Rotational Thromboelastometry (ROTEM)-Based Coagulation Management in Cardiac Surgery and Major Trauma

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FOR MAJOR BLEEDING related to severe trauma, major surgery, or chronic anticoagulation, a rapid assessment of hemostatic function is crucial so that optimal fluid replacements and blood transfusion can be administered without delays.1-6 Although the safety of blood products with regard to viral transmission risks has improved in recent years,7,8 transfusions of allogeneic erythrocyte and plasma products have been implicated in serious adverse events, including nosocomial infections, acute lung injury, and organ dysfunction.9-12 Obtaining conventional laboratory tests, such as the prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level, during acute bleeding is difficult because of a long turn-around time (>30 min).13,14 Furthermore, laboratory PT/international normalized ratio and aPTT may not be particularly useful in predicting bleeding after trauma or invasive procedures.15,16

The prime example of bleeding management is preemptive transfusions of fresh-frozen plasma (FFP) and platelet concentrates according to the erythrocyte requirement in major trauma cases.17,18 This so-called “damage control resuscitation” (DCR; Table 1) originally was advocated for battlefield resuscitation in which laboratory testing and transfusion resources were limited. However, plasma product transfusion according to DCR became increasingly popular in US civilian trauma centers and operating rooms.17,19 The prevention of trauma-induced coagulopathy and subsequent nonsurgical bleeding is a major advantage of DCR,20 but the DCR approach lacks a specific target for replacement and a consideration for interindividual variability in coagulation factor levels and vascular (endothelial) responses. Implementing transfusion algorithms based on point-of-care (POC) coagulation testing can be effective in decreasing transfusion requirements in elective or urgent cardiac surgical settings.21-23 In this review, the practical use of thromboelastometry is discussed relating to the diagnosis of coagulopathy and optimizing hemostatic interventions.

**POC TESTING AND TIMING OF HEMOSTATIC INTERVENTION**

PT (or international normalized ratio), aPTT, fibrinogen level (Clauss method and its modifications), and platelet count are the tests performed most commonly in managing perioperative bleeding. Except for the platelet count, these laboratory tests require a separation of plasma from whole blood before testing, and, thus, a typical turn-around time is in the range of 30-90 minutes.13,24 Abnormalities detected in these tests are followed by requests for specific blood components. The choice of hemostatic therapies also affects the lag time before intervention. The time required for thawing FFP and cryoprecipitate is typically 30-60 minutes, but less time is needed for platelet concentrates and thawed plasma. Factor concentrates, such as fibrinogen concentrate, and recombinant activated factor VII (rFVIIa) can be administered rapidly (<10 min) because they are reconstituted in small volumes and infused irrespective of blood type.

One of the key facts behind DCR is to prevent the delay of transfusion therapy for patients in whom the risk of hemorrhagic death is considerably greater than transfusion-associated complications.25 However, a substantial number of patients may receive allogeneic plasma products inappropriately or in excess, which collectively increase the risk for transfusion-related adverse events.26 By implementing rapid POC coagulation testing, hemostatic interventions can be more individualized and goal directed (targeted) instead of indiscriminate applications of DCR. Currently available POC coagulation tests are classified into 3 categories. The first category includes POC whole-blood PT and aPTT for a rapid evaluation (5-10 min) of plasmatic coagulation. POC PT has been shown to have a reasonable agreement with plasma-based PT.13,27,28 However, PT and aPTT are sensitive only to severe hypofibrinogenemia (<60-70 mg/dL) and are insensitive to FXIII deficiency or...
fibrinolysis. Further, PT and aPTT have different sensitivities to hemodilution-induced decreases in procoagulant factor levels, and neither test reflects the total amount of thrombin that can be generated in plasma. The second category includes whole-blood platelet function tests, which are used increasingly to monitor therapeutic responses to aspirin, clopidogrel, and other platelet adenosine-5'-diphosphate antagonists. Evaluating the extent of platelet inhibition by antiplatelet agents may be useful in optimizing the perioperative risks of thrombosis and hemorrhage. Although a detailed discussion of platelet function monitoring is beyond the scope of this review, Platelet Mapping will be discussed later as a modified technique of thrombelastography (TEG; Haemonetics-Haemoscope, Niles, IL). The third category includes TEG and rotational thromboelastometry (ROTEM; TEM Systems, Raleigh, NC). These 2 systems are suitable for timely decision making (within 20 min) in hemostatic interventions. Indeed, the decrease of postoperative blood loss without increasing the blood component usage or mortality has been shown in a recent meta-analysis, including TEG and ROTEM. Rapid detection of coagulopathy by TEG or ROTEM allows a timely preparation (thawing) of blood products or a prompt intervention using plasma-derived or recombinant factor concentrate.

**COAGULATION TESTING ON ROTEM**

The basic principles and technical aspects of TEG and ROTEM have been reviewed elsewhere. In this article, the practical applications of ROTEM are described because this system currently offers comprehensive tests of coagulation. For standard ROTEM measurements, a citrated whole-blood sample (300 μL) is placed in a plastic cup using an automated pipette (Fig 1). The sample is recalcified with CaCl₂, 0.2 mmol/L (StarTEM; 30 μL) and activated with 20 μL of an EXTEM (tissue factor [TF]) or INTEM (ellagic acid) reagent. Subsequently, the plastic pin is immersed in the blood. Once thrombin is generated in the blood, platelets are activated to express glycoprotein (GP) IIb/IIIa receptors, and fibrin is formed and polymerized. The interactions of GP IIb/IIIa receptors and polymerized fibrin increase the torque (viscoelasticity) between the cup and the rotating pin (at a 4.75° angle). The breakdown of fibrin strands by fibrinolysis decreases the torque. The change in torque is detected optically and is processed by the microprocessor to trace the clot formation and breakdown.

The commonly used ROTEM variables include coagulation time (CT; seconds), clot formation time (seconds), α-angle (degrees), amplitude at 10 minutes after CT (A10; millimeters), and maximum lysis (ML; percent decrease in amplitude 60 min after MCF).
maximum clot firmness (MCF; millimeters), and maximum lysis (ML; percent decrease in amplitude 60 min after MCF; Fig 1). CT represents the onset of coagulation, whereas the clot formation time and α-angle represent the initial rate of fibrin polymerization. MCF is a measurement of the maximal viscoelastic strength of the clot. An ML >15% is used for the diagnosis of a premature breakdown of clot (hyperfibrinolysis). Normal ranges are summarized in Table 2. The reference ranges of TEG differ from those of ROTEM because of different sample types (citrated vs noncitrated) and coagulation activators (kaolin vs INTEM or EXTEM).

In addition to EXTEM and INTEM, several other tests can be used in conjunction to diagnose specific coagulation problems. FIBTEM is a modified EXTEM test (Fig 2A) with cytochalasin D, which inhibits platelet cytoskeletal reorganization and, thus, fibrin(ogen) binding to platelet GP Ib/IIa. By combining EXTEM and FIBTEM, the differential diagnosis of thrombocytopenia and/or hypofibrinogenemia is feasible within 20 minutes (Fig 2B, C). APTEM is also a modified EXTEM, in which aprotinin inhibits plasmin in vitro if systemic fibrinolysis was present (Fig 2D).

HEPTEM contains heparinase in addition to the INTEM reagent. It is used as a pair with INTEM for the diagnosis of systemic heparin activity (Fig 2E). Although INTEM and kaolin-activated TEG are intrinsic pathway tests, the sensitivity and specificity are considerably different. Therefore, the cutoff values for ROTEM cannot be applied simply to TEG.

HEMOSTATIC MECHANISMS IN VIVO

In the event of a vascular injury (Fig 3A), a localized hemostatic response is triggered by subendothelial collagen and TF, which are exposed to the circulating blood. Circulating platelets play a particularly important role in arterial hemostasis. The initial tethering of platelets to collagen is mediated by TF, which are exposed to the circulating blood. Circulating platelets, GP Ib/IX, and other platelet agonists are minimally activated (depicted as S-E-A in Fig 3C) on the activated platelet surface to augment the local generation of thrombin and polymerized fibrin. After the initial activation of thrombin by the extrinsic pathway, the propagation of thrombin formation mainly involves the “intrinsic pathway.” Thrombin can activate FXI, which efficiently converts FIX to FIXa. On the activated platelet surface, FIXa in combination with thrombin-activated FVIIa becomes the major activator (intrinsic tenase) of FX. Subsequently, FXa and thrombin-activated FVa form a complex (prothrombinase), which exponentially increases the conversion of prothrombin (FII) to thrombin. Once activated by adenosine-5'-diphosphate-stimulated, each platelet expresses a large number of GP Ib/IIa receptors (>12,000) for fibrinogen binding. Platelet-bound fibrinogen is converted to a fibrin monomer by thrombin. Fibrin monomers are polymerized by plasma and platelet-derived FXIIIa, a transglutaminase, which requires thrombin-mediated activation. Polymerization of fibrin on platelets stabilizes the primary hemostatic plug. On ROTEM and TEG, major hemostatic responses involving thrombin-activated platelets (GP Ib/IIa), fibrin, and FXIIIa are reflected, although the contributions of the von Willebrand factor, platelet GP Ib/IX, and other platelet agonists are minimal.

HEMOSTATIC INTERVENTIONS

It is well known that blood transfusion practice varies among individuals and institutions. In case of bleeding, FFP, platelet concentrates, and cryoprecipitate often are transfused empirically without laboratory testing. In addition to these allogeneic products, plasma-derived or recombinant factor concentrates, such as fibrinogen concentrates, prothrombin complex concentrates, and rFVIIa, have been used for perioperative hemostasis. Recent clinical data have shown that ROTEM testing is a practical method to standardize the local transfusion practice. Normal ranges of ROTEM testing are based on a multicenter study in healthy adult volunteers (Table 2). Hemositc intervention(s) should be considered for nonsurgical bleeding in the presence of abnormal ROTEM results. Threshold ROTEM values for interventions may vary among different types of vascular injury. In this section, several hemostatic products are discussed in relation to ROTEM parameters, but the availability of products differs among institutions and countries. Therefore, it is prudent to validate or modify the herein-described algorithm for suitability at each institution.
Fig 2. Examples of rotational thromboelastometric tracings. (A) Normal (EXTEM, FIBTEM): EXTEM-MCF (normal, 49-71 mm) and FIBTEM (normal, 9-25 mm). (B) Thrombocytopenia (EXTEM, FIBTEM): platelet count 74 \times 10^9/L and fibrinogen 170 mg/dL. (C) Thrombocytopenia and hypofibrinogenemia (EXTEM, FIBTEM): platelet count 57 \times 10^9/L and fibrinogen 78 mg/dL. (D) Systemic fibrinolysis (EXTEM, APTEM): normal ML is <15%. (E) Heparin effect (INTEM, HEPTEM): prolonged CT (1,500 s) at INTEM (normal range, 137-246 s) is corrected at HEPTEM (ie, \text{CT}_{\text{INTEM}}/\text{CT}_{\text{HEPTEM}} = 1.0 in the absence of heparin). APTEM, modified EXTEM test with aprotinin; CT, coagulation time; EXTEM, tissue factor reagent; FIBTEM, modified EXTEM test with cytochalasin D; HEPTEM, heparinase plus INTEM reagent; INTEM, ellagic acid reagent; MCF, maximum clot firmness; ML, maximum lysis (percent decrease in amplitude 60 min after MCF). (Color version of figure is available online.)
Collagen

EXTEM-MCF is 55.5 mm (Table 3). When the FIBTEM-MCF is 45 mm and the FIBTEM-A10 values can be used differentially to diagnose GP IIb/IIIa receptors. For microvascular bleeding, EXTEM-thrombin-activated platelets and polymerized fibrin via platelet factor VIIa.

Platelets

The clot firmness of EXTEM shows the tensile strength of the whole-blood clot, which reflects the interaction between thrombin-activated platelets and polymerized fibrin via platelet GP Ib/IX receptors. For microvascular bleeding, EXTEM- and FIBTEM-A10 values can be used differentially to diagnose the need for platelet transfusion or fibrinogen replacement. Thrombocytopenia (<50-100 × 109/L) is suspected when the EXTEM-MCF is <45 mm and the FIBTEM-MCF is >8-10 mm (Table 3). When the FIBTEM-MCF is >10 mm, cryoprecipitate or fibrinogen is withheld unless bleeding is likely to continue and lower fibrinogen levels. Platelet transfusion and fibrinogen replacement usually are indicated when the EXTEM-MCF is <35 mm. When the EXTEM-MCF is >45 mm, severe thrombocytopenia (<50 × 109/L) is unlikely, but hereditary platelet dysfunction or antiplatelet effects of aspirin and P2Y12 antagonists (ticlopidine, clopidogrel, prasugrel, etc) may not be excluded. Platelet function tests can be used preoperatively to screen high-risk patients. PFA-100 (Siemens, Tarrytown, NY) can be useful in screening patients with von Willebrand disease or a platelet GP Ib defect (Bernard-Soulier syndrome). The VerifyNow system (Accumetrics, Inc., San Diego, CA) and whole-blood impedance aggregometry (Multiplate, DynaBite, Munich, Germany) are used increasingly to monitor therapeutic responses to aspirin and P2Y12 antagonists. For TEG, PlateletMapping is available for the evaluation of platelet inhibition by aspirin or clopidogrel. For this assay, a heparin-anticoagulated blood sample is used specifically to inhibit thrombin, which masks the antiplatelet effects of aspirin and clopidogrel. For PlateletMapping, fibrin polymerization is achieved by the mixture of reptilase and activated FXIII. Platelets are activated separately by the specific platelet activator (arachidonic acid for aspirin and adenosine-5'-diphosphate for clopidogrel). Decreased maximum amplitudes on PlateletMapping compared with kaolin-activated TEG have been observed in perioperative patients with gross platelet inhibition by aspirin or clopidogrel.

Plasma and Prothrombin Complex Concentrate

The CT of EXTEM or INTEM can be used in determining the need for administering FFP or prothrombin complex concentration (PCC). The latter refers to plasma-derived concentrates of vitamin K-dependent factors (FVII, FIX, FX, prothrombin, protein C, and protein S). Coagulation factor replacements are considered when CT values are prolonged (EXTEM-CT >100 s or INTEM-CT >240 s) and when residual heparin effects, thrombocytopenia, and hypofibrinogenemia have been addressed appropriately (Table 3). In patients who have received intravenous heparin, a proper neutralization of heparin can be confirmed by equal CT values between INTEM and HEPTEM (Fig 2E). Plasma or PCC can be used to correct a factor deficiency for a prolonged CT on HEPTEM.

Similar to PT and aPTT, EXTEM-CT and INTEM-CT are defined as the onset of blood coagulation after activation with TF and ellagic acid, respectively. However, ROTEM-CT values are not equivalent to PT and aPTT. In trauma-induced coagulopathy, the correlation between the CT value and PT/ aPTT was found to be rather poor (r = 0.47-0.53). The reaction time (equivalent of CT) of kaolin-activated TEG has been reported to correlate poorly with PT or aPTT. Abnormal PT/aPTT values (>1.5 times normal) are found frequently when ROTEM parameters related to fibrin polymerization (EXTEM-A15 or clot formation time) are abnormal. Severe hypofibrinogenemia (<60-70 mg/dL) can be the cause of prolonged CT and PT/aPTT.

Fibrinogen-Rich Components

Cryoprecipitate is used commonly in North America for fibrinogen replacement. In many European countries, this product is no longer available, and plasma-derived fibrinogen concentrate is used as a substitute. The minimal level of fibrinogen previously was thought to be 80-100 mg/dL. However, higher fibrinogen levels (150-200 mg/dL) have been recommended in recent guidelines. It is plausible that a minimal fibrinogen level of 80-100 mg/dL is adequate for congenital afibrinogenemia (ie, normal factor levels other than fibrinogen), but higher fibrinogen levels (150-200 mg/dL) are necessary for a multifactorial deficiency associated with perioperative coagulopathy. There are several published data that support the efficacy of fibrinogen-rich components. In pediatric
Recently, Rahe-Meyer et al. reported that perioperative blood 
level was 158 to correct microvascular bleeding. The post-treatment fibrino-
cryoprecipitate when the platelet transfusion was not effective 
of plasma fibrinogen at 200 mg/dL. For microvascular 
bypass (CPB), a FIBTEM-MCF of 10 mm was a good estimate 
plasma fibrinogen. Therefore, it is reasonable to maintain a 
bleeding, fluid resuscitation and blood loss continuously lower 
precipitate (39.8 platelet and FFP transfusions compared with platelet and cryo-
concentrate; TXA, tranexamic acid.

Table 3. Hemostatic Interventions Based on Rotational Thromboelastometric Results

<table>
<thead>
<tr>
<th>Clot Firmness</th>
<th>EXTEM-MCF Parameters</th>
<th>EXTEM-MCF</th>
</tr>
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<tbody>
<tr>
<td>&lt;35 mm</td>
<td>Cryo/fibrinogen +</td>
<td>Platelet 1 U</td>
</tr>
<tr>
<td>≥35 mm</td>
<td>Cryo/fibrinogen +</td>
<td>Platelet 1 U</td>
</tr>
</tbody>
</table>

If bleeding is uncontrolled, consider FFP or PCC based on EXTEM-CT as below or consider platelet transfusion in patients on P2Y12 inhibitors.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Management</th>
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</thead>
<tbody>
<tr>
<td>Prolonged CT Values</td>
<td></td>
</tr>
<tr>
<td>INTEM-CT/HEPTEM-CT ratio &gt;1.0</td>
<td>Residual heparin</td>
</tr>
<tr>
<td>EXTEN-CT &gt;100 s or</td>
<td></td>
</tr>
<tr>
<td>INTEM-CT &gt;240 s</td>
<td>Low coagulation factors</td>
</tr>
<tr>
<td>FIBTEM-A10 &lt;5 mm</td>
<td>Very low fibrinogen (&lt;100 mg/dL)</td>
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</tbody>
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Fibrinolysis Patterns†

<table>
<thead>
<tr>
<th>Fibrinolysis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolysis &lt;20 min</td>
<td>Fulminant fibrinolysis</td>
</tr>
<tr>
<td>Fibrinolysis 20-40 min</td>
<td>Early fibrinolysis</td>
</tr>
<tr>
<td>Fibrinolysis &lt;40 min</td>
<td>Clot retraction or late fibrinolysis</td>
</tr>
</tbody>
</table>

Abbreviations: A10, amplitude at 10 minutes after coagulation time; APTEM, modified EXTEM test with aprotinin; Cryo, cryoprecipitate; CT, coagulation time; EACA, 6-aminocaproic acid; EXTEM, tissue factor reagent; FIBTEM, modified EXTEM test with cytochalasin D; FFP, fresh-frozen plasma; HEPTEM, heparinase plus INTEM reagent; INTEM, ellagic acid reagent; MCF, maximum clot firmness; PCC, prothrombin complex concentrate; TXA, tranexamic acid.

†FIBTEM-A10 at 8 mm may be used as a cutoff instead of FIBTEM-MCF at 10 mm. For fibrinogen replacement, Cryo, 10 U, or plasma-derived fibrinogen concentrate, 2 g, is administered. If FIBTEM-A10 is <5 mm, the dose of Cryo or fibrinogen concentrate is doubled.

†Antifibrinolytic agents are used only after the risk of bleeding is greater than the risk of thrombosis or worsening of disseminated intravascular coagulation.

Cardiac surgical patients (body weight >8 kg), Miller et al. reported that 24-hour chest tube drainage was greater after platelet and FFP transfusions compared with platelet and cryo-
cryoprecipitate (39.8 v 20.2 mL/kg). These patients received FFP or cryoprecipitate when the platelet transfusion was not effective 
correct microvascular bleeding. The post-treatment fibrino-
gen level was 158 ± 27 mg/dL in the platelet-FFP group versus 
237 ± 67 mg/dL in the platelet-cryoprecipitate group. More 
recently, Rahe-Meyer et al. reported that perioperative blood 
usage (erythrocytes, FFP, and platelets) was decreased by 
maintaining a higher plasma fibrinogen level (mean, 360 ± 60 
mg/dL) using a purified fibrinogen concentrate compared with the 
conventional management (mean fibrinogen, 210 ± 30 
mg/dL) for replacement of the ascending aorta.

The FIBTEM test has been used commonly in ROTEM for 
the clinical assessment of fibrin polymerization in whole blood. FIBTEM-MCF is well correlated with plasma fibrinogen levels (r = 0.85-0.87). In trauma-induced coagulopathy, a FIB-
TEM-A10 of <5 mm was reported to be a good predictor of 
low plasma fibrinogen (<100 mg/dL), with a sensitivity of 91% 
and a specificity of 85%. In patients after cardiopulmonary 
bypass (CPB), a FIBTEM-MCF of 10 mm was a good estimate 
of plasma fibrinogen at 200 mg/dL. For microvascular 
bleeding, fluid resuscitation and blood loss continuously lower 
plasma fibrinogen. Therefore, it is reasonable to maintain a 
FIBTEM-MCF at 10 mm using a cryoprecipitate or fibrinogen 
concentrate (Table 3).

FIBTEM testing can be performed in heparinized samples 
(e.g., during CPB), and, therefore, hypofibrinogenemia can be 
detected early so that the fibrinogen level can be thawed or fibrinogen concentrates can be prepared.

Recombinant Activated Factor VIIa

The use of rFVIIa is indicated in hemophilia patients who 
have developed neutralizing antibodies against FVIII or FIX. Its use also is common in severe perioperative bleeding after 
cardiac surgery and major trauma. The efficacy of rFVIIa to 
generate thrombin depends on the available TF. High TF 
concentrations in PT and EXTEM make these tests insensitive 
for delineating the in vivo efficacy of rFVIIa in surgical pa-
ents and in hemophilic patients. Alternatively, diluted TF 
(eg, innovin, 1:17,000) has been tried, with mixed results, in 
monitoring the therapeutic response to rFVIIa in hemophilia. 
Kaolin-activated TEG has been used to evaluate the TF-inde-
dent hemostatic activity of rFVIIa in hemophilia. In nonhe-
mophilic surgical patients, rFVIIa continues to be used as a 
second-line intervention after the failure of platelet and plasma 
transfusions. In this regard, TEG and ROTEM can be used to 
diagnose major causes of bleeding, such as thrombocytopenia,
hypofibrinogenemia, and fibrinolysis, which preclude the optimal hemostatic effect of rFVIIa.84,86

Antifibrinolytic Therapy

Systemic fibrinolysis can be caused by an increased endothelial release of tissue plasminogen activator87 or by a decreased protease inhibition of tissue plasminogen activator and plasmin.85 In ROTEM, hyperfibrinolysis is suspected when the decrease of the amplitude over 1 hour is >15% of MCF (Table 3, Fig 2D). The APTEM test is a modified EXTEM test with added aprotinin (plasmin inhibitor) at ROTEM. The resolution of fibrinolysis on APTEM compared with EXTEM confirms ongoing systemic fibrinolysis.14 In 15%-20% of patients with major trauma, overt hyperfibrinolysis is observed at ROTEM and TEG.36,37,88 Even in the absence of systemic fibrinolysis, a fibrin clot tends to be more susceptible to a plasmin-mediated breakdown after hemodilution owing to a progressive loss of endogenous fibrinolysis inhibitors.89 Using ROTEM, it may be feasible to use antifibrinolytic therapy selectively in patients at risk for systemic fibrinolysis,90 which can be associated with severe injuries and increased mortality.74,88

ROTEM-BASED TRANSFUSION ALGORITHMS IN CARDIAC SURGERY

Cardiovascular surgical patients are at increased risk for vascular thrombosis associated with atheromatous vascular disease, atrial fibrillation, implanted coronary stents, and mechanical heart valves.90 Antiplatelet and antithrombotic therapies often are prescribed for preoperative patients. Balancing the risk of thrombosis against hemorrhage is one of the most difficult tasks for perioperative physicians.90,91 Intraoperatively, these patients are anticoagulated with heparin for CPB or vascular anastomosis. Hemorrhage and hemodilution decrease circulating levels of coagulation factors and inhibitors.85 At the conclusion of surgery, heparin anticoagulation requires a prompt reversal using protamine to establish hemostasis (clot formation). Antifibrinolytic therapy with tranexamic acid or e-aminocaproic acid commonly is used during CPB as a prophylactic measure to decrease bleeding.92,93 However, the transfusion of allogeneic plasma and platelet products often is necessary to achieve hemostasis in complex CPB cases.83,95

Transfusion algorithms using TEG or ROTEM have been shown previously to decrease postoperative blood loss and transfusion requirements in cardiac surgery.22,23 An example of ROTEM-based coagulation management in cardiac surgery is presented (Fig 4). EXTEM and FIBTEM are insensitive to heparin (<6 U/mL), and they can be tested toward the end of CPB (eg, rewarming).30,51 Based on EXTEM/FIBTEM results (Table 3), hemostatic therapy after CPB can be planned in advance, which may decrease the long interval from protamine administration to hemostatic intervention(s). After the correction of surgical bleeding and metabolic parameters (eg, pH status, body temperature), a ROTEM-based protocol allows patient-specific hemostatic therapy targeted to replace deficient coagulation element(s) rather than indiscriminately transfusing platelets and plasma products.94

The initial approach to hemostasis generally involves the restoration of plasma fibrinogen to the range of 150-200 mg/dL (FIBTEM-MCF 8-10 mm; Table 3) with continuous antifibrinolytic therapy.5,6 Platelet transfusion is used in patients with thrombocytopenia (EXTEM-MCF <45 mm and FIBTEM >8-10 mm) and those with platelet dysfunction from antiplatelet therapy. Preoperative platelet function tests may be helpful to diagnose and manage bleeding related to platelet dysfunction.30,32 In patients who continue preoperative vitamin K antagonist therapy and in those who underwent extensive hemodilution or cell salvage, plasma or PCC may be necessary to restore procoagulant zymogens. EXTEM-CT values >100 seconds may indicate a procoagulant factor deficiency, particularly FVII, FIX, FX, and prothrombin (Table 3). INTEM-CT values >240 seconds also may be used to diagnose procoagulant factor deficiency, but excess heparin or protamine can prolong INTEM-CT.43 As much as 20-30 mL/kg of plasma may be required to correct moderate-to-severe factor deficiency, whereas PCC can be given in smaller volumes (80 mL per 25-IU/kg dose for an 80-kg person) to supplement key hemostatic factors.96,97 In patients who required acute vitamin K antagonist reversal for cardiac surgery, PCC was shown to be hemostatically more effective by increasing plasma FX and prothrombin levels compared with FFP.91,98

Additional clinical studies are necessary to establish the safety and efficacy of plasma-derived and recombinant factor concentrates in combination with conventional plasma and platelet transfusions. The transfusion protocol based on ROTEM and TEG should be useful in the evaluation of coagulopathy and in the patient-specific allocation of transfusion products in cardiac surgical patients.22,23,48,50,51

Rewarming on CPB

<table>
<thead>
<tr>
<th>Protamine administration</th>
<th>EXTEM/FIBTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostatic therapy or additional protamine</td>
<td>EXTEM/FIBTEM</td>
</tr>
<tr>
<td>Evaluate therapeutic response, if indicated, INTEM/HEPTEM/APTEM or PLT function tests</td>
<td>EXTEM/FIBTEM</td>
</tr>
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</table>

Fig 4. Rotational thromboelastometry-based coagulation management in cardiac surgery. Early detection of coagulopathy and preparations for hemostatic therapies are feasible using EXTEM and FIBTEM in the late phase of cardiopulmonary bypass (CPB; at rewarming). Clinical bleeding consistent with coagulopathy can be confirmed after repeating EXTEM and FIBTEM and optimizing heparin neutralization (CTINTEM/CTHEPTEM = 1.0). If antifibrinolytic therapy is not used routinely, APTEM can be useful to exclude systemic fibrinolysis as a cause of bleeding. Platelet (PLT) function test results should be considered in patients who recently used aspirin and P2Y12 antagonists. APTEM, modified EXTEM test with aprotinin; CT, coagulation time; EXTEM, tissue factor reagent; FFP, fresh-frozen plasma; FIBTEM, modified EXTEM test with cytochalasin D; HEPTEM, heparinase plus INTEM reagent; INTEM, ellagic acid reagent.
with cytochalasin D; INTEM, ellagic acid reagent; FFP, fresh-frozen plasma; FIBTEM, modified EXTEM test; TEM, modified EXTEM test with aprotinin; EXTEM, tissue factor mediated test.

Initial ROTEM testing should be performed immediately to establish a baseline of coagulation status. If the patient has significant hypocoagulability, an extended test protocol may be indicated. The standard ROTEM test battery includes EXTEM, FIBTEM, and APTEM. These tests can provide a rapid evaluation of thrombocytopenia, hypofibrinogenemia, and the profibrinolytic state.

EXTEM/FIBTEM/ APTEM allows a rapid evaluation of thrombocytopenia, hypofibrinogenemia, and the profibrinolytic state. Specific component replacement and antifibrinolytic therapy can be included in the damage control resuscitation (DCR). Rotational thromboelastometry (ROTEM) assessment can be repeated during and after surgical intervention, if indicated. For persistent microvascular bleeding, platelet (PLT) function testing should be considered to evaluate the defect in the primary hemostasis (eg, aspirin and P2Y12 antagonists). APTEM, modified EXTEM test with aprotinin; INTEM, tissue factor reagent; FFP, fresh-frozen plasma; FIBTEM, modified EXTEM test with cytochalasin D; INTEM, ellagic acid reagent.

ROTEM-BASED TRANSFUSION ALGORITHMS IN MAJOR TRAUMA

Most patients with major traumatic injuries are admitted with various degrees of cardiorespiratory and metabolic disturbances. With an ongoing need for >4 U of erythrocyte concentrates or a blood loss of >150 mL/min, DCR should be triggered to coordinate timely and sufficient provision of blood products (Fig 5). Although damage-control surgery is pivotal to the survival of patients with multiple injuries, massive fluid resuscitation often is required to counter systemic hypoperfusion and worsening acidosis.20,25 The rapid infusion of crystalloid, albumin, or hydroxyethyl starch can lead to hypothermia and extensive hemodilution of erythrocytes, fibrinogen, and other coagulation factors and inhibitors.100 It is crucial to prevent the lethal triad of coagulopathy, hypothermia, and acidosis by early resuscitative and hemostatic therapies. In view of dynamic changes in the coagulation system and the paucity of hematologic information (eg, chronic antithrombotic therapy), the use of ROTEM is most practical for the comprehensive assessment of hemostatic function in trauma patients. Initial ROTEM testing using EXTEM, FIBTEM, and APTEM allows a rapid evaluation of thrombocytopenia, hypofibrinogenemia, and the profibrinolytic state (Fig 2).

The initial approach based on ROTEM involves the restoration of plasma fibrinogen to the range of 150-200 mg/dL (FIBTEM-MCF 8-10 mm) using plasma (when a large volume is permitted), cryoprecipitate, or fibrinogen concentrates.14 Platelet transfusion is used in patients with thrombocytopenia (EXTEM-MCF <45 mm) and those with suspected platelet dysfunction. Once residual heparin effects and hypofibrinogenemia are excluded, EXTEM-CT values >100 seconds can be addressed with coagulation factor replacements using plasma or PCC (Table 3). EXTEM-CT seems to be more responsive to hemodilution-induced factor deficiency compared with INTEM-CT or kaolin TEG R-time because increased FVIII in stress shortens contact-activated tests.16 In severe injury, low EXTEM-MCF values (<35 mm consistent with thrombocytopenia and hypofibrinogenemia) are accompanied by a profibrinolytic state (ML >15%).36,57,88 The resolution of clot breakdown on APTEM confirms systemic fibrinolysis (Fig 2), and intravenous administration of tranexamic acid, 1-2 g, should be considered unless ongoing intravascular coagulation is suspected clinically (Table 3).89 A coexisting hypocoagulable and profibrinolytic state in major trauma seems to indicate the severity of illness, which demonstrates a correlation with mortality.37,57,88,101

Hemostatic interventions used in DCR are different among trauma centers based on the institutional blood usage policy and the availability of specific components and concentrates.87,69,102,103 It is acceptable to initiate DCR early using allogeneic plasma and platelet products if the risk of hemorrhagic death is considered high.25 Once surgical controls of hemorrhage are attained, more individualized, goal-directed (targeted) transfusions is preferred because of the cumulative risks of transfusion, including acute lung injury, multiple organ failure, immunomodulation, thromboembolic complications, infection, and death.10,12,26,104,105

CONCLUSIONS

Timely hemostatic interventions are pivotal in controlling coagulopathy and bleeding after major surgery and trauma. However, the risks of hemorrhage and transfusion-related complications are to be weighed constantly against each other.12,25,26,104 ROTEM has become increasingly popular in perioperative coagulation management that involves the replacement of multiple coagulation factors. Unlike hereditary hemorrhagic disorders, which usually involve a single factor replacement, perioperative hemorrhage in major surgery and trauma often demands sequential treatments using multiple allogeneic components or factor concentrates.6,8,63,100 Using the goal-oriented transfusion algorithm, clinicians appropriately may select necessary transfusion component(s) instead of empirically administering all components, with potential hazardous effects.34 Recent clinical data have supported the use of ROTEM or TEG in evaluating the clinical efficacies of various hemostatic therapies, which had been seldom studied.64,71,72 Further clinical investigations of hemostatic therapies under the guidance of ROTEM and TEG are warranted to establish the safety, efficacy, and economic impact of various hemostatic components.

REFERENCES


