We strongly believe that this technique may occasionally be an attractive approach when pedicled ITA is not long enough to be used for sequential bypass grafting.

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Activated recombinant factor VII for refractory bleeding during extracorporeal membrane oxygenation

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Hemorrhagic complications are a major concern for patients undergoing extracorporeal membrane oxygenation (ECMO) after cardiac surgery. Transfusions of platelets, fresh-frozen plasma and cryoprecipitates are commonly used to improve hemostasis, sometimes in association with antifibrinolytic agents or protease inhibitors.

Activated recombinant factor VII (rFVIIa; Novoseven, Novo Nordisk, Denmark) was originally envisioned for the treatment of bleeding in patients with hemophilia in whom inhibiting antibodies to factor VIII developed. Most recently, rFVIIa has also been successfully used among critically ill patients with impaired thrombin generation and severe hemorrhage after major trauma, liver failure or transplantation, and overdose of oral anticoagulants. We report the case of a child undergoing ECMO with refractory thoracic bleeding, which was controlled by a single dose of rFVIIa (30 µg/kg).

Clinical Summary

A term, 3.2-kg male neonate had dextro-transposition of the great arteries diagnosed on the first day after birth. Prostaglandin E₁ infusion was started, and a Rashkind atrial septostomy was performed on the second day after birth. The arterial switch operation was postponed until the 12th day of life because of intracerebral hemorrhages with subdural, subarachnoidal, and intraventricular components (diameter 8 mm).

The platelet count and coagulogram were within normal limits. Results of screening studies for congenital coagulation factor deficiencies were also normal. Although the child remained free of symptoms and repeated cerebral computed tomography showed a decreased size of the hematoma, he received seizure prophylaxis with phenobarbital. After uneventful anesthetic induction, an arterial switch operation was performed, with ligation of the arterial duct and closure of the atrial septostomy under cardiopulmonary bypass (221 minutes) with moderate hypothermia (29°C) and aortic crossclamping (83 minutes). Aprotinin was administered during surgery, followed by protamine during weaning. Abnormal circumflex coronary artery originating from the right coronary artery was felt to be responsible for persistent left ventricular failure, leading to unsuccessful weaning from cardiopulmonary bypass and the requirement for venoarterial ECMO support with a Carmeda coated circuit (Medtronic, Minneapolis, Minn). During the first 2 days, the postoperative phase was characterized by severe bleeding from the chest tubes (10 mL/kg/h), despite massive transfusion of blood products (7.7 mL/kg/h packed red blood cells, 4.1 mL/kg/h platelets, and 2.6 mL/kg/h fresh-frozen plasma) and calcium chloride.

Surgical reexplorations at 24 and 36 hours after the operation failed to reveal any active surgical bleeding site. Because of persistent hemorrhage from the thoracic chest tubes, aminocaproic

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acid (100 mg/kg) was given intravenously, without any effect. Subsequently, rFVIIa (30 μ g/kg) was administered intravenously. The hematologic parameters before and after rFVIIa administration are shown in Table 1. On the following days, the patient's condition remained stable with a significant reduction in the amount of blood loss and without any apparent thrombotic event. On the fifth postoperative day, the child was weaned from ECMO. Despite maximal supportive therapy, he died of persistent left ventricular failure on the 11th postoperative day. Autopsy was refused by the parents.

Discussion

In this study, we noted that a single 30- μ g/kg dose of rFVIIa decreased persistent thoracic bleeding associated to cardiac ECMO. Similar findings have been reported by Tobias and colleagues,¹ who used 70 μ g/kg rFVIIa in a 4-month-old child who had postoperative hemorrhage after repair of an atrial septal defect. Recently, Leibovitch and associates² reported the successful uncomplicated use of 4 doses of rFVIIa (100 μ g/kg in each dose) in the treatment of pulmonary hemorrhage after cardiac surgery in a 10-week-old infant.

During ECMO, nonsurgical bleeding may result from heparin overdose or consumptive coagulopathy related to hemodilution, thrombocytopenia, decreased platelet function, deficiency of coagulation factors, and hyperfibrinolysis. In addition to conventional therapy with transfusion of blood components, antifibrinolytic agents may decrease the bleeding tendency at the site of tissue damage without significant risk of vascular thrombosis. When these conventional therapies fail, as in our case, rFVIIa becomes a potentially interesting alternative. This drug may bind tissue factor at sites of vascular damage, thereby leading to thrombin formation, a process involving factors IX and X. Alternatively rFVIIa may activate factor X on activated platelets independently of the presence of tissue factor.³⁻⁴

In addition, rFVIIa may play a significant role as a more general hemostatic agent beyond its indications in the treatment of hemophilia complicated by inhibiting antibodies. Experience with its use in cardiac surgery remains limited, mainly out of fear of thrombotic complications in patients with underlying atherosclerotic disease and areas of tissue factor expression in addition to their bleeding source on atherosclerotic plaques. The successful perioperative or postoperative use of rFVIIa has been reported in a limited number of adult cardiac surgery patients without any apparent thrombotic event. However, Bui and colleagues⁵ reported that the use of rFVIIa (90 μ g/kg) followed by administration of activated prothrombin complex in a patient undergoing ECMO resulted in massive thrombosis of the circuit and death.

TABLE 1. Hematologic parameters before and after recombinant activated factor VII (rFVIIa) during venoarterial extracorporeal membrane oxygenation

	Before	After
Chest tube bleeding* (mL/[kg · h])	9.1	3.5
Platelet count (cells/mm ³)	89000	125,000
Prothrombin time (s)†	15.3	10
International normalized ratio†	1.24	0.72
Activated partial thromboplastin time† (s)	135	114
Activated clotting time‡ (s)	164	148

*Represents the mean chest tube drainage during 4 hours before (41, 26, 28, 22 mL) and after (22, 4, 15, 5 mL) the use of rFVIIa (30 μ g/kg). Because rFVIIa was administered half an hour after the last measurement of thoracic tube drainage, which was calculated on an hourly basis, data during the first hour most likely underestimate the effect of the maneuver. †Represents the prothrombin time, international normalized ratio, and activated partial thromboplastin time before and 30 minutes after rFVIIa. The prothrombin time increased to 12.1 (international normalized ratio 0.92) 4 hours later.

‡Heparin was administered before (45 U/kg/h) and after (72 U/kg/h) rFVIIa.

In conclusion, we report here the first case of a child undergoing ECMO with refractory thoracic bleeding that was controlled with a single dose of rFVIIa. We emphasize that the risk-benefit ratio and the cost-effectiveness of rFVIIa in this population remain unclear. Further characterization of the mechanisms of action of rFVIIa may lead to well-designed, controlled studies.

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