

## Active, Personalized, and Balanced Coagulation Management Saves Lives in Patients with Massive Bleeding

**M**ASSIVE hemorrhage originates from severe injury of blood vessels caused by major trauma, surgery, underlying medical conditions, or any combination thereof. If not diagnosed and treated readily, patients exsanguinate and die from hypovolemic shock. In this issue of *ANESTHESIOLOGY*, Bolliger *et al.*<sup>1</sup> review the mechanisms of coagulopathy in massive hemorrhage with a special emphasis on the hemodilutional effects of fluid therapy on thrombin generation, fibrin polymerization, and fibrinolysis.

A proper understanding of the complex pathophysiology of coagulopathy in massive bleeding is essential for effective treatment. The coagulation system represents a delicate balance between procoagulant and anticoagulant as well as profibrinolytic and antifibrinolytic protein activities. Modern coagulation management of bleeding patients implies ongoing monitoring of coagulation status with subsequent individual and goal-directed treatment. The key to success in terms of patient outcomes is to keep the above-mentioned four elements of the coagulation system in optimal equilibrium so that bleeding is adequately controlled without thromboembolic adverse events.<sup>2</sup>

The coagulation system is a complex network of interacting proteins and cells with extensive sensitivity, amplification, and control pathways. There is no simple answer to coagulation management; instead, optimal coagulation intervention and management needs to be defined for each patient.<sup>3</sup>

Advanced coagulation monitoring will employ a combination of routine laboratory tests using single factor measurements and whole blood as well as point-of-care coagulation testing—always keeping in mind patient history and clinical findings.<sup>4</sup> Whole-blood coagulation tests like Thrombelastography® (Haemonetics Corporation, Braintree, MA) or rotation Thromboelastometry® (Tem International GmbH, Munich, Germany) may overcome some of the limitations of routine laboratory coagulation tests and are increasingly being used in massive bleeding. With minimal time delays, they provide valuable information on overall kinetics of clot for-

mation, clot strength, platelet function, and overt fibrinolysis in whole blood.<sup>5</sup> However, these tests are still *in vitro* assays; they do not reflect *in vivo* contributions of local tissue and the endothelium, tissue factor-bearing cells, and blood flow to the naturally occurring coagulation process. Therefore, any coagulation test requires skilled interpretation and clinical correlation to evaluate its significance for bleeding or thrombosis.

Patients with massive hemorrhage become coagulopathic due to several mechanisms. Trauma and shock directly activate the thrombomodulin-protein C pathway, resulting in the acute coagulopathy of trauma and shock.<sup>6–8</sup> Thereby, key players of the propagation phase of coagulation, the tenase (VIIIa-IXa) and prothrombinase (Xa-Va) complex, are getting degraded and inactivated by activated protein C. Furthermore, plasminogen activator inhibitor 1, the principal inhibitor of tissue plasminogen activator and urokinase, is inhibited through activated protein C, resulting in increased fibrinolysis. The developing coagulopathy then worsens through the better known pathogenetic factors: consumption and dilution of coagulation factors, hypothermia, and acidosis.

Fibrinogen is the substrate of coagulation and is usually the first coagulation factor to become critically low in massive bleeding.<sup>2</sup> According to Hiippala,<sup>9</sup> fibrinogen levels fall below 1 g/l after a loss of 150% of the calculated blood volume. Factors II, V, and VII as well as platelet levels become critical later, after a blood volume loss of more than 200%. However, these figures are very general and do not help greatly in individual cases. In addition, the arbitrary definition of the critical level determines when the corresponding level will be reached (*i.e.*, after what blood volume loss).

If patients present with clinical and objective signs of coagulopathic bleeding, treatment with allogeneic blood products (*e.g.*, fresh frozen plasma, cryoprecipitate, platelet concentrates), factor concentrates, pharmacological interventions, or a combination thereof has to be initiated. Evidence-based recommendations, such as the recent one from the multidisciplinary Task Force for Advanced bleeding Care in Trauma,<sup>2</sup> are very helpful for optimal patient care. One

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request of the review by Bolliger *et al.*<sup>1</sup> is that the efficacy and safety of novel hemostatic therapies such as factor concentrates are to be assessed in clinical studies. This is certainly correct, but this also applies for the traditional use of fresh frozen plasma, cryoprecipitate, and platelets.

Transfusion of allogeneic blood products is independently associated with increased mortality and major adverse cardiac and noncardiac outcomes.<sup>10</sup> One strategy to reduce bleeding and avoid allogeneic blood transfusion in surgical patients at increased risk of bleeding is the use of antifibrinolytics. For almost two decades, published literature has demonstrated the relative safety and efficacy of aprotinin, a non-specific serine protease inhibitor, especially in adult cardiac surgical patients at increased risk of bleeding. However, since the 2007 Blood Conservation Using Antifibrinolytics in a Randomized Trial,<sup>11</sup> aprotinin has been withdrawn from the market. The Blood Conservation Using Antifibrinolytics in a Randomized Trial represented the largest prospective, randomized, blinded head-to-head comparison of three major antifibrinolytic agents in current clinical usage.<sup>12</sup> The study was terminated early because of a trend toward higher mortality in patients treated with aprotinin.<sup>11,12</sup>

Since marketing of aprotinin was suspended, only two antifibrinolytics remained commercially available in the United States and European Union for patient use,  $\epsilon$ -aminocaproic acid and tranexamic acid (TXA)—favorable evidence being stronger for the latter. Both drugs are lysine analogs and inhibit fibrinolysis by competitively blocking the lysine binding site on plasminogen.<sup>13</sup> Lysine analogs have been shown to reduce blood loss and the need for allogeneic red cell transfusion, especially in cardiac, liver, and orthopedic surgery. The lysine analogs were probably as effective as aprotinin in most studies but at lower costs.<sup>14</sup> The results of the cutting-edge, landmark CRASH-2 trial (NCT00375258) on the use of TXA in trauma patients have just been published.<sup>15</sup>

CRASH-2 is a multicenter (274 hospitals in 40 countries), randomized, blinded, and placebo-controlled trial on the effects of TXA administration on death, vascular occlusive events, surgical interventions, and blood transfusion in 20,211 adult trauma patients.<sup>15</sup> Within 8 h of injury, patients with significant hemorrhage or hemorrhage risk received either 2 g TXA (1 g loading dose, followed by a maintenance dose of 1 g over 8 h) or placebo. TXA administration reduced all-cause mortality (14.5 *vs.* 16.0%; relative risk, 0.91; 95% CI 0.85–0.97;  $P = 0.0035$ ) and the risk of death from hemorrhage (4.9 *vs.* 5.7%; relative risk, 0.85; 95% CI 0.76–0.96;  $P = 0.0077$ ) without an increase in fatal or nonfatal vascular occlusive events. Surprisingly however, there was no statistical difference in blood transfusion between the groups. Exactly how TXA reduced the risk of death in bleeding patients remains unanswered by the CRASH-2 study, however. It may be speculated that TXA has additional, beneficial effects on patient outcome beyond simply inhibiting fibrinolysis.<sup>16</sup>

Another large-scale prospective, randomized, double-blind, placebo-controlled trial on the use of antifibrinolytics is plan-

ning to enroll 15,000 women with a clinical diagnosis of postpartum hemorrhage (WOMAN trial; NCT00872469).<sup>17</sup> Data should be available after completion in 2015.

How should all these aspects translate into perioperative, hemostatic management? First, we have to thoroughly understand the pathophysiology of the deranged coagulation system in massive bleeding, in particular that blood coagulation does not consist of procoagulant proteins only. We always have to consider the four elements of the coagulation system and keep them in balance (*i.e.*, procoagulant and anticoagulant as well as profibrinolytic and antifibrinolytic subsystems).

Second, we have to carefully diagnose the main problem of the disturbed coagulation system with patient history, clinical findings, and adequate blood tests. Because blood coagulation may change rapidly during massive hemorrhage, frequent reassessment is necessary. Furthermore, we need to know exactly how to interpret the blood tests ordered, what they can tell us, and where their limitations are.

Third, we are to initiate the specific treatment needed by the individual patient early. The review by Bolliger *et al.*<sup>1</sup> is an important contribution toward better understanding of coagulopathy in massive hemorrhage and hemodilution. The better we know the underlying pathophysiology, the better we can diagnose and treat our patients in a way that is targeted to their individual needs.

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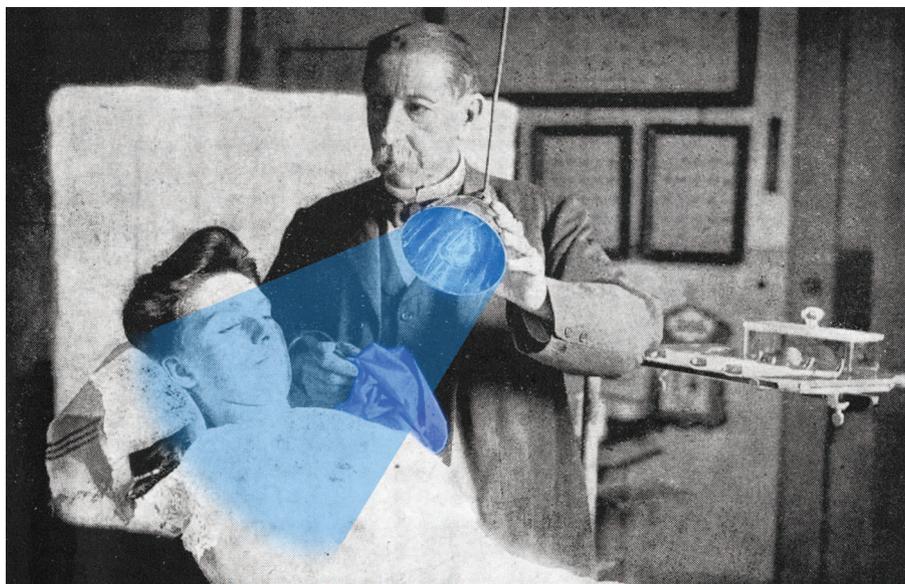
## References

- Bolliger D, Görlinger K, Tanaka KA: Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *ANESTHESIOLOGY* 2010; 113:1205–19
- Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Stahel PF, Vincent JL, Spahn DR: Management of bleeding following major trauma: An updated European guideline. *Crit Care* 2010; 14:R52
- Hoffman M, Monroe DM 3rd: A cell-based model of hemostasis. *Thromb Haemost* 2001; 85:958–65
- Theusinger OM, Spahn DR, Ganter MT: Transfusion in trauma: Why and how should we change our current practice? *Curr Opin Anaesthesiol* 2009; 22:305–12
- Ganter MT, Hofer CK: Coagulation monitoring: Current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg* 2008; 106:1366–75
- Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF: Acute traumatic coagulopathy: Initiated by hypoperfusion: Modulated through the protein C pathway? *Ann Surg* 2007; 245:812–8
- Frith D, Brohi K: The acute coagulopathy of trauma shock: Clinical relevance. *Surgeon* 2010; 8:159–63
- Ganter MT, Pittet JF: New insights into acute coagulopathy in trauma patients. *Best Pract Res Clin Anaesthesiol* 2010; 24:15–25
- Hiippala ST: Dextran and hydroxyethyl starch interfere with fibrinogen assays. *Blood Coagul Fibrinolysis* 1995; 6:743–6
- Spahn DR, Moch H, Hofmann A, Isbister JP: Patient blood management: The pragmatic solution for the problems with blood transfusions. *ANESTHESIOLOGY* 2008; 109:951–3

11. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussi eres JS, C ot e D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R, BART Investigators: A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008; 358:2319–31
12. Murkin JM: Lessons learned in antifibrinolytic therapy: The BART trial. *Semin Cardiothorac Vasc Anesth* 2009; 13:127–31
13. Ide M, Bolliger D, Taketomi T, Tanaka KA: Lessons from the aprotinin saga: Current perspective on antifibrinolytic therapy in cardiac surgery. *J Anesth* 2010; 24:96–106
14. Henry DA, Carless PA, Moxey AJ, O’Connell D, Stokes BJ, McClelland B, Laupacis A, Fergusson D: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2007:CD001886
15. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mej a-Mantilla J, Miranda J, Morales C, Olaomi O, Ollidashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S, CRASH-2 trial collaborators: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet* 2010; 376:23–32
16. Levy JH: Antifibrinolytic therapy: New data and new concepts. *Lancet* 2010; 376:3–4
17. Shakur H, Elbourne D, Gulmezoglu M, Alfirevic Z, Ronsmans C, Allen E, Roberts I: The WOMAN Trial (World Maternal Antifibrinolytic Trial): Tranexamic acid for the treatment of postpartum haemorrhage: An international randomised, double blind placebo controlled trial. *Trials* 2010; 11:40

## ANESTHESIOLOGY REFLECTIONS

### The “Blue Light Anaesthesia” of Redard



Some 14 yr after his 1890 presentations on ethyl chloride and cocaine as local anesthetics in Berlin, Swiss physician Camille Redard (1841–1910) received publicity worldwide (see *above*) for using blue light as an anesthetic for dental extractions. He asked patients “to gaze fixedly” at a reflector-fitted light bulb and then to open their eyes while assuring them that they would “feel no pain.” Redard enhanced blueness of the light by draping a “blue veil of satinette” over both light and patient. Sleep occurred in 3 min — or less time, if soothing music was played. Although Redard felt that hypnosis might be occurring, he suggested that “an optic nerve effect” was involved, since only blue-colored light rays were soporific. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at [www.anesthesiology.org](http://www.anesthesiology.org).)

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