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ABSTRACT

Recombinant activated factor VII (rFVIIa) has been approved for treatment of bleeding episodes in patients with haemophilia and in non-haemophilia patients with acquired antibodies against factor VIII or IX. The application of rFVIIa in non-approved settings, as in cardiac surgery, has not been established. It raises concerns about its safety. We used rFVIIa in a patient with excessive non-surgical bleeding on extracorporeal membrane oxygenation (ECMO), which was established for early graft failure after heart transplantation, following three months of biventricular assist device support. After rFVIIa administration, cardiac thrombosis developed and caused the patient’s death.
BACKGROUND

Although only approved for application in haemophilia patients, rFVIIa has also been used successfully in non-approved settings, such as non-surgical bleeding situations with dilution or consumptive coagulopathies in cardiac surgery (1, 2). Few reports exist about usage of rFVIIa in patients on ECMO after heart surgery. They are case reports and small series of paediatric or adolescent patients. We want to share our experience of a fatal rFVIIa application in an adult on ECMO, implanted for early graft failure, following heart transplantation after three months of biventricular assist device support.

CASE REPORT:

A 58-year-old male Caucasian, 1.86m for 85kg, with a history of mechanical mitral valve replacement in 1995 for severe mitral insufficiency was listed for heart transplantation in July 2007 because of rapidly progressive heart failure. After resuscitation in September 2007, emergency ECMO implantation was performed via cannulation of the femoral vessels, and the patient was put on the urgent waiting list. Since no suitable donor heart was found, the patient was switched 9 days later to a biventricular assist device (Berlin Heart Excor, Berlin, Germany). A mycotic infection at the former femoral ECMO cannulation site caused serious bleeding: an extraanatomic iliacofemoral bypass was implanted three weeks later, and the groin was treated with vacuum therapy. After increasing recovery on the regular ward, a suitable donor heart was found in January 2008, and BVAD explantation and heart transplantation was performed. Intraoperatively, a mycotic infection caused by C. albicans was detected underneath the sternum and subepicardially around the left pulmonary veins and pulmonary artery. After intense irrigation of the pericardium, the donor heart was implanted. Recipient aortic cross-clamp time was 73 min, and donor heart ischemia time was 189 min. Despite transfusion of 39 units of packed red blood cells, 54 units of fresh frozen plasma, 6 units of platelets, 6 g fibrinogen, 1800 units activated prothrombin complex concentrates [APCC]), massive diffuse, non-surgical, bleeding persisted, leading to severe haemodynamic instability. Due to rapid deterioration of right heart function, the patient was taken on ECMO, and transferred to the ICU with an open sternum. Activated clotting time (ACT) at this moment was 155 sec, platelet count $87 \times 10^3 / \mu l$, D-Dimers 0.68 µg/ml,
Fibrinogen was 2.3 g/l. The bleeding persisted, impairing the ECMO function. As salvage therapy, after consent of the local committee on off-label use of rFVIIa was obtained, a bolus of 7.2 mg rFVIIa (NovoSeven®, Novo Nordisk Inc., Bagsvaerd, Denmark) was given. At that moment, blood temperature was 36°C, Lactate was 1.8 mmol/l, blood pH was 7.38. Haemorrhage ceased. Within minutes, however, thrombosis of the left atrium developed (fig.1). After local urokinase lysis failed, embolectomy of the left atrium was performed. Since shortly thereafter left atrial thrombosis recurred, the situation was considered untreatable, and therapy was discontinued. Autopsy showed mycotic necrotizing pericarditis of the explanted heart. In the transplanted heart, multiple disseminated new myocardial necroses were found, together with fresh thrombi in large pulmonary veins and in intramyocardial vessels (fig.2).

DISCUSSION
In cardiac surgery, rFVIIa was used successfully in a variety of procedures, including coronary artery bypass surgery, valve replacement, aortic surgery, assist device implantation and heart transplantation (2, 3). In some cases, however, severe thrombotic events occurred, such as thrombosis of heart chambers, aorta and peripheral arteries, as well as myocardial and cerebral infarction (2-4). Few reports exist about usage of rFVIIa in patients with ECMO, comprising a total of 30 patients (5-9). All but one were neonates, children or adolescents, who received ECMO following cardiac surgery or for severe heart failure (5, 7-9). Eight of those 29 patients (28%) developed thrombotic complications such as clots in the oxygenator, ECMO circuit, left atrium, pericardium, or peripheral arteries, one of which was lethal (3,5%). The only adult patient who was given rFVIIa on ECMO received the device during lung-retransplantation (6). He developed clots in the heart and in the ECMO tubing after administration of APCC in addition to rFVIIa. Our patient is the first adult reported in the literature who received rFVIIa on ECMO following heart surgery. The intracardiac thrombosis in our patient might have been initiated by a thrombogenic interaction between rFVIIa and APCC, as reported in the lung transplant patient (6). The inguinal and mediastinal mycotic infection could also have promoted the hypercoagulable state (1).
As evident from our and other authors’ experience, the risk-benefit profile of rFVIIa in cardiac surgery, especially when artificial devices are present, remains unclear. There is need for randomized controlled trials to establish the safety and efficacy of rFVIIa use in such situations. Until further evidence exists, we advise strong caution for administration of rFVIIa in patients on ECMO, with concomitant APCC administration, or in presence of chronic infection.

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LITERATURE


FIGURE LEGENDS:

Fig.1: Large thrombus in the left atrium (LA) as seen in transesophageal echocardiography. MV: mitral valve, LV: left ventricle.

Fig.2: Focal acute necrosis of the myocardium of the transplanted heart. Arrow: Acute thrombus in a small intramyocardial artery.