



## Management of massive operative blood loss

S. KOZEK-LANGENECKER

Clinical Division B, Department of Anesthesiology and General Intensive Care Vienna Medical University, Vienna, Austria

### ABSTRACT

Coagulopathy associated with massive operative blood loss is an intricate, multicellular and multifactorial event. Massive bleeding can either be anticipated (during major surgery with high risk of bleeding) or unexpected. Management requires preoperative risk evaluation and preoperative optimization (discontinuation or modification of anticoagulant drugs, prophylactic coagulation therapy). Intraoperatively, the causal diagnosis of the complex pathophysiology of massive bleeding requiring rapid and specific coagulation management is critical for the patient's outcome. Treatment and transfusion algorithms, based on repeated and timely point-of-care coagulation testing and on the clinical judgment, are to be encouraged. The time lapse for reporting results and insufficient identification of the hemostatic defect are obstacles for conventional laboratory coagulation tests. The evidence is growing that rotational thrombelastometry or modified thrombelastography are superior to routine laboratory tests in guiding intraoperative coagulation management. Specific platelet function tests may be of value in platelet-dependent bleeding associated e.g. with extracorporeal circulation, antiplatelet therapy, inherited or acquired platelet defects. Therapeutic approaches include the use of blood products (red cell concentrates, platelets, plasma), coagulation factor concentrates (fibrinogen, prothrombin complex, von Willebrand factor), pharmacological agents (antifibrinolytic drugs, desmopressin), and local factors (fibrin glue). The importance of normothermia, normovolemia, and homeostasis for hemostasis must not be overlooked. The present article reviews pathomechanisms of coagulopathy in massive bleeding, as well as routine laboratory tests and viscoelastic point-of-care hemostasis monitoring as the diagnostic basis for therapeutic interventions.

**Key words:** Hemorrhage - Anesthesia - Blood component transfusion.

### Pathomechanisms of coagulopathy in massive transfusion

Massive transfusion is commonly defined as the replacement of 1 blood volume over a period of 24 h or transfusion of at least 4 red blood cell concentrates (packed red blood cells, PRBC) within 1 h when ongoing need is foreseeable. Massively transfused patients will show evidence of coagulopathy in a high percentage of cases. The pathophysiology of coagulopathy in massively transfused adult and previously hemostatically competent patients in both the elective surgical and trauma settings has recently been reviewed.<sup>1,2</sup> Figure 1 summarizes the numerous factors stress-

ing hemostasis in massively bleeding patients. Most retrospective or uncontrolled observational studies of massive transfusion have been conducted in trauma patients where exsanguination still is a major cause of death.<sup>3, 4</sup> Also in major surgery uncontrolled hemorrhage requiring massive transfusion is a frequent and serious complication. However, in elective surgery, bleeding diathesis may be foreseen, tissue trauma is more controlled, tissue anoxia is better avoided, blood losses are replaced in a timely manner, and coagulopathy is treated at earlier stages.

Uncontrolled bleeding initially leads to loss of coagulation factors and platelets.<sup>5, 6</sup> Trauma-induced exposure of the thromboplastin-rich

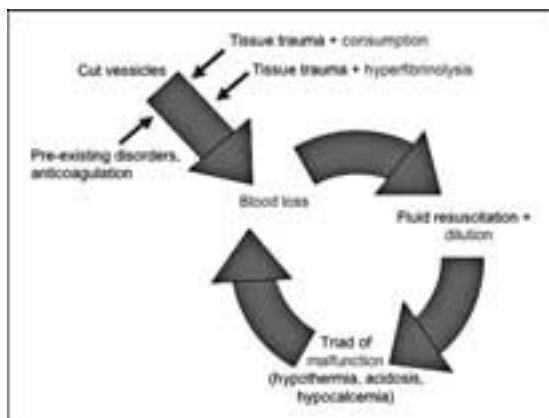


Figure 1.—Pathomechanism of trauma-associated coagulopathy: a bloody vicious cycle.

subendothelial tissue to flowing blood induces the activation of coagulation,<sup>7</sup> which may trigger consumptive coagulopathy.<sup>8-10</sup> The majority of blunt trauma and brain injury victims are hypercoagulable early after trauma, with tissue trauma being the key stimulus for coagulation.<sup>8, 11, 12</sup> When tissue anoxia is avoided, normotension maintained, and surgical trauma controlled, the occurrence of consumptive coagulopathy may remain low in elective surgery despite massive transfusion.<sup>13, 14</sup> In hypocoagulable patients, the remaining procoagulatory potential is reduced by dilution during fluid resuscitation required to restore intravascular volume and to maintain hemodynamic stability. The degree of dilutional coagulopathy also depends on the type of fluid used: hydroxyethyl starch solutions, gelatins, and dextrans impair platelet function, inhibit fibrin polymerization, and induce an acquired von Willebrand syndrome at varying degrees, depending on the physicochemical characteristics of the colloidal solution.<sup>15, 16</sup> Resuscitation with hypertonic saline appears to aggravate bleeding by its potent anticoagulatory and antiplatelet effect,<sup>17</sup> while other hypertonic solutions (glycine, glucose, sorbitol) exhibit a significantly reduced impairment. Moderate degrees of *in vitro* hemodilution with crystalloids induced hypercoagulability in viscoelastic tests.<sup>18</sup> It remains unclear whether this effect is an artifact produced in native whole blood only (not other anticoagulants) or whether it has any clinical relevance in massively bleeding patients.<sup>19</sup> Prior to the era of blood fractionation,

the transfusion of large volumes of stored bank blood did not result in a hemorrhagic diathesis.<sup>20</sup> Dilution often is not an issue until more than 10-12 U of PRBC (1 blood volume) is given.<sup>21</sup> Tissue injury in trauma or surgery may lead to the exposure of tissue plasminogen activator resulting in hyperfibrinolysis if the delicate balance between coagulation and fibrinolysis is lost.<sup>22</sup> Coagulopathy is confounded by hypothermia, acidosis, and pre-existing disorders: trauma patients are prone to hypothermia, which slows down enzymatic reactions,<sup>23</sup> modifies platelet function,<sup>24, 25</sup> decreases platelet counts,<sup>26</sup> and stimulates fibrinolysis.<sup>27</sup> Acidosis worsens fibrin polymerization and strengthening of the clot.<sup>28</sup> In a study including both blunt and penetrating injuries, the vicious cycle induced by severity of tissue injury (injury severity score >25), progressive core hypothermia (<34 °C), and ongoing cellular shock (pH <7 and low arterial blood pressure) in an adversely affected coagulation and predicted life-threatening coagulopathy in massively transfused patients.<sup>10</sup> Low ionized calcium (after massive PRBC transfusions containing citrate) and low hematocrit (<30%) further aggravate bleeding diathesis. Red cells contribute to the margination of platelets against the vessel wall and their availability to act at the site of a vascular lesion.<sup>29</sup> They have also been shown to modulate the biochemical and functional responsiveness of activated platelets. Activation and consecutive exhaustion of platelet function after extracorporeal circulation and anticoagulation and its reversal are additional etiologies for cardiopulmonary bypass-induced hemostatic defects. Since surgery and trauma are not restricted to previously healthy people, the increasing number of patients taking oral anticoagulants and platelet-inhibiting drugs poses a rapidly increasing problem.<sup>30</sup> Patients with inherited coagulation defects may exsanguinate with trauma unless specific factor replacement is provided.

The vicious cycle of coagulopathy in massive transfusion results in: 1) a defect in clot firmness due to fibrinogen deficiency (being an early phenomenon) and thrombocytopenia; 2) impaired clot stability due to hyperfibrinolysis and factor XIII deficiency (being a late phenomenon); and 3) prolonged clot generation due to various coagulation factor deficiencies.

## Diagnosis of coagulopathy in massive transfusion

### *Preoperative evaluation and preparation*

The preoperatively assessed bleeding history of the patient and of his/her relatives remains the most important tool for making correct diagnosis of inherited and acquired bleeding disorders, which increase the risk of operative bleeding.<sup>31</sup> Standardized questionnaires have been designed in order to assess the type of bleeding (mucosal *versus* non-mucosal) and the timing of bleeding (immediate *versus* delayed, since early childhood *versus* late in life) among other items, such as use of anticoagulatory or antiplatelet drugs.<sup>32</sup> Preoperative clinical examination may also reveal hematoma, petechia, or wound healing defects indicating bleeding disorders. The most common cause of clinical non-surgical bleeding is associated with abnormalities in platelet function, with von Willebrand syndrome being considered as the most frequent inherited bleeding disorder.<sup>33, 34</sup> Only if bleeding history is positive (abnormal), further laboratory investigation of hemostasis is indicated and requires a stepwise approach.<sup>35</sup> Recommended baseline screening tests involve the routine coagulation tests investigating the plasmatic coagulation profile, as well as tests allowing analysis of platelet function.<sup>32</sup>

If preoperative evaluation anticipates an increased operative bleeding risk, preoperative patient preparation includes discontinuation or modification of anticoagulant drugs if clinically possible, prophylactic coagulation therapy to promote coagulation (*e.g.* antifibrinolytic drugs, desmopressin, vitamin K), and prevention of allogeneic transfusion requirements (*e.g.* erythropoietin, preadmission blood collection).<sup>31</sup> The risks and benefits of instituting preoperative optimization should be assessed on a case-by-case basis.<sup>36</sup> Preoperative evaluation should be done well enough in advance to elective surgery to correct bleeding risk factors and blood and blood components have to be available perioperatively.

### *Intraoperative monitoring of blood loss*

Periodic visual assessment of the surgical field and communication with the surgical team is rec-

ommended as standard practice to detect impending or established coagulopathy, and entails the assessment of the amount of blood lost and the presence of microvascular bleeding from mucosal lesions, serosal surfaces, catheter insertion sites and wounds. The diagnosis of intra- and postoperative coagulopathy in massive transfusion needs to be verified by appropriate coagulation tests.<sup>31</sup> Due to the complex nature of hemorrhage in this setting, physicians require coagulation monitoring strategies sensitive to all major possible pathomechanisms. In contrast to massive bleeding in elective surgery, monitoring of hemostasis occurs late in traumatic hemorrhage when coagulopathy is already installed and treatment becomes more difficult.<sup>1</sup> At present, several routine coagulation monitoring tests are available for this purpose. Point-of-care coagulation monitoring devices have become available and are likely to overcome several limitations of routine coagulation testing.

### *Routine coagulation testing*

Even though these tests were not developed to predict bleeding or guide coagulation management in the surgical setting, most centers in clinical practice draw blood perioperatively for the following routine coagulation tests (routine coagulation panel).

#### ACTIVATED PARTIAL THROMBOPLASTIN TIME

The activated partial thromboplastin time (aPTT) was developed to monitor heparinization in the treatment of thromboembolic disorders, to characterize clotting factors, and for research purposes on hemophilia. Activation of coagulation factors, formerly known as intrinsic coagulation cascade, is performed by incubating plasma with partial thromboplastins, calcium, and kaolin powder at 37 °C at a standardized pH. The endpoint of measurement is the formation of fibrin strands. Standardization, however, is difficult due to the large variation in calibration constants and methods of endpoint detection, as well as the wide range of pro- and anticoagulant factors affecting aPTT results. The aPTT is sensitive to coagulation factors VIII, IX, XI, XII, V, II, and I, heparin, fibrinogen degradation products, inhibitors, hypothermia, and hypofibrinogenemia. Multiple

factor deficiencies tend to show a greater prolongation for a given factor level than single factor deficiencies.

#### PROTHROMBIN TIME

This test was developed to monitor and adjust the doses of coumarins. Activation of coagulation factors, formerly known as extrinsic coagulation cascade, is performed by incubating plasma with tissue thromboplastin and calcium at 37 °C at a standardized pH. The time until fibrin strand formation is determined. This test is sensitive to coagulation factors II, VII, X, V, and I. Standardization of the prothrombin time (PT) for laboratory control of oral anticoagulant treatment is based on the responsiveness of one type of thromboplastin, measured by its international sensitivity index, and conversion into the international normalized ratio (INR). Direct INR determination is performed by local calibration using plasma of certified levels of PT. A PT activity above 30-40% generally ensures normal coagulation within a safe margin.

#### PLATELET COUNT

Platelet counting is routinely performed by automated machines. The number of platelets, however, does not reflect the quality of platelet function.

#### FIBRINOGEN CONCENTRATION

Fibrinogen plays a major role in routine coagulation tests, such as PT and aPTT. There are two methods used in specific fibrinogen assays: 1) determination of the amount of fibrinogen molecules *per se*, e.g. by immunologic, gravimetric, or heat precipitation, and 2) determination of clottable fibrinogen. In the conventional Clauss method, where thrombin is added to plasma, the fibrinogen concentration is proportional to the coagulation time measured. This test is affected by heparin and fibrinogen degradation products. Excessive bleeding has been reported at fibrinogen levels <50 mg/dL.<sup>37</sup>

#### SECOND LEVEL COAGULATION TESTS

Because of long turnaround times and limited availability in many laboratories, coagulation fac-

tor levels and molecular markers of the coagulation and fibrinolytic system are rarely assayed in the acute preoperative setting.

#### *Routine coagulation monitoring: predictor of bleeding and mortality*

Severe aPTT prolongations >1.8 times normal are associated with bleeding.<sup>37, 38</sup> Similarly, INR elevations in trauma patients are only indicative for risk of generalized bleeding if they are >1.5-1.8 times normal and are associated with an elevated aPTT.<sup>37, 39</sup> A severely prolonged activated clotting time may indicate exhaustion of the coagulation system's reserve.<sup>6</sup> In trauma victims, an initially abnormal PT increases the adjusted odds of dying by 35%, a prolonged aPTT by 326%.<sup>4</sup>

Although severely abnormal PTs and aPTTs are predictors of mortality, the poor predictive power of moderately impaired routine coagulation tests has repeatedly been argued as a major limitation.<sup>38</sup> In a multiple regression model, platelet count was not an independent predictor of mortality in emergency medicine.<sup>4</sup> The decline of platelet count is a highly individual phenomenon, some patients are even able to recruit platelets from storage pools. Most patients approach the critical platelet count of 50000  $\mu$ /L after losing two blood volumes.<sup>40</sup>

#### *Limitations of routine coagulation tests*

In perioperative settings, where events may proceed at a fast and dramatic pace, real-time monitoring of the patient's coagulation profile and repeated laboratory tests are vital in administering proper replacement therapy. However, tests results of routine coagulation monitoring performed at the hospital's central laboratory are generally only available with a delay of at least 30 min (sample preparation including centrifugation and buffering, transportation of blood samples and test results).<sup>41</sup> In this light, it seems frustrating that it is recommended to transfuse patients empirically, based on clinical probability and dogmatic guidelines for massive transfusion, before routine coagulation test results are available.<sup>31</sup> The bedside determination of PT and aPTT in whole blood using the CoaguCheck (Roche Diagnostics, Switzerland), aimed at overcoming this limitation,

however, correlation with central laboratory test results is inadequate.

Routine coagulation tests are performed in plasma at a standardized temperature of 37 °C, without the presence of platelets and other blood cells. Accordingly, routine laboratory tests cannot assess the effect of hypothermia on hemostasis in hypothermic patients. Furthermore, fibrinolysis and platelet dysfunction pose diagnostic gaps. Since the hemostatic response to injury or surgery is a complex interaction of plasma proteins, platelets, and the vessel wall (cell-based model of hemostasis), it cannot be pictured by tests performed in plasma. Although aPTT, PT, fibrinogen concentration, and platelet count determination are well validated, methodological problems include variable sensitivity of test reagents, high variability between labs and investigators, as well as insufficient standardization.

Routine tests pick up abnormalities in hemostasis due to single or multiple deficiencies in coagulation factors, but do not identify them. The PT is a more reliable marker of critically low coagulation factor levels than the aPTT, possibly due to the high rate of false negative aPTT results when acute phase reactant factor VIII is elevated.<sup>39</sup> Several studies demonstrate a poor correlation between the amount of blood products given and the severity of coagulation defects.<sup>37, 38</sup> Obviously, simplistic formulas or flow charts for predicting factor deficiencies from blood loss are not applicable.<sup>42</sup>

The most important limitation of routine coagulation tests is the fact that the predominant pathomechanism of bleeding in the complex *scenario* of trauma-associated coagulopathy or massive intraoperative blood loss cannot be differentiated: prolonged aPTT may be due to *intrinsic* coagulation factor deficiency requiring specific substitution, fibrinogen deficiency requiring fibrinogen substitution, hypothermia requiring rewarming, heparinization requiring protamin reversal, or hyperfibrinolysis requiring antifibrinolytic drugs. Thus, a false differential diagnosis may lead to therapeutic misadventures.

In this light, the discouraging statement in recent reviews that there is no simple, reliable, and rapid diagnostic routine coagulation test that allows clinicians to manage massively transfused blood prove to be accurate.<sup>1</sup> Hardy *et al.*<sup>1</sup> concluded that

bedside monitors of hemostasis are needed urgently for the management of operative and trauma-associated bleeding. By assisting clinicians in making the correct diagnosis in a timely manner, monitors will contribute to the optimal use of blood products.

### Near-patient coagulation monitoring

#### *Thrombelastography and rotational thrombelastometry*

The viscoelastic whole blood test was invented by Hartert in 1948<sup>43</sup> and has recently been included in the panel of laboratory monitoring for coagulopathy by the American Society of Anesthesiologists.<sup>31</sup> Thrombelastography (TEG)/rotational thrombelastometry (ROTEM) measure the viscoelastic properties of non-anticoagulated or (citrate) anticoagulated blood after induction of clotting under low shear conditions, resembling the rheologic properties in venous vessels *in vivo*. The pattern of changes in viscoelasticity reflect the kinetics of all stages of thrombus formation (reaction [r] and coagulation [k] time, clotting time [CT] and clot formation time [CFT]), the stability and firmness of the clot, which is a function of platelet-fibrin interaction and fibrin polymerization (maximum amplitude [MA], maximum clot firmness [MCF]), as well as dissolution (fibrinolysis).<sup>44</sup> A normal trace is shown in Figure 2.

TEG/ROTEM is a fibrinolysis-sensitive assay and allows for diagnosis of hyperfibrinolysis in bleeding patients.<sup>45</sup> Standardized operating procedures required for quality control testing are available. A multicenter investigation yielded consistent values between centers and provided general orientating reference ranges for the ROTEM.<sup>46</sup> TEG/ROTEM are easy to use by non-laboratory personnel in the Emergency Unit or the operating room (OR). Interpretation of TEG/ROTEM results is simplified by both graphical and numerical presentation of results and highlighting of abnormal results. While conventional TEG has been described as an insufficient monitoring in trauma patients because of unclear interpretation and limited run-to-run variation,<sup>47</sup> the ROTEM (Pentapharm GmbH, Germany) improved the original TEG procedure by reducing the interference with vibrations and

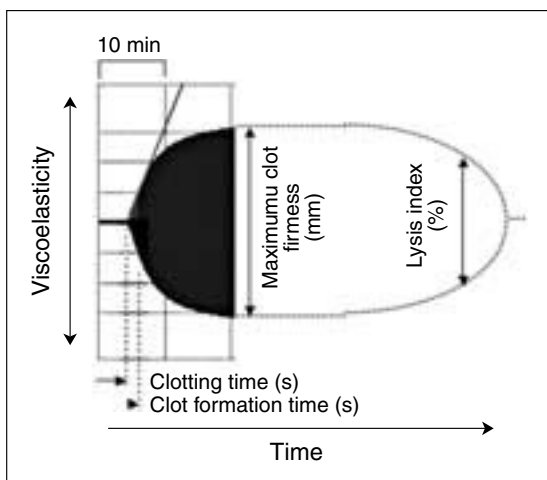


Figure 2.—Rotational thrombelastometry parameters, normal trace.

limited transportability, and allowing a computerized analysis of the trace. Addition of different coagulation-activating agents and/or platelet inhibiting agents allows the detection and quantification of specific coagulation defects, such as hypofibrinogenemia, factor deficiency, thrombocytopenia, heparin effect, and hyperfibrinolysis. All these aspects of the coagulation *scenario* come into play when an individual is injured or undergoing surgery. Thus, ROTEM not only provides a global picture of the injured patient's hemostatic status, but also permits differential diagnosis of the major underlying pathomechanism of coagulopathy: EXTEM is a baseline test that uses recombinant tissue factor to activate coagulation (comparable to the PT), which causes rapid generation of the clot. The clotting time (EXTEM CT) gives information about the initial activation and dynamics of clot formation, thus allowing analysis of factor deficiencies (and the detection of anticoagulants). The critical cut-off value for CT, indicating the necessity to administer prothrombin complex concentrates (PCC) or fresh frozen plasma (FFP), appears about 80 s after test initiation. Practical considerations in the perioperative setting are that viscoelastic tests are initiated immediately after blood withdrawal. EXTEM MCF gives information on the maximum clot strength and stability, which is largely dependent on platelet count and fibrinogen level. Prepared disposable wells containing cytochalasin D, a platelet inhibitor, are used in the FIBTEM test. FIBTEM MCF rep-

resents the contribution of fibrinogen to the clot strength. Critical MCF cut-off values appear within 10-15 min after test initiation (depending on hemostatic function). A low FIBTEM MCF is indicative for administration of fibrinogen concentrates. A normal FIBTEM MCF in the presence of a low EXTEM MCF indicates the need for platelet substitution. Thus, comparing EXTEM MCF to FIBTEM MCF permits differentiation of a low platelet count from dys- or hypofibrinogenemia. Practical consideration: FIBTEM and EXTEM should be performed simultaneously as first line ROTEM tests in surgical patients.

EXTEM allows for the visual diagnosis of hyperfibrinolysis, when a typical tapering trace is shown. In addition, wells containing aprotinin (APTEM) permit the quantitative assessment of fibrinolysis and the estimation of the therapeutic benefit from antifibrinolytic agents. Any improvement in CT, CFT, and MCF in APTEM compared to EXTEM demasks low grade hyperfibrinolysis.

INTEM uses ellagic acid contact activator (comparable to the reagent used for aPTT) to analyze the general coagulation status. Wells containing heparinase (HEPTEM) or ecarin can be used to detect specific anticoagulant effects. The comparison of INTEM CT and HEPTEM CT permits the quantification of heparinization and the effect of protamin reversal.<sup>48</sup> Practical consideration: INTEM and HEPTEM should be performed as first line ROTEM tests in heparinized (cardiac) patients and as second line ROTEM tests in all other surgical patients if (endogenous or exogenous) heparinization is suggested to complicate bleeding. Point-of-care ROTEM monitoring including EXTEM, FIBTEM, APTEM, and depending on the results and medical history also INTEM, HEPTEM, theoretically represent the best option available at present for monitoring hemostasis in the perioperative setting of massive bleeding.

Inadvertent hypothermia is a frequent problem in surgical patients increasing blood loss.<sup>49</sup> TEG/TEM measurements can be performed at the actual body core temperature of the patient at adjusted test temperatures between 22 °C and 42 °C, thus allowing quantitative analysis of the anticoagulant effect induced by hypothermia.<sup>50</sup> Test temperature adaptations, however, are impracticable

in the OR, because physicians may be tempted in treating abnormal test results with coagulation factor substitution while only rewarming is indicated.

In contrast to routine coagulation testing in plasma, TEG/ROTEM can be performed at the bedside, relevant information can be obtained within a few minutes and, therefore, goal-directed coagulation therapy can be readily initiated. Each routine test is specific for some portion of the hemostatic mechanism and none can stand alone. Similarly, ROTEM test combinations (EXTEM + FIBTEM) are required as a basic panel in massive bleeding. The approximate cost of such test combinations of routine coagulation and ROTEM are equivalent (at the author's institution). However, if ROTEM helps to shorten surgical procedures, lowers the frequency of re-openings, shortens the stay in the Intensive Care Unit, and minimizes the direct costs of blood products by also avoiding costly adverse effects of transfusion, the ability of ROTEM coagulation monitoring to save costs is significant in clinical practice.

*Thrombelastography/rotational thrombelastometry: predictor of surgical bleeding*

Many articles using TEG/ROTEM have been published so far (PubMed search >2 500 hits). However, the evidence for its usefulness as a predictor of bleeding is scarce. TEG was found to be an early predictor of transfusion in blunt injury patients.<sup>12</sup> Normal viscoelastic test results are unlikely to coincide with bleeding (high negative predictive value).<sup>51</sup> As a consequence, another important implication of TEG/ROTEM monitoring is the immediate initiation of surgical re-exploration if no hemostaseological cause of bleeding is observed.

**Management-algorithm for coagulation therapy**

Indications for management algorithms are: 1) the correction of bleeding, and 2) the prevention of bleeding before invasive procedures. The pure optimization of coagulation parameters in the absence of bleeding, however, is no indication.

TABLE I.—*Recommended time points for intraoperative hemostasis monitoring and massive transfusion.*

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— At admission to the Trauma Unit or at baseline of surgery with high risk of bleeding (according to the amount of bleeding or into a confined space (e.g. brain))
— When relevant bleeding occurs (overt or not surgically correctable bleeding)
— After each blood volume exchange
— After procoagulant therapeutic intervention
— Postoperatively to detect hypercoagulability

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Although blood transfusion can be life-saving, its numerous negative effects have been well documented (transfusion-associated infections, hemolytic reactions, volume overload for red cell transfusion, major allergic reactions, immunological reactions, consequences of derangements in oxygen delivery). Our transfusion behavior should aim at minimizing the occurrence of indiscriminate transfusion and empiric hemostatic intervention. Indiscriminate blood transfusion and hemostatic agent use may be due to lack of sensitive and timely coagulation data. Because of the multifactorial nature of bleeding, especially in trauma and major surgery, a point-of-care guided transfusion algorithm should definitely support the clinician's discretion. Because of the dynamic changes of hemostasis in massive bleeding, testing should be performed repeatedly (Table I). The institution of transfusion algorithms based on thrombelastographic parameters reduces transfusion requirements (and in some study designs also blood loss) in both routine and high-risk cardiac surgery in adults and children and liver transplantation.<sup>52-59</sup> TEG-guided administration of clotting factors was superior to routine coagulation testing.<sup>60</sup> Transfusion requirements before and after the implementation of the ROTEM were statistically significantly lower and clinically more accurate.<sup>61</sup> Point-of-care monitoring with TEG/ROTEM should also be available in labor wards, where the detection of hyperfibrinolysis and other major hemostatic defects may occur.<sup>62</sup> In summary, in the absence of a gold standard, TEG/ROTEM algorithms have been developed after their implementation showed decreases in blood loss (rather than by hard evidence). Nevertheless, routine laboratory-based transfu-

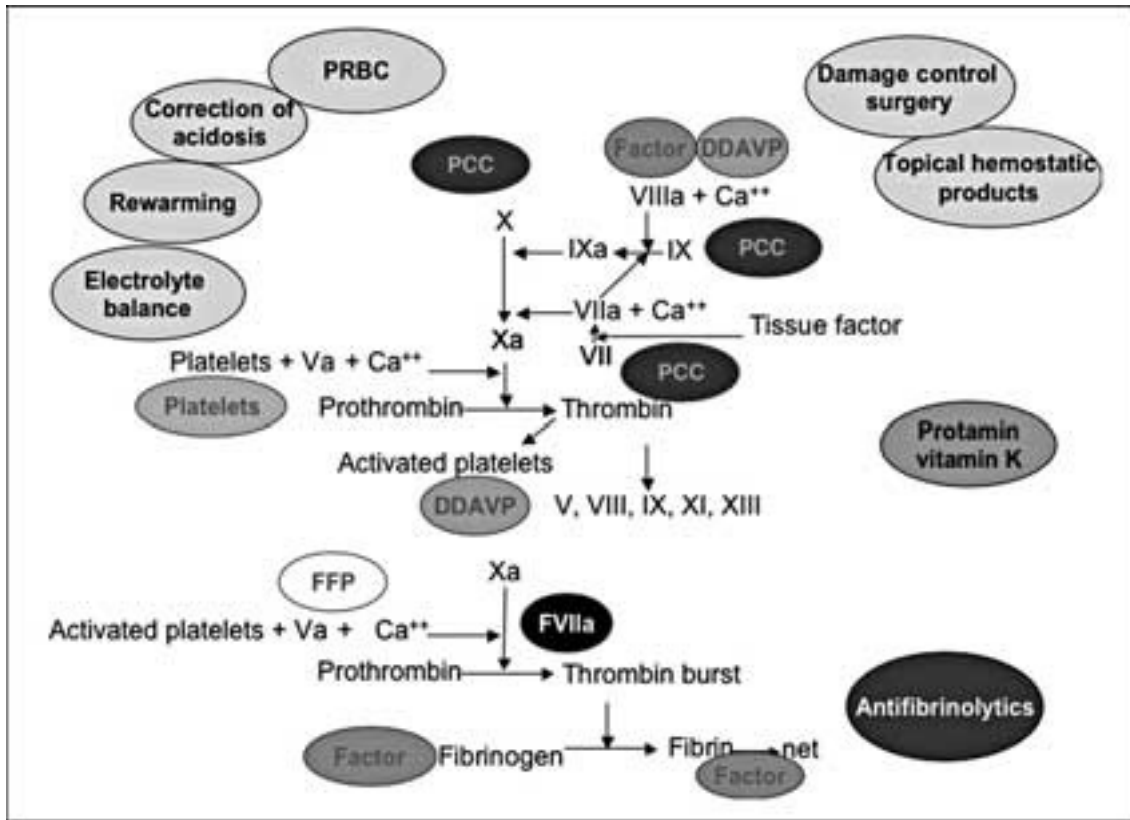


Figure 3.—Coagulation management in trauma patients. PRBC: packed red blood cells; PCC: prothrombin complex concentrates; FFP: fresh frozen plasma.

sion algorithm still is superior to treatment solely based on the clinician's experience.<sup>1,30</sup> A treatment algorithm with normal values in routine coagulation tests and *in vivo* bleeding time as trigger for antifibrinolytic drugs (indication by exclusion)<sup>63</sup> does not permit inappropriate coagulation management based on pathophysiological criteria.

*Blood products and hemostatic agents*

According to international recommendations and/or hospital-internal agreements, massively bleeding patients receive PRBC, plasma (*e.g.* FFP), and platelet concentrates (*e.g.* apheresis concentrate), as well as coagulation factor concentrates (*e.g.* fibrinogen concentrate, PCC, purified factor concentrates, recombinant activated factor VII), and hemostatic agents (*e.g.* antifibrinolytic drugs, desmopressin). Surgical attempts to control the source of hemorrhage as well as therapeutic options in the perioperative coagulation management are

summarized in Figure 3 and have been reviewed recently.<sup>1, 41, 64-67</sup>

Fibrinogen, the final effector of the clotting system, is vulnerable in trauma-associated coagulability because it reaches critical values before several other coagulation factors do.<sup>14, 40</sup> Replacement of only one blood volume may lead to a clinically relevant fibrinogen deficiency.<sup>37, 40</sup> The administration of virus-inactivated fibrinogen concentrates is faster and more effective in reversing a fibrinogen deficiency than the administration of FFP.<sup>60</sup> Alternatively, cryoprecipitates containing factor VIII, von Willebrand factor and (lower amounts of) fibrinogen are recommended in the Anglo-American literature.<sup>68</sup> Empiric transfusion triggers in bleeding trauma patients are fibrinogen <100 mg/dL or alternatively in a ROTEM-based transfusion algorithm EXTEM MCF <50 mm plus FIBTEM MCF <12 mm (Figure 4). European ROTEM users recommend EXTEM



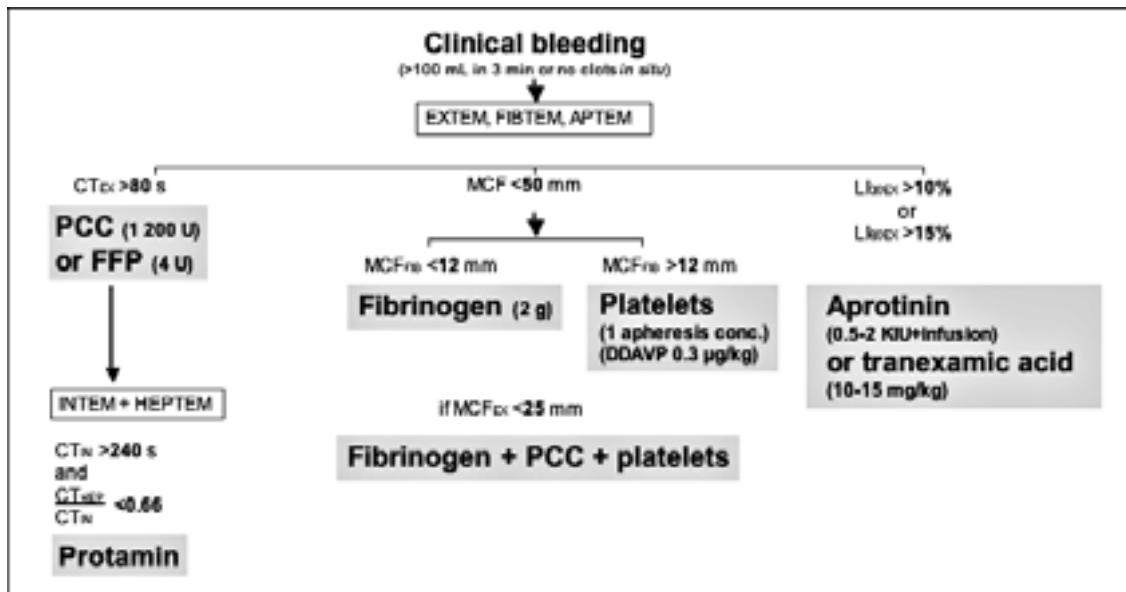


Figure 4.—Rotational thrombelastometry -based algorithm in trauma patients (expert advice). PCC: prothrombin complex concentrates; FFP: fresh frozen plasma; MCF: maximum clot firmness; CT: clotting time.

MCF of 55-60 mm and FIBTEM MCF of 16-20 mm as target values in massively bleeding trauma patients. Due to the dynamic nature of the hemostatic defect, these cut-off values are higher for traumatized patients with ongoing bleeding than for patients undergoing elective surgery, such as liver transplantation and cardiac surgery (EXTEM MCF <45 mm plus FIBTEM MCF <8 mm).<sup>69, 70</sup> If no active bleeding is present, cut-off values may be even lower (EXTEM MCF <35 mm). It is important to note the practical consideration that, in contrast to the published literature, the algorithm has to include the pathway leading to the indication of fibrinogen administration and platelet transfusion (EXTEM and FIBTEM) (Figure 4).

Fibrinogen substitution partially reverses the dilutional coagulopathy induced by crystalloids and colloids *in vitro* and *in vivo*.<sup>71</sup> Clinical TEG/ROTEM experience indicates that the addition of fibrinogen can increase clot strength even in the presence of reduced platelet counts and function.

Replacement of 2.5 blood volumes may lead to clinically relevant thrombocytopenia.<sup>40</sup> Empiric indicators for transfusion of platelet concentrates are platelet counts 50 000 (-100 000)  $\mu$ /L<sup>72</sup> or EXTEM MCF <45 mm combined with FIBTEM

MCF >12 mm. Bearing in mind the individual response (release and sequestration of platelets), recommendations for fixed transfusion ratios for platelet concentrates *versus* PRBC (ratio of 0.5-0.8) are useless.<sup>41, 73</sup> Prophylactic platelet administration fail to prevent massive transfusion.<sup>74</sup>

In contrast to FFP, PCCs are rapidly available in the Trauma Unit or OR. Empiric transfusion triggers are aPTT or PT >1.5 (-1.8) times normal or EXTEM CT >100 s, which indicates clinically relevant loss of coagulation factors II, VII, IX, X. Co-administration of PCC and antithrombin is not required in traumatized bleeding patients. The content of heparin in PCCs has to be considered in patients with (suspected) heparin-induced thrombocytopenia. Adequate doses to increase coagulation factor levels by FFP are >20-30 mL/kg.<sup>60</sup> Prophylactic administration of FFP has been shown to be ineffective in massively transfused patients.<sup>38, 73, 74</sup> FFP transfusion is also indicated for correction of known coagulation deficiencies (*e.g.* factor V) for which specific concentrates are unavailable.

The efficacy of recombinant activated factor VIIa (rFVIIa) appears to extend to non-hemophilic patients with severe trauma. rFVIIa at supraphysiological doses (up to 90  $\mu$ g/kg BW per

bolus) binds to activated platelets and induces the generation of a stable fibrin clot *via* a thrombin burst. rFVIIa is a promising hemostatic agent in massive operative blood loss, but the optimal timing of administration of rFVIIa remains to be determined. Data on the hemostasis monitoring before administration of rFVIIa to acutely bleeding patients are scarce. Activation of factor X appears to predict hemostatic efficacy.<sup>75</sup> Data on modified TEG monitoring using low tissue factor activation have been described in hemophilia.<sup>76</sup> The most consistent effect of rFVIIa on TEG/TEM is the shortening of R/CT and K/CFT, as well as increased MA/MCF.<sup>77</sup> Additional TEG/ROTEM parameters (maximum velocity of clot formation and time to reach maximum clot formation) appear to be more sensitive to rFVIIa than standard kinetic parameters.<sup>78</sup> Current data do not support the use of the platelet function analyzer PFA-100 (described below) in monitoring rFVIIa therapy in trauma.<sup>77</sup> Simple reductions of prolonged PT and aPTT are not useful in identifying responders to rFVIIa, however, the lack of reduction may identify nonresponders.<sup>77</sup> Before rFVIIa becomes a universal hemostatic agent, transfusion replacement should aim to correct coagulopathy, aiming at fibrinogen levels >100 mg/dL, platelet counts 50 000 (-100 000)  $\mu$ /L, and PT and aPTT approximating normal.<sup>30</sup> Severe coagulopathy may render rFVIIa ineffective. It must be kept in mind that patients, if over-supported in the pre- and intraoperative period, may rapidly swing back to a thrombotic state postoperatively with the risk of myocardial infarction, pulmonary embolism, or deep vein thrombosis.

Therapy should take into account all the factors known to affect hemostasis in these patients who bleed actively. During massive transfusion and dilutional coagulopathy, factor XIII deficiencies may occur which may be treated by a specific factor concentrate.<sup>79</sup> Monitoring of factor XIII levels (or EXTEM assay with *ex vivo* spiking with factor XIII) may guide factor XIII concentrate supplementation.

Patients with inherited coagulation defects may exsanguinate with trauma or major surgery unless specific factor replacement is provided (such as factor VIII, IX, von Willebrand factor concentrate).

Contraindications have to be considered before institution of procoagulant interventions.

Antifibrinolytic drugs and desmopressin have been studied extensively as pharmacological interventions to improve hemostasis and to decrease perioperative exposure of patients to blood products. Aprotinin inhibits the activity of various serine proteases including plasmin, coagulation factors, and inhibitors. Aprotinin preserves platelet function. It inhibits accelerated fibrinolysis and proinflammatory mediators. Lysine analogues, such as tranexamic acid and aminocaproic acid, inhibit plasminogen activation. A meta-analysis of all randomized, controlled trials of the three most frequently used pharmacological strategies to decrease postoperative blood loss, aprotinin, lysine analogues, and desmopressin, showed that aprotinin decreased mortality in cardiac surgery almost two-fold compared with placebo.<sup>65</sup> All antifibrinolytics decreased the frequency of re-explorations and the proportion of patients receiving any allogeneic blood transfusion.<sup>65</sup> Risks associated with antifibrinolytic drugs have to be considered.<sup>36</sup> If detected in the ROTEM or TEG, first line therapy has to correct hyperfibrinolysis followed by replacement of consumed coagulation factors.

Desmopressin (DDAVP) is a vasopressin analogue that induces the release of von Willebrand factor and factor VIII from endothelial cells. Desmopressin results in a small decrease in blood loss in cardiac surgery, but is not associated with a beneficial effect on other clinical outcomes.<sup>65</sup> Indications in massively bleeding patients are limited to inherited and acquired platelet dysfunctions, von Willebrand syndrome, and pre-existing antiplatelet medication.

Adequate hematocrit, adequate tissue perfusion and prevention of acidosis are crucial in the correction of bleeding. PRBC should be transfused to correct a physiologic deficit likely to be detrimental to the patient. Transfusion of PRBC shortens the bleeding time in anemic thrombocytopenic patients despite persistent thrombocytopenia.<sup>80</sup> Collection of fresh autologous whole blood prior to heparinization and reinfusion following cardiopulmonary bypass is associated with greater improvement of coagulation status after bypass in infants.<sup>81</sup> These data support the concept of a minimal hematocrit for optimal hemostasis. However,

the optimal hematocrit to sustain hemostasis in the context of massive transfusion remains unknown, but is probably higher (>30-35%) than that required for oxygen transport and delivery.

Maintaining a normal body temperature is a first-line and effective strategy to improve hemostasis during massive transfusion. There is a limit on the level of hemostasis that can be restored by replacement therapy in the presence of hypothermia and acidosis.

A large retrospective study suggested that the use of old generation hetastarch in primary cardiac surgery with cardiopulmonary bypass may increase bleeding and transfusion requirements, despite the infusion of volumes smaller than the manufacturer's recommended dose.<sup>82</sup> Novel rapidly degradable hydroxyethyl starch solutions or gelatins with negligible effects on plasmatic coagulation and platelet function are preferred for the resuscitation of patients requiring massive transfusion.

#### *Limitations of point-of-care algorithms based on thrombelastography/rotational thrombelastometry*

When performed by anesthesiologists or nursing personnel within the OR or Trauma Unit, the possibility for handling mistakes and false data interpretation have to be considered. Point-of-care monitoring with ROTEM is still an evolving field. Concomitant training, education, and quality control are critical. Another limitation of these point-of-care tests is their lack of robustness. Future studies in emergency medicine are highly warranted to validate critical cut-off values for procoagulant therapy and transfusion. Not only the amount of bleeding, but also the site will determine cut-off values. Acceptance of the method not only by anesthesiologists but also biologists has to be gained and, most important, the improvements in the patient's outcome as well as health cost reductions have to be verified. It needs to be determined if goal-directed coagulation management based on a point-of-care algorithm can help to prevent coagulopathy during massive transfusion.

Because of the inability to detect platelet function disorders such as von Willebrand syndrome and antiplatelet drug effects (except for the novel TEG aggregation test, platelet mapping), it is recommended to perform more specific tests in

platelet-dependent bleeding. Thus, although TEG has been listed as a laboratory test in preoperative evaluation,<sup>31</sup> the author's opinion is that TEG/ROTEM is of limited value preoperatively.

### **Platelet function tests**

Widespread adoption of antiplatelet agents into everyday clinical practice has revolutionized contemporary care of cardiovascular patients. The bleeding risks these drugs pose perioperatively will become increasingly important.<sup>83, 84</sup> Platelet function tests are first level tests in the preoperative evaluation of patients with positive bleeding history<sup>32, 34</sup> and second level tests in actively bleeding patients if antiplatelet therapy, inherited or acquired platelet defects, or extracorporeal circulation are involved, and if ROTEM and routine coagulation panel tests cannot reveal a defect in hemostasis responsible for bleeding. However, the relationship between platelet function abnormalities and abnormal clinical bleeding still remains unclear. It may be helpful to assign a hematologist or transfusion specialist to a multidisciplinary team treating acutely bleeding patients, if proper blood component therapy cannot be achieved by the OR unit team, including anesthesiologists trained in coagulation management and point-of-care monitoring.

There is still no generally accepted simple reliable method for measuring platelet function. Static tests, such as the measure of b-thromboglobulin, capture only one single point in time and cannot accurately reflect the dynamic processes encountered intraoperatively. Dynamic tests, such as the *in vivo* bleeding time, reflect the time-dependent contribution of platelets to overall clot formation. However, the *in vivo* bleeding time is an old test method in which the time until cessation of bleeding after incision of the skin by a specific device is determined. The bleeding time is poorly standardized, temperature and drug dependent (catecholamines), influenced by vascular disorders, lacks specificity and sensitivity, and is not predictive of bleeding.<sup>85</sup> The bleeding time increases unspecifically during surgery and transfusion,<sup>73</sup> and does not allow the differentiation between bleeding and non-bleeding patients.<sup>38</sup>

Several modern tests on the verge of clinical implementation test the platelet's response to an agonist. The Platelet Function Analyzer PFA-100 (Dade) provides a measure of platelet function in citrated whole blood. The device measures platelet function at high shear rates. The blood sample of 800  $\mu\text{L}$  is added to a reservoir well in a disposable cartridge. The instrument aspirates the blood sample under constant vacuum through a capillary and the microscopic aperture within a membrane coated with platelet agonists, collagen and either epinephrine or adenosine diphosphate (ADP). This leads to the attachment, activation and aggregation of platelets forming a plug. The time taken to occlude the aperture is known as closure time and is a function of platelet count and reactivity, von Willebrand factor activity, and hematocrit.<sup>86</sup> This method rapidly identifies aspirin effects and platelet disorders prior to surgery.<sup>32, 34, 87</sup> In patients with preoperatively identified platelet dysfunctions shortening of the PFA-closure time after desmopressin infusion should be assessed (desmopressin response test). In cardiac surgical patients, the preoperative PFA-100 closure time correlated with postoperative blood loss in some studies,<sup>88</sup> but not in others.<sup>89</sup> A Medline search on the use of the PFA-100 during massive transfusion failed to retrieve any relevant references. Major limitations of the PFA-100, as an intraoperative point-of-care system in massive transfusion, include its strong dependence on platelet count (100 000  $\mu\text{L}$ ) and hematocrit (>30%).

Optical and impedance platelet aggregometry assess platelet reactivity by measuring changes in luminescence or impedance upon platelet agonist stimulation. Originally, these techniques have only been performed in specialized laboratories by experienced technicians. The need for preparation of platelet rich plasma at a certain number of platelets limited widespread application of optical aggregometry (Born). Further limitations were the dependence of temperature, stirring rate, and limited standardization. Nevertheless, optical aggregometry remains the accepted gold standard for the detection of platelet function until now. The novel impedance aggregometer Multiplate (Dynabyte) is a significant step forward and avoids several methodological problems of the original platelet aggregometry, especially by using whole

blood, disposable test cuvettes, various commercially available test reagents at standardized concentrations (collagen, arachidonic acid, ADP, thrombin receptor activator peptide, ristocetin), and an automated pipetting system. The Multiplate could potentially provide differential diagnostic information required for evidence based therapy in acute bleeding problems. This device has been used successfully in the diagnosis of antiplatelet drugs, and the prediction of blood loss in cardiac surgery.<sup>90, 91</sup> Although aggregometry has recently been reviewed as evidence based coagulation monitoring,<sup>52</sup> the Multiplate assay has not been validated for low platelet counts and, thus, its use in hemorrhagic thrombocytopenia remains to be determined.

A modified thrombelastographic assay has been introduced as platelet mapping assay (Haemoscope): heparin-anticoagulated whole blood is clotted by a reptilase-factor XIIIa activator mixture.<sup>92</sup> This  $\text{MA}_0$  is proportionate to platelet activation and is compared to the  $\text{MA}_{\text{ADP/AA}}$  in clotted blood with additional ADP or arachidonic acid activation, as well as to the  $\text{MA}_{\text{KH}}$  in citrated blood with kaolin activation and heparinase addition. Platelet reactivity is calculated by:  $\text{MA}\% = 100 \times (\text{MA}_{\text{ADP/AA}} - \text{MA}_0) / (\text{MA}_{\text{KH}} - \text{MA}_0)$ . This assay has been recommended for monitoring the reversal of clopidogrel and nonsteroidal anti-inflammatory drugs inhibition before surgery.<sup>93</sup>

Platelet monitoring techniques assessing the platelet's response to various agonists are emerging, such as Hemostatus (Medtronic), Rapid Platelet Function Analyser (Ultegra, Accumetrics), Clot Signature Analyzer (CSA, Xylum), and Platelet Works (ICHOR, Helena Bio Science). These tests are approved in the United States of America for monitoring platelet function during cardiac surgery (Hemostatus) and for monitoring glycoprotein IIb/IIIa inhibitors (Rapid Platelet Function Analyser). Clot Signature Analyzer and Platelet Works were independent predictors for transfusion after cardiac surgery. Hemodyne Platelet Analysis System (Hemodyne Inc.) and Cone and Plate Analyser (CPA Impact; Diamed) measure platelet/fibrin network and platelet deposition on an artificial surface, respectively, and share a high sensitivity for glycoprotein IIb/IIIa inhibitors. Costs, long observation times, diffi-

culties in interpretation of the complex reaction tracings limited broad clinical adoption of these tests in the treatment of platelet-related bleeding.

Flow cytometric assay for adhesive protein expression and receptor activation involved in adhesion, aggregation, and secretion, as well as intracellular signal transduction have been developed. None of the methods has yet entered clinical routine applications, but they are valuable tools in scientific platelet research.

### *Predictors of hypercoagulability*

Major surgical procedures induce an acquired postoperative hypercoagulable state with increased platelet reactivity, decreased fibrinolysis, and decreased anticoagulants (antithrombin). The TEG has been used successfully in the detection of an increased risk for thromboembolic events.<sup>94</sup> Thrombus generation is calculated from the first derivative of the TEG waveform.<sup>95</sup> Validation of ROTEM in a model of systemic coagulation activation has recently been published.<sup>96</sup> In patients with postoperative myocardial ischemia, increased platelet reactivity was identified by significantly shorter ADP-induced PFA-100 closure times.<sup>97</sup> Aspirin and clopidogrel resistance has been observed as a transient phenomenon early after cardiac surgery and monitoring of the antiplatelet effectiveness has been recommended.<sup>98</sup> Close coagulation monitoring with ROTEM and PFA-100 to achieve sufficient, but not overwhelming, multimodal anticoagulation has been recommended in patients with cardiac assist devices.<sup>99</sup>

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Address reprint requests to: S. Kozek-Langenecker, M.D. Prof., Department of Anesthesiology and General Intensive Care, Clinical Division B, Vienna Medical University, Währinger Gürtel 18-20, A-1090 Vienna, Austria. E-mail: sibylle.kozek@meduniwien.ac.at