Fibrinolysis

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Case Vignette

A 62-year-old male patient is referred to a cardiac program because of progressive dyspnea. The patient presents with severe aortic valve insufficiency in the context of bicuspid aortic valve and calcified cusps due to an ascending aorta and aortic root aneurysms. The patient was admitted for an elective Bentall operation. After cardiopulmonary bypass, the patient presented severe bleeding requiring the administration of multiple units of allogenic red blood cells, plasma, and platelets. Two hours later, the patient is still bleeding and thromboelastometry shows severe fibrinolytic activation (Fig. 12.1a). Because no antifibrinolytic agents were used, 1 g of tranexamic acid and 50 mg/kg of fibrinogen concentrate were administered. After 10 min, the thromboelastometry tracing is normal (Fig. 12.1b) and the bleeding slowly decreases. The patient is transferred to the cardiac intensive care unit 45 min later.

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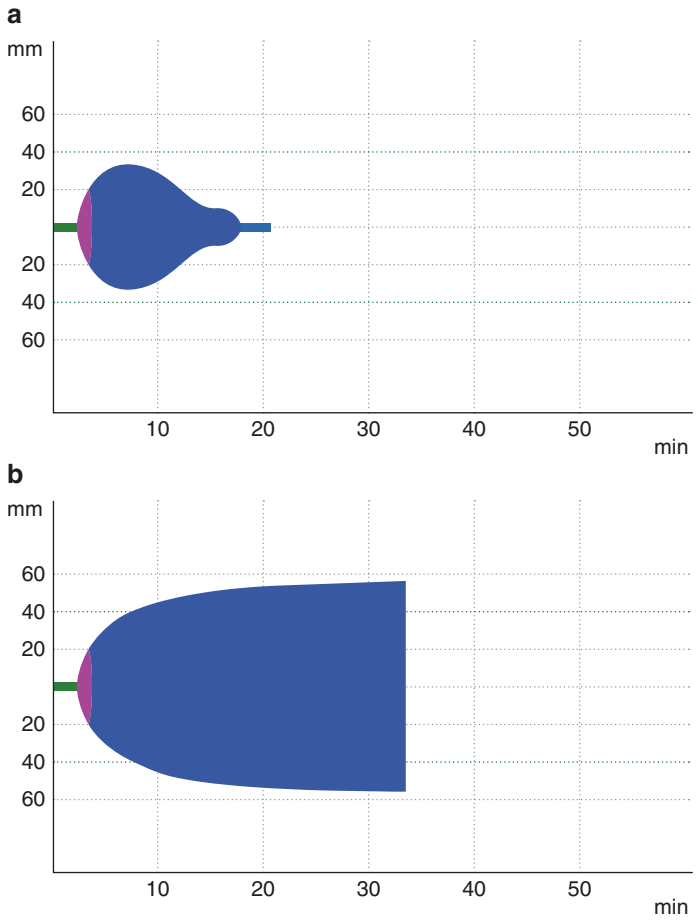

Fig. 12.1 Rotational thromboelastometry (ROTEM™) of a patient with severe fibrinolytic activation (**a**) and restoration of clot formation after administration of antifibrinolytic agents and fibrinogen (**b**)

Why Is It Important?

Perioperative bleeding is one of the most common complications of cardiac surgery. Patients undergoing cardiac surgery are sometimes exposed to large volumes of allogenic blood products and/or concentrates of coagulation factors. Although the requirement for blood transfusion is correlated to the severity of bleeding, both transfusion, bleeding, and even more the association of both have been shown to increase the incidence of postoperative complications and mortality [1]. The pathophysiology of the coagulopathy observed in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) is complex and multifactorial, and can be summarized as follows:

1. Hemodilution coagulopathy due to CPB prime, cardioplegia, and administration of fluids in the perioperative period
2. Contact activation (activation of factor X and thrombin generation) due to tissue injury, tissue factor production, and activation of fibrinolytic pathways, and
3. Consumption coagulopathy due to thrombin, plasmin, and inflammation mediated processes.

All of these factors can generate a vicious circle leading to coagulopathy and systemic inflammatory response [2]. The activation of the fibrinolytic pathway plays an important role in the coagulopathy observed during and after cardiac surgery. The fibrinolytic system begins when plasminogen is cleaved to plasmin and is important because it limits thrombus growth. During cardiac surgery, large amount of thrombin is generated which will lead to the polymerization of fibrinogen. Thrombin also causes a conformational change such that FXIII, (synonymous: plasminogen inhibitor), and tissue-type plasminogen activator (t-PA) become attached to fibrin. Fibrin stimulates t-PA synthesis by endothelial cells and urokinase plasminogen activator (u-PA) synthesis by monocytes, macrophages, and fibroblasts. Both t-PA and u-PA activate plasminogen. Plasminogen can also be activated by FXIIa formed during the contact phase of coagulation. Plasmin is an endopeptidase that cleaves both fibrinogen and fibrin, disrupting them into fibrin degradation products without clotting ability. Plasmin also interacts with the inflammatory system stimulating the complement system and kallikrein. Plasminogen activator inhibitor 1 (PAI-1) is released after t-PA and u-PA as a natural endogenous inhibitor of fibrinolysis (Fig. 12.2).

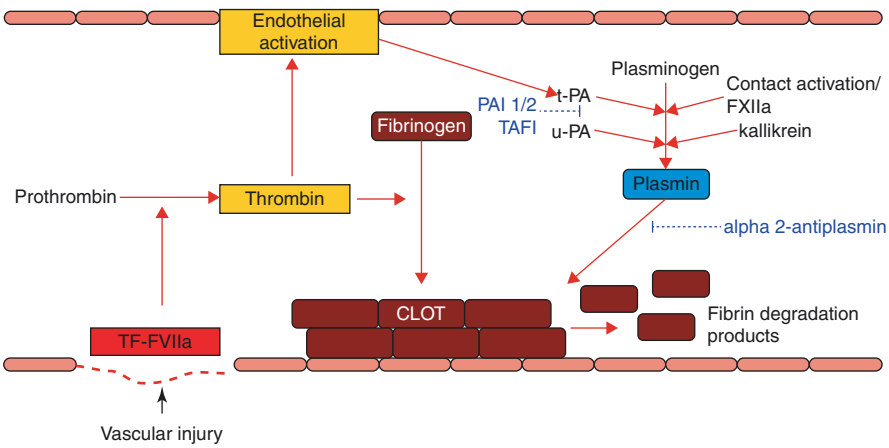

Fig. 12.2 Simplified representation of fibrinolytic activation. *t-PA* tissue plasminogen activator, *u-PA* urokinase-type plasminogen activator, *FXIIa* activated factor XII, *PAI 1/2* plasminogen activator inhibitor type 1 and 2, *TAFI* thrombin activatable fibrinolysis inhibitor

Activation of fibrinolysis at CPB initiation is mainly limited to FXIIa-induced activation related to the contact of the patient's blood with the non-endothelial CPB surface. Fibrinolysis then becomes activated by the release of t-PA from the vascular walls. Overall, cardiopulmonary bypass results in an increase in t-PA, D-dimers, and t-PA–PAI-1 complexes and a decrease in PAI-1 levels, indicating an activation of the fibrinolytic pathway and the consumption of its natural inhibitors. Thrombin and fibrin are known to be important activators of the fibrinolytic pathway. The degree of fibrinolytic activation is significantly correlated to the degree of thrombin generation, suggesting a strong correlation between activation of the coagulation and fibrinolytic pathways. In addition to thrombin, inflammatory markers such as cytokines and endotoxins are also able to promote the activation of plasminogen and its inhibitors. Because both plasmin and t-PA are known to impair platelet function, fibrinolytic activation is also associated with impaired platelet function during and after CPB.

Overall, fibrinolysis can be considered a protective physiologic response that appropriately limits clot formation. However, after major tissue damage and activation of CPB-induced coagulopathy, inhibiting fibrinolysis may potentially limit other responses that contribute to bleeding. Indeed, activation of the coagulation and fibrinolytic systems will lead to a vicious circle promoting bleeding and inhibiting the ability to form stable clot. Even though it would be extremely challenging to study the relationship between the sole activation of the fibrinolytic system and the severity of the bleeding in patients undergoing cardiac surgery, a strong correlation between biomarkers of fibrinolysis and the magnitude of postoperative bleeding has been reported.

The purpose of this chapter is to illustrate the importance of the fibrinolytic system in CPB-induced coagulopathy and bleeding, and to give an overview of agents capable of inhibiting fibrinolysis that can be administered prophylactically to avoid initiation of the fibrinolytic activation [3, 4].

Description of Antifibrinolytic Agents

Antifibrinolytic agents include aprotinin and the lysine analogs (ε-aminocaproic acid [EACA] and tranexamic acid [TXA]). Aprotinin is a broad-spectrum protease inhibitor, isolated from bovine lung and structurally similar to tissue factor pathway inhibitor, that reversibly complexes with the active serine residue in various proteases in plasma (e.g., trypsin, kallikrein, plasmin, and elastase). Aprotinin offers the most complete and potent fibrinolytic inhibition. Apart from these direct effects on the plasmatic coagulation system, aprotinin also inhibits the protease-activated receptor 1 thrombin receptor involved in both coagulation and inflammation. This action has been identified as a possible mechanism for stroke reduction after aprotinin administration in patients undergoing cardiac surgery.

Lysine analogs, TXA and EACA, are the most extensively used antifibrinolytic agents. As discussed above, activation of plasminogen by endogenous plasminogen activators results in plasmin, which causes degradation of fibrin. Binding of

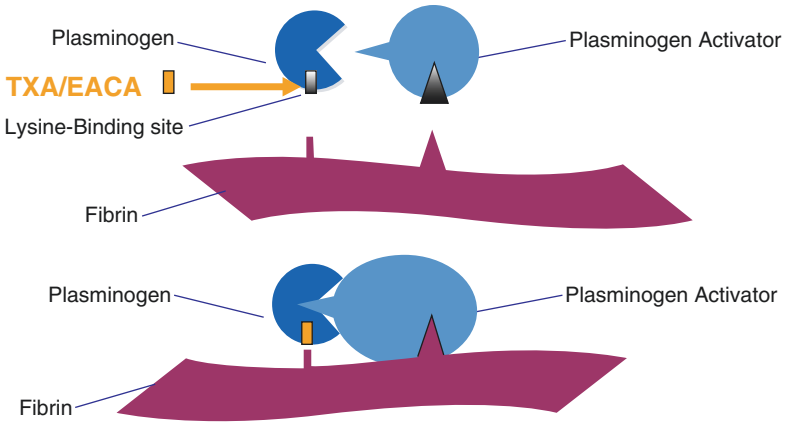

Fig. 12.3 Mode of action of lysine analogs. *TXA* tranexamic acid, *EACA* ε-aminocaproic acid

plasminogen to fibrin makes this process more efficient and occurs through lysine residues in fibrin that bind to lysine-binding sites on plasminogen. In the presence of lysine analogs, these lysine-binding sites are occupied, resulting in an inhibition of fibrin binding to plasminogen and impairment of endogenous fibrinolysis (Fig. 12.3) [5]. Because plasmin generation after tissue injury can induce many other responses, including thrombin generation, complement activation, and activation of monocytes, neutrophils, and platelets, attenuation of these pathophysiologic responses with lysine analogs might provide additional mechanisms to restore hemostatic balance and control of plasmin generation and fibrinolysis [6].

Efficacy of Antifibrinolytic Agents

The efficacy of prophylactic administration of antifibrinolytic agents in patients undergoing cardiac surgery has been extensively studied and discussed. After the publication of the first study in 1987, the efficacy of aprotinin to reduce the requirements for transfusion of red blood cells, platelets, and plasma has been reported in more than 70 studies performed in patients undergoing cardiac surgical procedures of various complexity. Randomized studies of TXA or EACA were much less numerous than trials of aprotinin. Until 2007, aprotinin was the most frequently used agent. In 2007, the efficacy of aprotinin and other lysine analogs was summarized in a Cochrane systematic review and meta-analysis [7]. When compared to a placebo, both aprotinin (77 studies), TXA (29 studies), and EACA (10 studies) significantly reduced the exposure to allogenic blood products (see Table 12.1). The effect of aprotinin and TXA on exposure to allogenic blood product transfusion was only assessed in 10 studies for a total of 1968 patients. Even though a trend in favor of aprotinin was observed, no statistical difference was reported between the two drugs. No difference in terms of adverse events was shown when antifibrinolytic agents were compared to a placebo or to each other. However, it is important to note

Table 12.1 Overview of comparative studies on antifibrinolytic agents in cardiac surgery with blood transfusion as primary endpoint [7]

	Studies	Patients	Risk ratio	95% CI
Aprotinin vs. control	77	8837	0.66	0.61–0.72
TXA vs. control	29	2488	0.69	0.60–0.79
EACA vs. control	10	596	0.65	0.47–0.91
Aprotinin vs. TXA	14	1968	0.85	0.66–1.09

TXA tranexamic acid, *EACA* ε-aminocaproic acid, *CI* confidence interval

that none of the studies published at that time were designed to adequately assess the safety of the drugs.

Safety Concerns of Aprotinin

In 2006, the first study raising safety concerns associated with the administration of aprotinin was published in the New England of Medicine [8]. In this observational analysis of 4374 patients undergoing cardiac surgery and after propensity analysis, the authors found that the use of aprotinin was associated with a significant increase in the risk of renal failure requiring dialysis (5%) when compared to EACA (1%) or TXA (1%). Similarly, the use of aprotinin was associated with an increase in the risk of myocardial infarction or heart failure as well as the risk of stroke or encephalopathy. Neither EACA nor TXA was associated with an increased risk of renal, cardiac, or cerebral events. Around the same time, Karkouti et al. published the results of a propensity analysis comparing aprotinin and TXA in high-transfusion-risk cardiac surgery [9]. Aprotinin and TXA showed similar hemostatic effectiveness in the study population. However, their results also suggested an association between the use of aprotinin and an increased incidence of renal dysfunction. In 2007, the results of the *B*lood conservation using *A*ntifibrinolytics in a *R*andomized *T*rial (BART) study [10], a prospective study performed in high-risk patients undergoing cardiac surgery, reported an increased mortality associated with aprotinin (6% 30-day mortality for aprotinin) compared with lysine analogs (3.9% for TXA and 4% for EACA), which was followed by a Food and Drug Administration (FDA) warning (Fig. 12.4).

In November 2007, following requests of German health authorities and the FDA, Bayer Healthcare (Leverkusen, Germany) announced the withdrawal of aprotinin from the market. In the following years, an intense, sometimes emotional, debate regarding the validity of the reported data and the safety profile of aprotinin ensued. The safety of aprotinin was reevaluated in several retrospective studies with conflicting results, but the overall impression is that the risk of adverse events is essentially observed in a subset of the cardiac population when aprotinin was administered and that the drug remains beneficial when used in patients undergoing procedures with high bleeding risk. In September 2011 Health Canada and in February 2012 the EMA lifted the suspension of aprotinin from the market. Aprotinin should only be given during the primary coronary artery bypass grafting

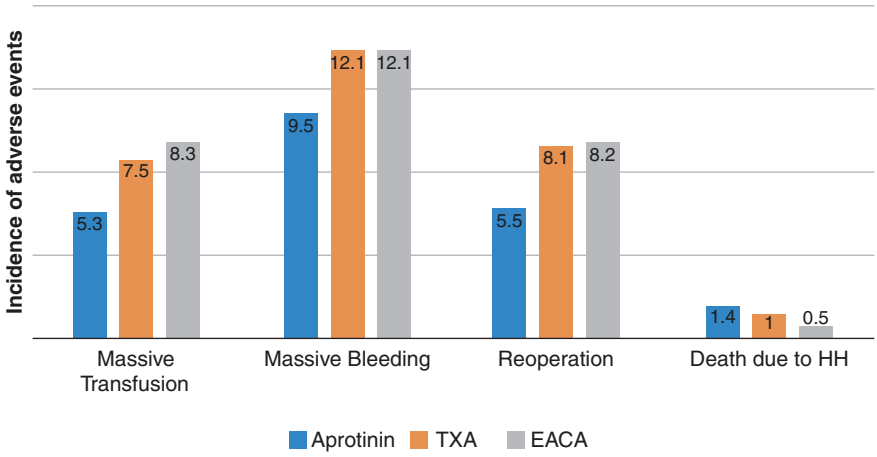

Fig. 12.4 Incidence of adverse events reported in the BART study. *TXA* tranexamic acid, *EACA* ε-aminocaproic acid, *HH* hemorrhage

surgery and should be avoided in patients with pre-operative renal dysfunction due to increased risks of postoperative renal failure and requirement for renal replacement therapy.

Despite this decision, scientific societies have mixed feelings regarding the use of aprotinin in cardiac surgery. As an example, the European Society of Anaesthesiology published the conclusion of a task force created to comment on the use of aprotinin in cardiac surgery [11]. The members argued that the approved indication (isolated CABG) is not really considered high risk and that aprotinin should only be used after careful consideration of the risk-to-benefit ratio, and after alternative treatments (e.g., lysine analogs) have been considered.

Safety Concerns of Tranexamic Acid

The safety of TXA has also been recently assessed in a trial with a 2-by-2 factorial design, where patients undergoing CABG surgery were randomly assigned to receive aspirin or placebo and tranexamic acid or placebo [12]. TXA was associated with a lower risk of bleeding than placebo was, without a higher risk of death or thrombotic complications within 30 days after surgery. However, TXA was associated with a higher risk of postoperative seizures. The risk of clinical seizures associated with the administration of high dose TXA has been highlighted in a few retrospective studies [13]. Although the underlying mechanisms are not fully elucidated, Kratzer et al. suggested that TXA enhances neuronal excitation by antagonizing inhibitory γ-aminobutyric acid (GABA) neurotransmission [14]. In another study it was shown that TXA inhibits neural glycine receptors, whereas inhibition of the inhibiting neurotransmitter glycine is an established cause of seizures [15]. Viewing the similarities in the chemical structures of TXA, GABA, and glycine, it

is conceivable that an interaction of TXA with both GABA and glycine receptors contributes to the increase in clinical seizures. Interestingly, the TXA peak concentration observed in the cerebral spinal fluid was reached approximately 5 hours after the plasma peak concentration. These pharmacokinetic properties might explain the delay reported between TXA administration and the development of clinical seizures after cardiac surgery. Although biochemical mechanisms may well explain the association between TXA and seizures, the special population of cardiac surgical patients and particularly the condition of CPB might also have a large impact on this observation. Understanding pharmacology and pharmacokinetics is crucial.

A recent study measured plasma TXA concentrations in cardiac surgical patients with chronic renal dysfunction for pharmacokinetic modelling and dose adjustment recommendations [16]. This study reported that plasma TXA levels were elevated in proportion to the severity of the renal dysfunction and the reduction in renal clearance. The authors have recommended a simple adjustment strategy to the BART dosing regimen to minimize drug overdosing, accumulation, and potential toxic effects of TXA. The authors also identified that single TXA bolus dosing in stages 1 and 2 chronic renal dysfunction was associated with a rapid decline in plasma levels to sub-therapeutic concentrations, without much risk of toxicity. This is important during prolonged surgeries where repeat doses may be warranted or an infusion is preferable. Bolus dosing among stages 4 and 5 chronic renal dysfunction provided near therapeutic plasma TXA levels with effective fibrinolytic inhibition for several hours. Even though the optimal dose remains to be determined, lower TXA doses should be preferred. The patient's co-morbidities and surgical complexity should be considered.

Implications for Daily Practice

Based on the published evidence, prophylactic administration of antifibrinolytic should be considered in patients undergoing cardiac surgery. If aprotinin can be used in some indications, the benefit-to-risk balance should be carefully evaluated before considering it.

Considering the safety profile of TXA and the non-inferior efficacy, lysine analogs might be preferred over aprotinin. In the absence of strong data regarding the optimal dose, the standard dose scheme should be applied. For tranexamic acid, a 30 mg/kg loading dose can be used followed by a 16 mg/kg/h infusion. In patients with acute or chronic renal dysfunction, the maintenance can be reduced to 5 mg/kg/h. Low doses have also been used in some studies. Sigaut et al. compared the efficacy of a standard dose (30 mg/kg followed by 16 mg/kg/h) to a low-dose scheme (10 mg/kg followed by 1 mg/kg/h) [17]. The incidence of blood products transfused during the first week, the primary outcome, was not different between the two doses, but the authors observed differences favoring the higher dose on blood loss, re-exploration for bleeding, and the incidence and amount of plasma and platelet concentrates transfused postoperatively. The difference might be explained by the low infusion dose used in patients included in the low-dose group. In the

presence of excessive bleeding, additional boluses or higher infusion rates are recommended in order to maintain adequate plasma levels. Further studies are needed to better define the optimal dose and to develop patient-based dosing schemes.

ε-Aminocaproic acid is most extensively used in the USA compared to most countries that use tranexamic acid, but this agent could be considered as an alternative. The dose scheme used in the BART study could be used: 1 g loading dose administered over 10 min followed by an infusion of 2 g/h.

In summary, prophylactic administration of antifibrinolytic drugs helps reduce bleeding and transfusion in patients undergoing cardiac surgery. The administration of antifibrinolytic is highly recommended in the most recent EACTS/EACTA guideline [18].

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