

CRITICAL CARE

Case report

Fibrinolysis during anaphylaxis, and its spontaneous resolution, as demonstrated by thromboelastography

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Key points

- Anaphylaxis is associated with fibrinolysis.
- Fibrinolysis is not always associated with increased clinical bleeding. Its treatment may be unnecessary.
- TEG is a useful monitoring tool to detect fibrinolysis. It should be used with the developing clinical picture.

Summary. A large and ever-growing number of agents used in anaesthesia can precipitate acute anaphylactic reactions after their administration. Anaphylaxis is a sudden onset (or rapidly progressive), severe systemic allergic reaction, affecting multiple organ systems. The number of people who suffer severe systemic allergic reactions is increasing. The incidence is about 1–3 reactions per 10 000 population per annum, although anaphylaxis is not always recognized; therefore, certain UK studies may underestimate the incidence. In this case report, we present an episode of acute fibrinolysis associated with life-threatening anaphylaxis, demonstrated by thromboelastography (TEG) and resolving spontaneously. This is despite an added fibrinolytic insult in the form of cardiopulmonary bypass. There is a paucity of literature detailing fibrinolysis occurring during anaphylaxis, most likely due to the limited availability of TEG in the acute setting and the primary clinical focus of delivering life-saving interventions.

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In this case report, we present an episode of acute fibrinolysis associated with life-threatening anaphylaxis, demonstrated by thromboelastography (TEG) and resolving spontaneously. This is despite an added fibrinolytic insult in the form of cardiopulmonary bypass. There is a paucity of literature detailing fibrinolysis occurring during anaphylaxis,^{2,3} most likely due to the limited availability of TEG in the acute setting and the primary clinical focus being on delivering life-saving interventions.

Case report

A 71-yr-old male presented for elective coronary artery bypass grafting and mitral valve repair. He had a past medical history of inferior myocardial infarction in 1997, which was complicated by early re-infarction. He

re-presented in 2003 with worsening symptoms of angina and underwent a percutaneous coronary intervention to the proximal right coronary artery. At the time of his operation, his angina was Canadian Cardiovascular Society score II (slight limitation of ordinary activity). He also had a history of controlled hypertension, hypercholesterolaemia, and peripheral vascular disease, with intermittent claudication of the legs. His regular medications on admission were lisinopril, furosemide, felodipine, atorvastatin, nicorandil, isosorbide mononitrate, bisoprolol, aspirin 75 mg (stopped 1 week before surgery) and glyceryl trinitrate spray (as required). He declared that he had no known drug allergies. A recent episode of cellulitis to both legs, thought to be secondary to peripheral vascular disease and treated with penicillins, had delayed the patient's cardiac surgery. Pre-operative blood tests were all within normal limits.

The patient received premedication of temazepam, ranitidine, and metoclopramide. A fluid preload of gelofusine was administered while anaesthesia was induced with fentanyl, propofol, and rocuronium. Anaesthesia was maintained with sevoflurane in oxygen 50%. A quadruple lumen central venous cannula and a Swan-Ganz introducer sheath were inserted in the right internal jugular vein. A small, initial dose of co-amoxiclav 180 mg was given and almost

immediately after this the systolic arterial pressure decreased precipitously to 50 mm Hg. This was unresponsive to metaraminol boluses. Bronchospasm was detected by an increase in peak airway pressure. Anaphylaxis was diagnosed, the $F_{I_{O_2}}$ was increased to 1.0, and compound sodium lactate was administered rapidly. I.V. epinephrine boluses of 50–100 μg administered every minute rapidly corrected the arterial pressure and bronchospasm. After a brief period of cardiovascular stability lasting 3 min, the patient went into ventricular fibrillation. A precordial thump was administered, and cardiopulmonary resuscitation (CPR) was commenced in accordance with Advanced Life Support guidelines. A biphasic shock of 150 J was administered via the defibrillator, and CPR was continued. A 1 mg bolus of epinephrine was given i.v.

After the first cycle of CPR was completed, a rhythm check revealed that there was a return of spontaneous circulation. Secondary treatment of the anaphylaxis was initiated with chlorphenamine 10 mg i.v. and hydrocortisone 200 mg i.v. A blood sample was obtained for serum tryptase. It was decided to continue surgery as the risks of returning the patient to the intensive care unit without revascularization were prohibitively high. Once in the operating theatre, an arterial blood gas, blood for activated clotting time (ACT), and blood for TEG were obtained. The first ACT was 143 s. At this point, the patient was requiring inotropic support in the form of dopamine at 3 $\mu\text{g kg}^{-1} \text{ min}^{-1}$. An intra-aortic balloon pump was inserted via his right common femoral artery to help promote haemodynamic stability. Anaesthesia was maintained by intermittent positive pressure ventilation with oxygen 50%, isoflurane 0.65%, propofol 5 mg $\text{kg}^{-1} \text{ h}^{-1}$, and alfentanil 0.5 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ infusions.

The results of the baseline TEG revealed fibrinolysis (Fig. 1). Despite this result, the patient was not clinically coagulopathic and the surgical field remained dry. A clinical decision was made not to treat the fibrinolysis with any anti-fibrinolytic agents. Surgery proceeded uneventfully.

After separation from cardiopulmonary bypass, heparin anti-coagulation was reversed with protamine. Ten minutes after protamine administration, a repeat blood sample was drawn for TEG. No clotting products or anti-fibrinolytics were used during the case. The TEG had normalized completely (Fig. 2).

Postoperative recovery was uneventful. The initial tryptase result came back at 126 $\mu\text{g litre}^{-1}$, the 3 h tryptase at 22.9 $\mu\text{g litre}^{-1}$, and the 24 h result at 8.3 $\mu\text{g litre}^{-1}$, suggesting that an anaphylactic or anaphylactoid reaction had taken place (normal value $<10 \mu\text{g litre}^{-1}$). At the allergy clinic 4 months later, skin prick testing revealed a positive result to amoxicillin.

Discussion

The coagulopathic effects of anaphylaxis are intimately linked to the haematological process of fibrinolysis. The mast cell plays an integral role in anaphylaxis, and this is associated with fibrinolysis. The anaphylactic reaction comprises Ig-E mediated mast cell degranulation and subsequent release of vasoactive mediators (histamine, serotonin, tryptase, and heparin).⁴ It is the release of tryptase from mast cells that induces fibrinolysis and this may result in a profound coagulopathy.

The release of tryptase from mast cells induces fibrinolysis by the following mechanisms:

- Degradation of procoagulant proteins, preventing deposition of fibrin.⁵

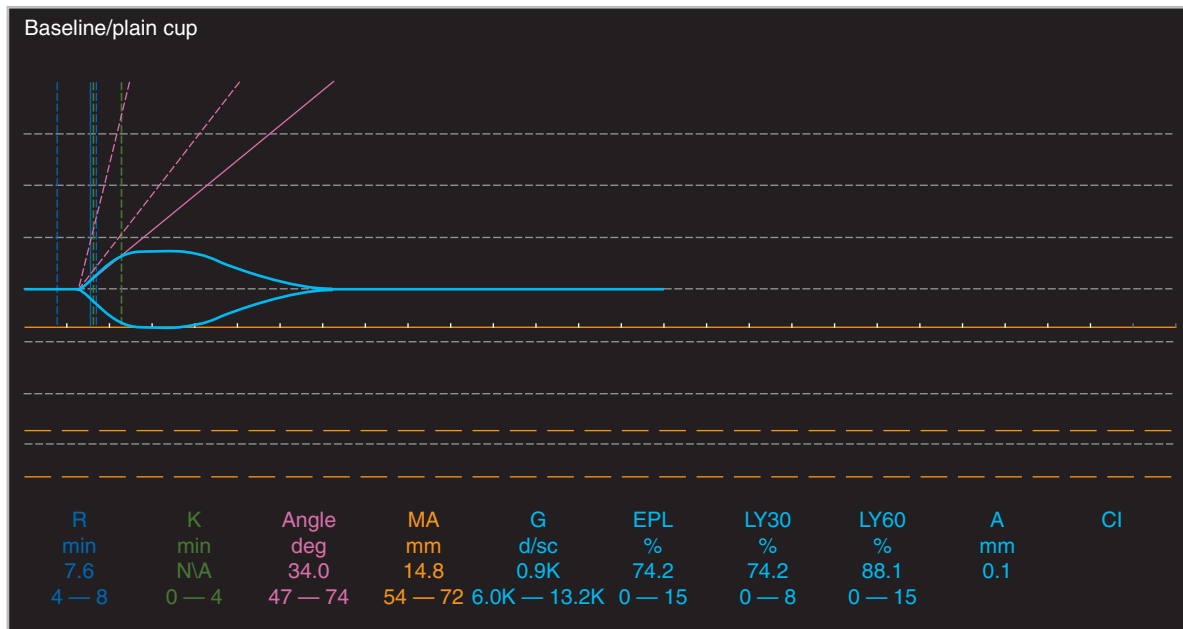


Fig 1 First TEG 20 min after the anaphylaxis incident, demonstrating primary fibrinolysis.

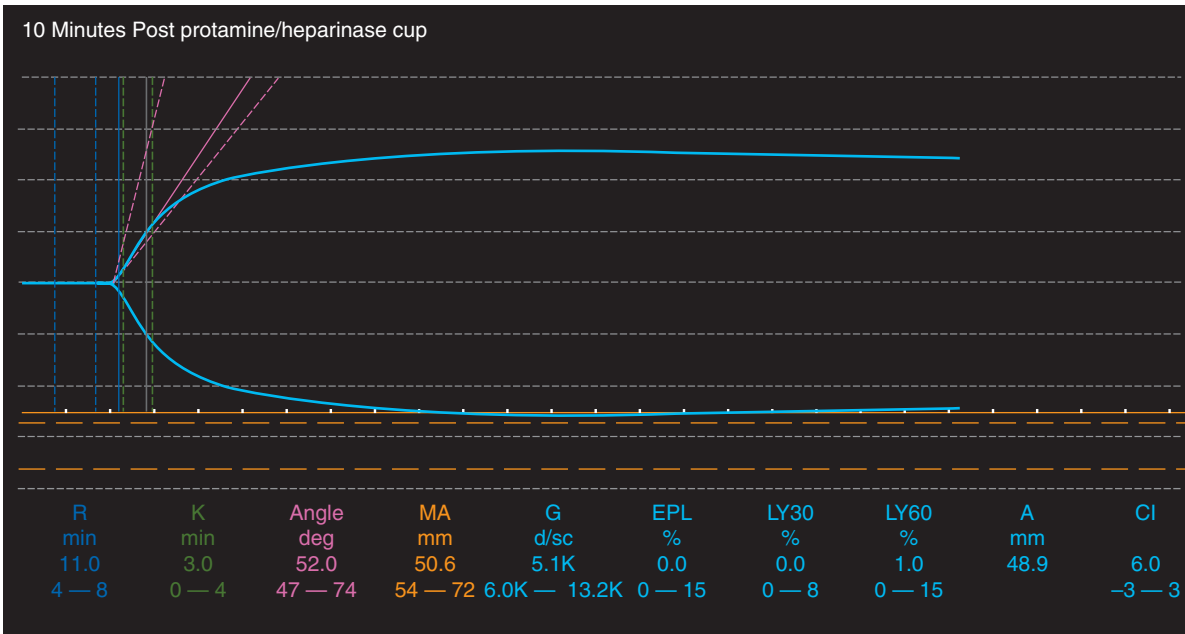


Fig 2 The same patient’s TEG after cardiopulmonary bypass and protamine administration, 4 h later.

Table 1 The grading of severity of anaphylactic reactions

Grade 1	Only have cutaneous and upper respiratory tract findings, such as - Generalized skin lesions - Pruritus - Rhinitis/conjunctivitis - Urticaria - Local oedema - Angio-oedema without any systemic symptoms or signs or evidence of other organ involvement
Grade 2	Mild to moderate anaphylaxis (grade 2) has evidence of grade 1 anaphylaxis and additional respiratory, cardiovascular, gastrointestinal, or neurological features, including - Shortness of breath or dyspnoea - Wheeze - Hoarseness - Nausea or vomiting with associated physical findings such as bronchospasm, but with systolic arterial pressure >90 mm Hg, ventilatory frequency more than 25 min ⁻¹ , and a normal Glasgow Coma Scale score
Grade 3	Severe anaphylaxis (grade 3) present with the findings listed for grade 2 and potentially life-threatening symptoms or signs. These include one or more of the following: - Loss of consciousness, syncope, dizziness, or lightheadedness at any time - Systolic arterial pressure <90 mm Hg - Glasgow Coma Scale score <15 (related to cardiovascular system collapse and/or neurological dysfunction from hypoperfusion, hypoxia)
Grade 4	Grade 4 anaphylaxis presents with the findings of grade 3 and subsequent cardiorespiratory arrest

- Cleavage of high molecular weight proteins (fibrinogen), slowing the process of coagulation by reducing the activation of factor XII.⁶
- Activation of urokinase, accelerating fibrinolysis.⁷

There is little evidence that heparin released from mast cells has an anticoagulant effect *in vivo*.⁶ This precludes the effect of protamine administration in normalization of our patient’s TEG.

Although fibrinolysis has been documented with anaphylaxis, the exact incidence and clinical significance of its occurrence is unknown. The only previous medical literature found regarding fibrinolysis in anaphylaxis details four case reports² of grade 3 anaphylaxis (Table 1), where the fibrinolysis was treated by varying doses of tranexamic acid (200 mg to 1 g) and fresh-frozen plasma (FFP). Interestingly, only one of the patients demonstrated evidence of clinically significant coagulopathy (oozing from the cut surface of the liver). The varying doses of tranexamic acid administered² raises questions about the efficacy of treatment, as complete resolution was documented in all cases and cannot definitely be ascribed to the effects of drug or FFP administration. Tranexamic acid and FFP are not benign agents with respect to their side-effect profiles.

Our case report (grade 4 anaphylaxis) demonstrates apparent spontaneous resolution of fibrinolysis without the administration of FFP or anti-fibrinolytics, despite the presence of another potential fibrinolytic insult (cardiopulmonary bypass). This raises some interesting areas for discussion. It may suggest that the fibrinolysis associated with anaphylaxis is a self-limiting process. Whether fibrinolysis occurs in grade 1 or 2 reactions is unknown and is a question for future research, to help determine its clinical significance. It is our assertion that FFP or anti-fibrinolytic agents should only be administered if clinically indicated (e.g. excessive oozing in the surgical field), not solely on the basis of a TEG result. The optimal dose of anti-fibrinolytics or clotting factors remains to be determined.

Although TEG is a useful point of care haemostatic measurement device, we accept that it is not universally available. It was only performed in our patient as part of this procedure in our institution (as in the other case reports).² The limited availability of TEG combined with the

primary clinical focus of delivering life-saving interventions during anaphylaxis may account for the lack of TEGs capturing this phenomenon.

While recognizing that our findings are limited to the observation of a single case report, they do nonetheless provide interesting areas for discussion and potential future research. Empirical treatment of anaphylactic coagulopathy with FFP or tranexamic acid may be an unnecessary intervention. TEG, if readily available, is a useful monitoring tool, but should be used in conjunction with the developing clinical picture, to guide any administration of anti-fibrinolytic drugs or FFP.

Conflict of interest

None declared.

References

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