease the requirements for transfusion is cost-effective and medically reasonable.

The therapeutic use of rFVIIa for postoperative bleeding in cardiac surgery was investigated in two retrospective case-control studies. Karkouti et al. published a matched-pair analysis on the efficacy and safety of rFVIIa in cardiac surgery (40). They used rFVIIa to treat 51 patients who had sustained bleeding during and after cardiac operation; this could not be stopped despite antifibrinolytic treatment, FFP, CP and PC. The patients were given a dose of between 2.4 and 4.8 mg rFVIIa and kept under observation from the moment of admission to the intensive care until 24 hours after having been given rFVIIa.

For the patients thus treated was compared with that of patients in a cardiac surgical databank who had not been given rFVIIa. The patients in the control group were matched to the treatment group by means of the propensity score. This score consisted of independent risk factors for the likelihood of at least five units of packed red cells having to be transfused within 24 hours of the operation and was taken as the criterion for severe bleeding. Despite a favourable propensity score, the patients who received rFVIIa were in worse condition before its administration, because they had severe bleeding significantly more often (92% vs 60%, p = 0.0003), were more often re-operated for severe bleeding (60% vs 40%, p = 0.004), and had been given significantly more blood products (PRBC: 14 units vs 7 units, p = 0.001; FFP: 10 vs 6 units, p = 0.001; PC: 15 vs 5 units, p = 0.001; and CP: 10 vs 0 units, p = 0.0004). Compared with the hour preceding rFVIIa administration, blood loss fell by 100 ml on average (25th and 75th percentiles: 70 and 285 ml, p =
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The authors concluded that rFVIIa can be effective in stopping otherwise intracatable bleeding after cardiac operations. They did not find an increased rate of thromboembolic complications. It is unclear whether the higher rate of impaired renal function was causally related to the administration of rFVIIa. The 21 patients in this study who had CABB and were given rFVIIa did not have a higher rate of acute myocardial infarction. This could be relevant, because operation on blood vessels could produce the expression of tissue factor at the anastomosis and as a result the formation of a complex with rFVIIa, thus placing patients receiving rFVIIa at high risk.

In our own retrospective study, we assessed 24 patients who developed intratable bleeding after cardiac surgery and were treated with rFVIIa. All of them had been given PRBC, FFP, and PC; 22 patients had also been treated with aprotinin but unsuccessfully, as it had not adequately reduced the blood loss. Eleven had already been re-operated because of the bleeding; 19 patients had been given coagulation factor concentrates (prothrombin complex concentrate (PCC), fibrinogen, factor XIII and antithrombin). Each of these patients was matched with a patient from a cardiac surgery-anaesthetics databank who had not been given rFVIIa. Matching criteria were blood loss after admission to the intensive care unit, type of surgical intervention – single intervention (CABG or valve surgery) vs combined (CABG plus valve replacement or CABG plus resection of a ventricular aneurysm, etc.) – and the use of recombinant hirudin for anticoagulation while on the HLM. Other risk factors that can predispose to bleeding (e.g. endocarditis with septicemia, preoperative liver failure with reduced synthesis of coagulation factors, preoperative administration of platelet-aggregation inhibitors, cardiac re-operation, temporary postoperative implantation of an artificial heart and need for an emergency operation) were analysed separately in a second step.

After admission to the intensive care unit, a median time of 14 hours elapsed before rFVIIa was given. The study patients and controls were monitored during this time and for 24 hours after the drug had been given. The analysis of risk factors for bleeding did not reveal any significant difference between the two groups. However, the small number of patients means the possibility that the patients given rFVIIa were in a worse condition cannot be excluded, because there was a five-fold greater incidence of liver failure in this group. Analysis of blood loss and required transfusion showed a significant median reduction of these parameters in the rFVIIa group (1805 vs 1340 ml, p = 0.032; PRBC: 9.8 vs 4 units, p = 0.004; FFP: 8.6 vs 3.9 units, p = 0.017; and PC: 3.3 vs 1.6 units, p = 0.013). But comparison with the data of the control group indicates that there was no statistically significant difference (blood loss: 1340 ml vs 595 ml, p = 0.18; PRBC: 4 vs 2.6 units, p = 0.44; FFP: 3.9 vs 1.9 units, p = 0.06). On the other hand, there was a statistically significant reduction in the need for PC compared with the control group (p = 0.04).

According to clinical criteria (reduction in blood loss to <100 ml/hour and of the need for re-operation to achieve haemostasis) administration of rFVIIa was effective in 75% of patients, which confirms the results of published reports (72). Treatment was effective in 71% of patients in the control group. The re-thoracotomy rate (6 vs 7 patients, p = 0.67) and the need for coagulation factor concentrates after rFVIIa (6 vs 5 patients, p = 1.0) did not differ from the control group. Likewise the duration of stay in the intensive care unit and the hospital (14 vs 15 days, p = 0.96 and 57 vs 62.5 days, p = 0.90), as well as hospital and 6-month survival (8 patients in both groups, p = 1.0; 14 vs 10 patients, p = 0.55) did not differ significantly. Contrary to published results (67, 72), there were no thromboembolic complications in either the rFVIIa or the control group.

We conclude from these findings that the administration of rFVIIa does not increase the risk of thromboembolic complications but significantly reduces blood loss and the need for transfusion. However, treatment with rFVIIa was not superior to conventional methods, although this result may perhaps have been influenced by the non-standardised initial dose of rFVIIa (median 60 µg/kg body weight), which was relatively low or may not have been given at the optimal time. The methodological limitations and the inadequate statistical power of retrospective studies demand that the efficacy and safety of rFVIIa administration in the treatment of bleeding after cardiac operations be determined in a prospective, placebo-controlled trial.

Even in adult cardiac surgery, the therapeutic use of rFVIIa cannot as yet be based on placebo-controlled studies so that the recommendation grade is C (expert opinion). The two retrospective case-controlled studies support the hypothesis that the use of rFVIIa is also safe in high-risk patients. In addition to many case reports and case series, these studies document that rFVIIa can reduce blood loss and the need for transfusion when bleeding is refractory to treatment. But, as the results and study designs are not uniform, the efficacy and safety of rFVIIa in the treatment of intratable bleeding after cardiac surgery in adults must now be confirmed by controlled studies.

Conclusion

The prophylactic use of low dose rFVIIa in paediatric cardiac surgery has shown to be not effective. In adult cardiac surgery the prophylactic administration of rFVIIa was effective in the per protocol analysis, but not in the intention to treat analysis. These results need to be confirmed, since both studies investigated a small sample size.

The therapeutic rather than prophylactic use of rFVIIa has not been assessed in pros-
uctive and controlled trials so far. The case reports and series on the therapeutic use have in common that blood loss was without exception stopped or significantly reduced. These results are subject to publication bias and have to be interpreted with caution. According to the criteria of evidence based medicine these results reach at best the evidence level of expert opinion. Despite this, in paediatric and adult cardiac surgery rFVIIa may be considered a new therapeutic option in life threatening bleeding after cardiac surgery when conventional treatment has failed.

Conflict of interest
Dr Christian von Heymann declares that he has received consultancy fees from NovoNordisk and was an advisor on the development of trials by NovoNordisk.

References
37. Hongoo RH, Ley J, Dick SE et al. The effect of clopidogrel in combination with aspirin when...


51. Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten. 3. Aufl. Wissenschaftlicher Bei-

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