We report the finding of a probable right atrial thrombus in a 33-yr-old male patient with severe head, chest, and abdominal trauma. Refractory coagulopathy and gross haemodynamic instability ensued, which was only partially controlled with massive blood product transfusion and high-dose inotropic support during laparotomy. Continuous transoesophageal echocardiography revealed a probable atrial thrombus partially occluding the right ventricular inflow tract, which appeared immediately after the patient received 100 μg kg⁻¹ of recombinant activated factor VII (rFVIIa) via a left internal jugular central line. This is the first report documenting an immediate temporal relationship between rFVIIa administration and a space-occupying lesion compatible with localized thrombosis, despite ongoing severe systemic coagulopathy. We review the clinical use of rFVIIa and discuss possible factors contributing to this event.

Uncontrolled massive haemorrhage is a leading cause of early in-hospital mortality and is frequently a combination of surgical and coagulopathic bleeding. Coagulopathy is correlated to the severity of trauma and is associated with an increased risk of mortality. Coagulopathic bleeding in this setting is often difficult to manage.

Recombinant activated factor VII (rFVIIa, eptacog alpha (activated) (bhk), NovoSeven®) is structurally similar to the naturally occurring human activated coagulation factor VII and is approved in Australia for the control of bleeding and surgical prophylaxis in haemophiliac patients with inhibitors to coagulation factors FVIII or FIX. Several reports¹⁻⁴ have suggested a life-saving role of rFVIIa in uncontrollable traumatic haemorrhage in non-haemophiliacs who have failed to respond to conventional therapy.

Balancing the pro-haemostatic properties of rFVIIa are concerns over the potential for thrombotic complications. We present the first case report of right atrial space-occupying lesion (SOL) consistent with thrombus detected immediately after administration of rFVIIa.

**Case report**

A 33-yr-old male was involved in a pedestrian road traffic accident. He sustained a closed head injury, blunt chest, and abdominal trauma. Initial observations were an unrecordable arterial blood pressure, a respiratory rate of 20, and a Glasgow Coma Scale (GCS) of 3. On arrival to our institution approximately 15 min later, his GCS improved to 9 (nil eye opening, inappropriate words, and localizing to pain) and arterial blood pressure to 150/60 mm Hg. His trachea was intubated in the Department of Emergency Medicine for progressive irritability in preparation for CT scanning. Shortly after, severe bradycardia (heart rate <10 beats min⁻¹) with an unrecordable arterial pressure ensued. The patient responded to 2 mg of adrenaline administered with cardiopulmonary resuscitation. Progressive abdominal distension was noted and a Focused Assessment with Sonography for Trauma (FAST) scan revealed free intraperitoneal fluid. Two litres of crystalloid and five units of packed red cells were commenced via an 8 French right femoral sheath. He was urgently transferred to the operating theatre for laparotomy without further investigation.

Bilateral upper limb 16 gauge cannulae, a left internal jugular triple lumen central venous line, and a left intercostal catheter were inserted. Continuous transoesophageal echocardiography (TOE) was instituted to confirm vigorous left ventricular function with reduced filling. In addition to ongoing blood and fluid resuscitation, mean...
arterial blood pressure was maintained at 40–60 mm Hg with adrenaline (1–2 mg boluses and infusions of 80 μg min⁻¹, total dose 21 mg), noradrenaline (infusions of 20 μg min⁻¹, total dose 6 mg), and vasopressin (10 unit boluses and infusions of 0.4 units min⁻¹, total dose 30 units). All pressors and inotropes were administered through the peripheral cannula and then transferred to the distal lumen of a left internal jugular central venous line once inserted.

Emergency laparotomy was performed revealing massive haemoperitoneum, multiple liver lacerations, portal venous injury, partial gallbladder avulsion, and a right perinephric retroperitoneal haematoma. A right nephrectomy was performed and prolonged attempts at exposure and definitive portal venous repair led to severe blood loss. Definitive portal venous repair was abandoned and several attempts to pack the four quadrants of the abdomen proved unsuccessful because of continued bleeding.

The patient was transfused 40 units of packed red cells, and despite aggressive attempts to correct coagulation with available fresh frozen plasma (16 units), cryoprecipitate (25 units), platelets (16 units), boluses and an infusion of calcium gluconate (total dose 9.5 g) and calcium chloride (total dose 5 g), active warming, sodium bicarbonate (total dose 50 mEq), and hyperventilation, haemorrhage continued.

In consultation with surgeons and a haematologist, the decision to administer rFVIIa 100 μg kg⁻¹ (9.6 mg) was made. Through the dedicated middle lumen of the left internal jugular central venous line, divided 4.8 mg boluses were administered, each over 3 min. Adrenaline, noradrenaline, vasopressin, and calcium were infused through the distal lumen and crystalloid through the proximal lumen. No other factor concentrates were coadministered in any of the three lumens. The tip of the central venous line was not visible in the right atrium on echocardiography. Before administration, the patient’s bladder temperature was 34.7°C, international normalized ratio (INR) 3.0, prothrombin time (PT) 34 s, activated partial thromboplastin time (aPPT) >150 s, fibrinogen 0.7 g litre⁻¹, and pH 6.9. There was no current platelet count at the time of rFVIIa infusion, the last recorded was 116×10⁹ litre⁻¹ more than 4 h previously. The patient’s arterial blood pressure was 60/45 mm Hg, despite an adrenaline infusion of 60 μg min⁻¹, noradrenaline infusion of 20 μg min⁻¹, and vasopressin infusion of 0.4 units min⁻¹.

After 3 h of continuous TOE monitoring, and within 2 min after the second 4.8 mg rFVIIa bolus, the TOE revealed the right atrium filling with echogenic material, partially occluding the right ventricular inflow (Fig. 1A). The TOE images were later independently reviewed by four TOE certified anaesthetists and a cardiologist, who agreed the echogenic material had characteristics most compatible with thrombus. Haemodynamics did not appear to deteriorate further (though remained critical), and there was no difference noted in the rate of bleeding.

Fragments were seen to embolize from the SOL, until the lesion was dispersed over the period of another 5 min.

Haemostasis could not be achieved, and despite 66 units of packed red cells and 21 litres of crystalloid, cardiovascular instability and bleeding continued. New bleeding from previously haemostatic puncture wounds was noted, with frank blood in the endotracheal tube and urethral catheter. The patient died shortly after in the intensive care unit.

Subsequent post-mortem did not find evidence of pulmonary embolism or right atrial thrombus, but did show multiple rib fractures, a right haemopneumothorax, multiple liver lacerations, and severe head injuries consisting of global subarachnoid haemorrhage, multiple cortical contusions, and pontine haemorrhage.

Discussion
rFVIIa is a synthetic activated clotting factor that enhances localized clot formation at the site of endothelial tissue factor (TF) exposure via both TF and non-TF (platelet)-dependent pathways.6 Therapeutic doses of factor VIIa produce plasma levels 1000 times that of normal.7 High plasma rFVIIa concentrations lead to faster and higher localized thrombin production, and in vitro analyses of clots produced in a thrombin-rich environment have
demonstrated a resistance to fibrinolysis. Because of the site-specific action, remote thrombosis is thought to be rare.

In conditions where there are high levels of TF expression, the thrombogenic potential of rFVIIa may be increased. Such conditions include disseminated intravascular coagulation, sepsicaemia, crush injury, and advanced atherosclerotic disease. TF is found in large quantities in the brain and traumatic brain injury models have found intravascular thrombosis even in mild and diffuse injuries. Cerebral sinus thrombosis has been reported in a patient with a mild head injury who received rFVIIa after femoral fracture fixation. Despite these concerns, several case reports suggest a role for rFVIIa in controlling coagulopathy associated with traumatic brain injury.

There is conflicting evidence regarding the risk of rFVIIa-associated thrombosis. Thromboembolism is rare in haemophilic patients, occurring in less than 0.05% of 480 000 administrations. Animal studies investigating the use of rFVIIa in haemorrhagic shock have not demonstrated any evidence of thrombotic complications. A double-blind, placebo-controlled human trial examining the use of rFVIIa in 277 trauma patients also did not demonstrate an increase in thromboembolism, although insufficient power and lower than expected rates of thromboembolism cast doubt on value of these findings.

Off-label use has a substantially higher incidence (estimated at 0.8–1.4% of thromboembolism, although some estimates are derived from a self-reported registry. Many rFVIIa trials are insufficiently powered to report reliably the true incidence of rarer adverse events, and observational self-reported adverse event registries can suffer from underreporting. Although the exact extent of underreporting is unknown, some estimate that 95% of adverse drug reactions remain unreported. Adverse events were associated with higher doses of rFVIIa, acidosis, and the treatment of haemorrhage rather than prevention. Case reports of deep vein thrombosis, truncus brachiocephalicus thrombosis, cerebral sinus thrombosis, portal vein thrombosis, arteriovenous fistula thrombosis, pulmonary embolism and renal artery thrombosis have implicated rFVIIa in clot formation. A direct link has been difficult to establish as the administration of rFVIIa was temporally remote from the diagnosis of thrombosis in patients with other factors potentially contributing to thrombus formation.

Israeli guidelines recommend normalization of patient temperature and correction of acidosis to a pH >7.2 before rFVIIa administration, but does not specify which methods of pH correction should be used. Attempts were made to raise the patient’s pH with sodium bicarbonate and hyperventilation before rFVIIa administration. Animal models of acidosis-induced coagulopathy were not immediately improved by bicarbonate pH neutralization. The observation of a probable atrial thrombus at a pH of 6.9 and temperature of 34.7°C is surprising, given that a decrease in pH from 7.4 to 7.0 reduces rFVIIa activity by 90% and FVIIa/TF complex activity by 60%, and a temperature of 33°C further decreases the activity of FVIIa/TF complex by 20%. The progressive fragmentation of the SOL and the lack of post-mortem confirmation of thromboembolism may have been a result of ongoing fibrinolysis. Although no laboratory measures of fibrinolysis were carried out, previously haemostatic i.v. cannulae sites, head and facial wounds started to haemorrhage soon after the dispersal of the SOL.

It is conceivable that rFVIIa interacted with other procoagulant agents. The patient received 16 units of fresh frozen plasma through peripheral i.v. cannulae and 25 units of cryoprecipitate through the same central venous line lumen as the subsequent rFVIIa. This central line lumen was then used to deliver 1 litre of normal saline before rFVIIa administration. The Australian prescribing information states that the risk of potential interaction between rFVIIa and coagulation concentrates is unknown, but warns against the simultaneous use with prothrombin concentrates.

A vasopressin bolus of 10 units was given 5 min before, and 0.4 units min−1 was infused during rFVIIa administration via a separate lumen in the same central venous line. Vasopressin stimulates the release of FVIII/von Willebrand factor (FVIII/vWF) and tissue plasminogen activator from the endothelium. Vasopressin is a ‘weak’ platelet agonist, with platelet aggregation occurring at vasopressin concentrations three to six orders of magnitude higher than physiological concentrations. Desmopressin, a predominantly V2 receptor agonist, has been shown to increase the expression of TF on the extracellular matrix, and in vitro enhance platelet adhesion to the extracellular matrix, but specific rFVIIa prothrombotic interactions with vasopressin or desmopressin infusions are unknown. Desmopressin in combination with rFVIIa has been used in a patient with Glanzmann’s thrombasthenia undergoing a dental extraction. The combination of rFVIIa with vasopressin has also been used successfully in a Jehovah’s Witness patient undergoing mitral valve replacement. Vasopressin and adrenaline in combination exert a synergistic effect on platelet activity.

Appropriate timing of rFVIIa administration is not known. rFVIIa was administered only after all surgical avenues where exhausted. Several reports have utilized rFVIIa successfully as a last resort. Animal studies suggest early administration may be more effective. Trauma.org propose rFVIIa should not be used too early, but neither should it be used only after ‘super-massive’ transfusions of 40–60 units. Therapy at between 8 and 20 red blood cell (RBC) infusions is recommended, based on expert opinion only.

Despite the many case reports of rFVIIa efficacy, this case demonstrates that rFVIIa is not a panacea for intractable haemorrhage. Several studies have highlighted that
the ‘last-ditch’ use rFVIIa does not alter mortality. The only randomized, placebo-controlled, double-blind rFVIIa trauma trial demonstrated a non-significant trend favouring survival for both penetrating and blunt injury. RBC concentrate requirement was significantly reduced by 2.6 units in patients with blunt trauma. The coagulopathic rFVIIa-treated subgroup consumed less blood products and had fewer incidences of multiorgan failure and acute respiratory distress syndrome.

Little information exists to indicate which patients may benefit from rFVIIa administration and in which patients its use will be futile. Several ‘determinants of futility’ have been reported. PT more than 17.6 s, Revised Trauma Score (RTS) less than 4.09, and lactate greater than 13 mg dl⁻¹ at the time of admission were all independent predictors of futile rFVIIa administration. Another analysis of the rFVIIa treated non-haemophilic patients, identified patients who had a high Sequential Organ Failure Assessment (SOFA) score and those who failed to respond to one adequate dose of rFVIIa as having a poor prognosis. This patient had an admission PT of 20 s, an RTS of 1.16, and a SOFA score of 17. These in combination suggest a low probability of success with rFVIIa, but should be used as a guide only as, in the authors’ experience, there are exceptions to these predictors.

Although we cannot be certain that the SOL was a thrombus, the serpiginous nature on echocardiography (Fig. 1n) is reportedly unique to migrating thromboemboli. The early observation of the SOL several minutes after the second dose of rFVIIa may be accounted for by the formation commencing some 6 min previously with the first dose of rFVIIa. This is within the observed time to clinical rFVIIa effect in animal and human series.

A plausible explanation of the appearance of the SOL is the low flow state, coupled with concomitant extremely high-localized adrenaline, vasopressin, and calcium concentrations acting to activate and aggregate platelets. Activated platelets under the influence of supraphysiologically rFVIIa and high levels of circulating TF may have produced a thrombin burst leading to thrombus formation in the superior vena cava or atrium.

Previous case reports of thromboembolism associated with rFVIIa use were in patients with high thromboembolic risk (multitrauma, head injury, perioperative, vasculopathy) where it was difficult directly to implicate rFVIIa as a causative agent. Although we cannot rule out a peripheral origin of the probable atrial thrombus, its appearance immediately after central venous administration of rFVIIa in the setting of severe systemic coagulopathy implicates rFVIIa as a causative agent. rFVIIa may be useful in life-threatening haemorrhage; however, this case report suggests a potential for thrombosis when used in states associated with high TF concentrations and platelet activation. Further studies are required to define the safety profile of this agent in massive haemorrhage.

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