Perioperative Coagulation Management and Control of Platelet Transfusion by Point-of-Care Platelet Function Analysis

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Key Words

Point-of-care coagulation management · Platelet function analysis · Impedance aggregometry · Thrombelastometry · Cardiac surgery

Summary

Background: About one third of all blood components transfused intraoperatively is used in cardiac surgery, whereas mortality of cardiosurgical patients correlates nearly linear with the number of transfused units of packed red blood cells. Acquired platelet function disorders play a major role in perioperative bleeding in cardiac surgery. Therefore, the use of point-of-care-suitable platelet function analyzers seems to be reasonable in this field. **Methods:** Platelet function analyzer PFA-100®, rotational thrombelastometry (ROTEM®), and multiple platelet function analyzer (Multiplate®) are in principle applicable for point-of-care testing. Since these three analyzers monitor different aspects of platelet function and have different limitations, the selection of the right test system depends on the right question. **Results:** Perioperative use of platelet function analyzers is helpful in prediction of blood loss in cardiac surgery. Perioperative usage of blood components and their respective costs can be reduced by an appropriate coagulation management. **Conclusion:** Algorithms for perioperative coagulation management based on point-of-care testing permit a fast diagnostic and goal-directed therapy of coagulation and functional platelet disorders. The possibility to reduce the mortality of patients and the overall cost for hospital stay is subject of further studies.

Schlüsselwörter

Point-of-Care-Gerinnungsmanagement · Thrombozytenfunktionsanalyse · Impedanz-Aggregometrie · Thrombelastometrie · Herzchirurgie

Zusammenfassung

Hintergrund: Etwa ein Drittel aller intraoperativ verbrauchten Blutkonserven werden im Bereich der Herzchirurgie transfundiert, wobei die Mortalität kardiologischer Patienten nahezu linear mit der Zahl der transfundierten Erythrozytenkonzentrate korreliert. Erworbene Thrombozytenfunktionsstörungen spielen bei perioperativen Blutungen in der Herzchirurgie eine wesentliche Rolle. Dies legt den Einsatz von Point-of-Care-tauglichen Thrombozytenfunktionsanalysatoren in diesem Bereich nahe. **Methoden:** Der Platelet Function Analyzer PFA-100®, die Rotationsthrombelastometrie (ROTEM®) und der Multiple Platelet Function Analyzer (Multiplate®) sind prinzipiell für den Point-of-Care-Einsatz geeignet. Da diese 3 Analysatoren jedoch unterschiedliche Aspekte der Thrombozytenfunktion untersuchen und auch unterschiedliche Limitationen aufweisen, hängt die Auswahl des richtigen Testsystems von der jeweiligen Fragestellung ab. **Ergebnisse:** Der perioperative Einsatz von Thrombozytenfunktionsanalysatoren ist für die Prädiktion des Blutverlusts bei kardiologischen Eingriffen hilfreich. Durch ein entsprechendes Gerinnungsmanagement lässt sich der perioperative Verbrauch an Blutprodukten und die daraus resultierenden Kosten reduzieren. **Schlussfolgerungen:** Auf Point-of-Care-Verfahren basierende Algorithmen zum perioperativen Gerinnungsmanagement ermöglichen eine zeitnahe Diagnostik und zielgerichtete Therapie von Gerinnungs- und Thrombozytenfunktionsstörungen. Ob dadurch auch die Mortalität der Patienten und die Gesamtkosten für den Krankenhausaufenthalt gesenkt werden können, ist Thema weiterer Untersuchungen.

Introduction

In 2004, one third of all intraoperatively used blood products (packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelet concentrates (PC)) have been transfused in thoracic and cardiovascular surgery at the university clinics of Essen. This finding is consistent with the literature that patients undergoing cardiac surgery are at high risk for excessive microvascular bleeding and re-exploration [1]. Laboratory evaluation of platelets and coagulation factors can facilitate the optimal administration of pharmacologic and transfusion-based therapy. However, their turnaround time makes laboratory-based methods impractical for concurrent coagulation management of patients during surgery [2]. Point-of-care (POC) tests enable contemporary and targeted therapy of coagulation disorders [3, 4]. Coupled with algorithms for coagulation management, the use of POC tests may be able to reduce transfusion requirements, re-exploration rates and costs [1, 5, 6].

As a result of our positive experience and a significant reduction in transfusion requirements after inauguration of a ROTEM®-based POC coagulation management scheme in the field of visceral surgery and liver transplantation in 2000, we introduced a POC coagulation management in thoracic and cardiovascular surgery in 2004 [7].

The reduction of transfusion requirements in cardiac surgery is of great importance because there is a nearly linear correlation between the mortality of cardiosurgical patients and the number of transfused PRBC [8]. Furthermore, transfusion of FFP is correlated with the risk of transfusion-related acute lung injury (TRALI) and transfusion-associated cardiocirculatory overload (TACO) [9–14]. In addition, the number of transfused PC shows a negative correlation with the outcome of cardiosurgical patients [15, 16]. This effect seems to be reduced by leucodepletion of PC, which by now is performed routinely in Germany and most parts of Europe [17]. However, with an incidence of 1:1,000 to 1:3,000 bacterial contamination of PC is the most common transfusion-associated risk of infection. Thereby, PC can induce septic complications (1:15,000) with a mortality rate of 1 per 60,000 PC [9, 13, 18–20]. Therefore, the indication for platelet transfusion should be evaluated very carefully, as could be possible with the use of POC analysis of platelet function.

Whereas detection and treatment of hyperfibrinolysis and plasmatic coagulation disorders are the most important aspects of perioperative coagulation management during liver transplantation and multiple trauma, in cardiac surgery heparin effects and disorders of the primary haemostasis – such as thrombocytopenia and especially acquired platelet function disorders – are of primary importance [1, 2, 21–25]. On the other hand therapy with platelet aggregation inhibitors is of vital importance in cardiology to avoid stent thrombosis after implantation of coronary stents – especially in the context of drug-eluting stents [26]. This area of conflict has to be consid-

ered in connection with the selection of the right tool for POC coagulation management.

Methods for Detection of Perioperative Coagulation and Platelet Function Disorders

POC Platelet Function Tests

Since standard methods of platelet function analysis – like Born aggregometry and flow cytometry – are subjected to specialised laboratories, because of the complexity of the tests, perioperative platelet diagnostics is limited primarily to the platelet count, and the response to platelet transfusion is monitored by calculating the platelet-corrected count increment (CCI) and by the clinical parameter ‘bleeding stopped’ [27–29].

Experiences and studies of the last years have shown that POC-suitable coagulation and platelet function analyzers can be helpful in detection of perioperative platelet function disorders and for decisions in context with the therapy with PC, coagulation factor concentrates, and haemostatic drugs. Furthermore, they are able to contribute to the reduction of transfusion requirements and costs [7, 30–34]. In this context, the aptitude of the following three systems has been proved particularly:

- platelet function analyzer 100 (PFA-100®; Dade-Behring, Marburg, Germany),
- rotational thrombelastometry (ROTEM®; Pentapharm GmbH, Munich, Germany),
- multiple platelet function analyzer (Multiplate®; Dynabyte GmbH, Munich, Germany).

These three analyzers are characterized by the following features, which enables their use as POC test systems:

- usage of anticoagulated whole blood (no centrifugation required),
- usage of disposable cartridges or cups (no preparation or cleaning required),
- ease of operation (automatic electronic pipette and computer-assisted operation procedures and analysis of the data for ROTEM and Multiplate).

Ask the Right Question

Since these three analyzers monitor different aspects of platelet function and have different limitations, the selection of the right test system depends on the right question [35] (table 1):

- When shall the analysis be done?
 - preoperative,
 - intraoperative,
 - postoperative.
- What kind of disorder shall be detected or excluded?

Table 1. Comparison of POC methods for platelet function analysis: PFA-100, Multiplate, and ROTEM – characteristics, indications, and limitations

Platelet function analysis	PFA-100	Multiplate	ROTEM
Blood sample	buffered citrated whole blood	heparin or thrombin inhibitor (hirudin) whole blood	citrated whole blood
Shear stress	high	no	low
Stimulator	collagen/ epinephrin (PFA-EPI) or collagen/ADP (PFA-ADP)	collagen (COLtest), AA (ASPItest), ADP (ADPtest), TRAP-6 (TRAPtest) or ristocetin (RISTOtest high or low)	only recalcification (NaTEM); recalcification and thromboplastin (tissue factor) (ExTEM); recalcification and partial thromboplastin (phospholipid) and ellagic acid (InTEM)
Additives	no	prostaglandin E1 (to increase sensitivity for clopidogrel (ADPtest HS)); ASA or tirofiban (to predict therapeutical efficiency or to controll patient's compliance)	cytochalasin D (FibTEM); aprotinin (ApTEM); heparin inhibitor (ExTEM, FibTEM and ApTEM); heparinase (HepTEM); ecarin (EcaTEM); factor VIIa, VIII, XIII, etc. (X-TEM)
Main parameters	closure time (in s)	AUC (in AU × min); <i>aggregation (in AU)</i> ; <i>velocity (in AU/min)</i>	clotting time (in s); clot formation time (CFT in s); amplitude after 5/10/15 min (A5/A10/A15 in mm); maximum clot firmness (MCF in mm); clot lysis index (CLI in %)
Mainly examined platelet function	platelet adhesion	platelet aggregation	platelet-fibrin(ogen) interaction
Focused on platelet receptor system	GPIb/V/IX	GPIIb/IIIa; GPIaIIa, P2Y ₁₂ , PAR1 and PAR4	GPIIb/IIIa; PAR1 and PAR4
Sensitive for	von Willebrand syndrome; Bernard-Soulier syndrome; Morbus Glanzmann; Storage pool disease; ASA effects (>7 days); GPIIb/IIIa receptor inhibitors (too high sensitivity!)	ASA and clopidogrel effects; GPIIb/IIIa receptor inhibitors (linearity within the therapeutic range); platelet function disorders	severe platelet function disorders with resistance to thrombin stimulation; fibrinogen deficiency and polymerisation disorders; hyperfibrinolysis; heparin and hirudin effects; severe coagulation factor deficiency
Control of therapeutical success	ASA; DDAVP	ASA; clopidogrel; GPIIb/IIIa receptor inhibitors	fibrinogen substitution; platelet transfusion; aprotinin; tranexamic acid; heparin; protamine; coagulation factor concentrates
Limitations	low sensitivity for clopidogrel effects; too high sensitivity for GPIIb/IIIa receptor inhibitors; thrombocytopenia < 100/nl; anaemia with Hkt < 35% (Hb < 11 g/dl); flow errors because of platelet aggregation during surgery	von Willebrand syndrome type I	low sensitivity to antiplatelet drugs (ASA, clopidogrel, GPIIb/IIIa receptor inhibitors), oral anticoagulants and low molecular weight heparin
Main field of application	preoperative screening in cases of positive bleeding history ('in vitro BT'); von Willebrand syndrome; control of success for ASA or DDAVP therapy	perioperative POC platelet function analysis; control of success for ASA, DDAVP, clopidogrel or GPIIb/IIIa receptor inhibitor therapy	perioperative POC coagulation management; whole blood coagulation test with special consideration of clot firmness and stability

ASA = acetylsalicylic acid; AU = aggregation units; DDAVP = desamino-delta-D-arginine vasopressin (desmopressin); PAR = protease-activated receptor; POC = point-of-care; TRAP = thrombin receptor activating peptide; TEM = thrombelastometry; NaTEM = native TEM; ExTEM extrinsic activated TEM; InTEM = intrinsic activated TEM; FibTEM = fibrin clot TEM; ApTEM = aprotinin TEM; HepTEM = heparinase TEM; EcaTEM = ecarin TEM; X-TEM = TEM with several coagulation factors as an additive (not commercially available).

- von Willebrand syndrome,
 - acetylsalicylic acid (ASA),
 - clopidogrel,
 - GPIIb/IIIa receptor inhibitors (abciximab, eptifibatide, tirofiban),
 - non-specific platelet function disturbances (e.g. in connection with uraemia, liver cirrhosis, cardiopulmonary bypass, ECMO therapy).
- Which function (receptor) shall be monitored?
- platelet adhesion (GPIb/V/IX receptor; von Willebrand factor),
 - stimulation with epinephrine (α_{2A} receptor),
 - stimulation with collagen (GPIa/IIa receptor),
 - stimulation with arachidonic acid (AA) (activity of cyclooxygenase (COX) 1),
 - stimulation with ADP (P2Y₁₂ ADP receptor),
 - stimulation with thrombin (PAR1 and PAR4 receptor),
 - platelet aggregation (activation of the GPIIb/IIIa receptor),
 - platelet aggregation (inhibition of the GPIIb/IIIa receptor),
 - clot firmness and stability (fibrinogen-platelet interaction).
- Which kind of treatment shall be monitored?
- DDAVP (desmopressin),
 - antifibrinolytics (e.g. aprotinin or tranexamic acid),
 - fibrinogen concentrate (or cryoprecipitate),
 - coagulation factor concentrates (e.g. prothrombin complex concentrate (PCC = PPSB)) or FFP,
 - PC.
- Under which flow condition shall be tested?
- dynamic (with high shear stress blood flow),
 - static (without high shear stress blood flow).

Standardized Questionnaire for Bleeding History

One main problem – not only in platelet function analysis – is to ask the right questions. Preoperative coagulation screening should answer the question ‘Will this patient bleed?’. Actual studies could demonstrate that tests, which were currently used for preoperative screening for coagulation disorders – like prothrombin time (PT), activated partial thromboplastin time (aPTT) and platelet count –, do often not adequately predict intra- or postoperative bleeding complications [36–40]. For example the aPTT was developed to assist the diagnostic use for patients with signs of haemophilia and the question was ‘Why does this patient bleed?’. As the aPTT was never intended to answer the question ‘Will this patient bleed?’, one has to be careful regarding interpretation of aPTT results in this direction. Prolonged aPTT is neither strongly predictive for haemorrhage, nor does a normal aPTT rules out haemorrhagic complications [41]. The main reason for this lack of sensitivity is that aPTT and PT focus on detection of plasmatic

coagulation disorders – like haemophilia (incidence 1:10,000) or deficiency of vitamin K-dependent coagulation factors – whereas hereditary (e.g. von Willebrand syndrome; incidence 1:1,000) or acquired impairment of primary haemostasis (acquired von Willebrand syndrome in patients with hypothyroidism or aortic stenosis; platelet function disorders in patients with antiplatelet or herbal medicine therapy) are the most frequent causes of unexpected bleeding in the perioperative phase [42–49]. Besides, factor XIII deficiency may play a major role in some cases of perioperative bleeding problems, which also often shows no correlation to routinely determined preoperative coagulation tests [47, 50–52]. Among all conventional coagulation tests, only the decrease of fibrinogen was an early predictor of the severity of postpartum haemorrhage in a multicentre study in France [53].

Koscielny et al. [54, 55] has shown in a large prospective study with 5,649 unselected adult patients that the use of a standardized questionnaire and – if indicated – platelet function analysis with PFA-100 is superior to commonly used coagulation tests (aPTT, PT and platelet count) in detection of impaired haemostasis before surgical interventions and also allows a significant reduction of laboratory costs. In addition, preoperative correction of impaired haemostasis results in a reduction of bleeding complications and homologous blood transfusions [56]. On the other hand, the study of Roschitz et al. [57] shows that the PFA-100 is probably only a good screening method when a haemostatic defect in a patient is clinically likely, especially to screen for von Willebrand syndrome, and the test should not be used in general unselective screening without positive bleeding history. Based on the above mentioned studies and consensus of experts, the scientific committee of the Deutsche Gesellschaft für Anästhesie und Intensivmedizin (DGAI) in agreement with the Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie (DGHNOKC) and the Gesellschaft für Thrombose- und Hämostaseforschung (GTH), as well as with the subcommittee for perioperative coagulation of the Österreichische Gesellschaft für Anaesthesiologie, Reanimation und Intensivmedizin (ÖGARI) recommend the use of a standardized questionnaire to detect an increased risk of bleeding [58, 59]. Accordingly, healthy patients of the ASA grades I and II without any suspicion of impaired haemostasis who are scheduled for procedures without expected transfusion requirements, need no standard tests for coagulation. In all other patients – including patients taking medication affecting coagulation, or patients who are unable to provide adequate information – platelet count, platelet function (i.e. with PFA-100), aPTT, PT, and fibrinogen levels should be assessed. In cases of positive history of coagulation disorders sophisticated diagnostic tests should be initiated after consulting a specialist in haemostasis. Since there are several modifications of standardized questionnaire for preexisting coagulation disorders in use, DGAI authorized the scientific committees for regional anaesthesia and paediatric anaesthesia to develop a common standardized questionnaire.

The decision to discontinue an antiplatelet therapy with ASA and clopidogrel – especially in patients with coronary artery (drug-eluting!) stents – has to be based on an interdisciplinary risk-benefit estimation [60–69]. Platelet function analysis with PFA-100 or Multiplate may be helpful in estimating the risk of bleeding in this population.

Platelet Function Analyzer 100 (PFA-100)

Blood Samples and Measuring Method

PFA-100 is a platelet function analyzer designed to examine platelet-related primary haemostasis. PFA-100 uses whole citrated blood and high shear stress blood flow to simulate primary haemostasis. The analysis has to be proceeded within 0.5–2 h after sampling. A small volume of blood is introduced into a disposable cartridge and forced through a capillary tube. Platelet adhesion and aggregation is then initiated following exposure to either collagen/epinephrine(PFA-EPI)- or collagen/adenosine-diphosphate(PFA-ADP)-coated membranes. The time needed for occluding the aperture in the collagen membrane by plug formation yields the measured endpoint called closure time (CT in s) [70–72].

Measurement and Reference Range

The measurement range is 40–300 s. The reference range for PFA-EPI is about 80–160 s and for PFA-ADP 60–120 s [70, 71, 73]. Duplicate analyses reveal mean coefficient of variations of 7.1% for PFA-EPI and 5.7% for PFA-ADP [72, 74]. The CT is longer in blood group O patients than in patients with other blood groups, and the CTs of blood samples collected in the evening are significantly longer than CTs of blood samples collected in the morning [72, 74].

Indications

PFA-100 is highly sensitive to the presence of von Willebrand syndrome. These patients give prolonged CTs using PFA-EPI (CT $\geq$ 200 s), whereas PFA-ADP is less sensitive. Haemophilia or fibrinogen deficiency do not influence CT. Thrombocytopenia offer normal or prolonged CTs, dependent on platelet count. Administration of ASA results in a prolongation of PFA-EPI, whereas PFA-ADP is not affected. PFA-EPI is more sensitive in detecting ASA ingestion than the bleeding time (BT). Furthermore, administration of desamino-delta-D-arginine vasopressin (DDAVP) in patients with von Willebrand syndrome or ASA intake results in a shortening of CT in PFA-EPI. Therefore, PFA-100 can be used as a marker for DDAVP responsiveness and monitoring of DDAVP therapy [55, 56, 73, 75].

Limitations

Thrombocytopenia with a platelet count below 100/nl and anaemia with a haematocrit below 35% resulted in a prolongation of CT. On the other hand, platelet activation during

surgery can cause the generation of platelet aggregates, which may lead to a shortening of CT. Therefore, PFA-100 results are not easy to interpret during surgery. The predictive value of PFA-100 for postoperative blood loss in routine cardiac surgery is low, but postoperative shortening of CT values may be helpful to identify patients with hyperreactivity of platelets associated with the risk of myocardial lesion and ischaemia [74, 76–78].

Whereas ASA resistance detected by Born aggregometry (incidence 5.5%) in a study conducted by Gum et al. [79] resulted in a three-fold increase in major adverse events (death, myocardial infarction, or cerebrovascular accident) within 2 years of ASA therapy in cardiovascular patients, in the same study population ASA resistance detected by PFA-100 (incidence 9.5%) was not associated with an increase in major adverse events [80]. This difference in terms of the incidence of in vitro ASA resistance detected by Born aggregometry and PFA-100 may be explained by the finding of Chakroun et al. [81] that ASA resistance in PFA-100 (PFA-EPI: CT < 200 s) is associated with increased plasma concentrations of von Willebrand factor in these patients.

Because of the very high sensitivity to effects of GPIIb/IIIa receptor inhibitors – like abciximab, eptifibatide, or tirofiban –, the CT of PFA-100 passes the measurement range already at low dosage. In contrast, whole blood impedance aggregometry (Multiplate) shows a dose-dependent correlation between AUC (area under the curve) values and blood concentration of GPIIb/IIIa receptor inhibitors within the whole therapeutic range [82].

Whereas PFA-100 is very sensitive for von Willebrand syndrome and ASA effects, clopidogrel effects cannot be definitely detected [83–85]. This limitation has to be considered in context with the increasing number of patients with a combined ASA/clopidogrel therapy after coronary stent implantation [61, 62, 65, 66]. Several studies demonstrated an association between preoperative use of clopidogrel in combination with ASA and increased risk of bleeding, increased transfusion requirements and need for surgical re-exploration [60, 64, 68, 69]. In this regard too, whole blood impedance aggregometry (Multiplate) is superior to PFA-100 [86–89].

Conclusions

PFA-100 is a useful tool for preoperative screening of patients for platelet-related haemostatic defects. PFA-100 ('in vitro BT') is sensitive to ASA intake and other abnormalities of primary haemostasis, like von Willebrand syndrome, Bernard-Soulier syndrome, storage pool disease or Glanzmann's thrombasthenia. Its use is preferable to BT determination because it is less invasive and more sensitive to abnormalities of primary haemostasis [72]. Since a prolonged CT not always is associated with clinically relevant bleeding disorders, PFA-100 is probably only a good screening method when a haemostatic defect in a patient is clinically likely, particularly in patients with positive bleeding history, hypothyroidism or aortic stenosis [42, 49, 90].

Therefore, the test should not be used in general unselective screening without positive bleeding history [54, 57, 58, 91, 92]. Furthermore, the limitations in drug monitoring for clopidogrel and GPIIb/IIIa receptor inhibitors have to be kept in mind.

Multiple Platelet Function Analyzer (Multiplate)

Blood Samples and Measuring Method

The Multiplate analyzer is a new platelet function analyzer based on whole blood impedance aggregometry. Impedance aggregometry was developed by Cardinal and Flower and has been used since the 1980s for the assessment of platelet function in whole blood. Impedance aggregometry is based on the principle that blood platelets are non-thrombogenic in their resting state, but expose receptors on their surface when they get activated, which allow them to attach on vascular injuries and artificial surfaces. Multiplate analysis takes place in a single use test cell which incorporates a dual sensor unit and a PTFE-coated stirring magnet. The sensor wires are silver-coated. When platelets stick on the Multiplate sensor wires, they enhance the electrical resistance between them, which is continuously recorded. In order to enhance resistance on the sensor wires a tight attachment of platelets is required. Increase in impedance is expressed in arbitrary 'Aggregation Units' (AU). Three parameters are calculated after Multiplate analysis: aggregation (in AU), velocity (in AU/min), AUC in (AU × min). Thereby, AUC highlighted as the parameter with the highest diagnostic power [93, 94].

The fact that aggregation in Multiplate takes place on surfaces is a major difference compared to other methods such as Born aggregometry and single platelet counting. In Born aggregometry and single platelet counting methods, platelets aggregate with each other in the liquid phase. This presumably happens only in severely ill patients – e.g. during heparin-induced thrombocytopenia type II or disseminated intravascular coagulation – as coagulation and platelet aggregation in vivo usually only take place on surfaces.

Multiplate uses anticoagulated whole blood for analysis. Whole blood is the physiological environment where platelet function takes place in vivo, and the use of whole blood for in vitro testing eliminates the need for time-consuming centrifugation steps required for Born aggregation measurements. By using citrated blood, platelet function is inhibited probably by a decrease in intracellular calcium concentration in platelets. Therefore, better results can be obtained by performing anticoagulation with heparin or hirudin [95–97]. The Multiplate results are most reproducible by using hirudin as an anticoagulant [95]. Under special conditions – like cardiac surgery – where the patient is already under complete anticoagulation with heparin, in our experience it is not necessary to add an additional anticoagulant to the blood sample.

The analysis should be proceeded within 0.5–2 h after sampling [95]. The analysis itself needs 3 min for incubation and 6

min for the measurement after stimulation. Several specific test reagents are available for stimulation of different receptors or activation of signal transduction pathways of platelets in order to detect changes induced by drugs as well as by acquired or hereditary platelet disorders. The following tests can be used:

- **ASPItest:** AA is the substrate for COX. COX forms thromboxane A₂ (TXA₂), which is a potent platelet agonist. COX is inactivated irreversibly by ASA and reversibly by several antiinflammatory drugs.
- **COLtest:** Collagen activates the collagen receptor (GPIa/IIa receptor), which leads to a release of endogenous AA. AA in turn is converted to TXA₂ and thereby results in a further activation of platelets.
- **ADPtest:** ADP activates platelet by stimulation of ADP receptors. The most important ADP receptor (P2Y₁₂) is blocked by clopidogrel, prasugrel and ticlopidine.
- **ADPtest HS:** Compared to ADPtest, the addition of the endogenous platelet inhibitor PGE₁ makes ADPtest HS more sensitive towards the effects of clopidogrel and related drugs.
- **TRAPtest:** TRAP-6 stimulates the thrombin receptors PAR1 and PAR4 on the platelet surface. Thrombin is the most potent platelet activator. Its action is not blocked by ASA or clopidogrel. TRAPtest allows to detect the effect of GPIIb/IIIa receptor inhibitors also in blood samples from patients treated with ASA or clopidogrel.
- **RISTOtest high and low:** These tests are based on ristocetin-induced platelet aggregation. The concentrations are chosen so that typically a sample will not or only weakly aggregate in RISTOtest low and will aggregate well in RISTOtest high. This allows the detection of samples with enhanced tendency of ristocetin-induced aggregation, particularly in von Willebrand syndrome type IIb. On the other hand, blood samples from patients with Bernard-Soulier syndrome, von Willebrand syndrome type III and severe von Willebrand syndrome type I and II are characterized by an absent or markedly reduced response to ristocetin [98].

Measurement and Reference Range

The reference range is dependent on the anticoagulant applied in the blood sample and the reagent used for stimulation in the Multiplate analysis (table 2). In contrast to PFA-100, no significant differences between blood group O and non-O individuals can be noted, and Multiplate values do not change significantly during the day [99].

Indications

Multiplate shows a high sensitivity towards the effects of platelet inhibitors such as ASA, clopidogrel and GPIIb/IIIa receptor inhibitors (abciximab, eptifibatide and tirofiban) and also towards the newer direct ADP receptor antagonists [86, 88, 89, 98, 100, 101]. In contrast to PFA-100, Multiplate shows

Table 2. Multiplate tests

	Multiplate tests				
	ASPItest	COLtest	ADPtest	ADPtest HS	TRAPtest
Activator	AA	collagen	ADP	ADP + PGE1	TRAP-6
Final concentration	0.5 mmol/l	3.2 µg/ml	6.4 µmol/l	6.4 µmol/l	32 µmol/l
Reference range (healthy blood donors), AU × min [98]	740–1,360	460–1,160	530–1,220	310–1,070	940–1,560
Target range for antiplatelet therapy ^a , AU × min [98]	<300	<550	<500	<250	<300
Cut-off for platelet transfusion in bleeding patients, AU × min [96, 106, 121]	<200	<200	<300	–	<500

^aAntiplatelet therapy with ASA, clopidogrel, and tirofiban.

Table 3. ROTEM reference values [110, 113]

ROTEM parameter	CT, s	CFT, s	A10, mm	A20, mm	MCF, mm	CLI ₆₀ , %
ExTEM	40–80	34–160	44–66	50–71	50–72	85–100
InTEM	100–240	30–110	44–66	50–71	50–72	85–100
HepTEM ^a	100–240	30–110			50–72	85–100
FibTEM ^b	–	–	7–23	8–24	8–24	–
ApTEM ^c	40–80	34–160	44–66	50–71	50–72	–

^aDistinct shortening of CT in HepTEM compared to InTEM indicates a heparin effect.

^bMCF_{FIB} <8 mm → fibrinogen deficiency (<1 g/l) or fibrinogen polymerisation disorder. MCF_{FIB} >24 mm → elevated fibrinogen concentration (≥3 g/l). This can result in normal MCF_{EX} even in thrombocytopenic patients.

^cShortening of CT or increase in MCF in ApTEM compared to ExTEM can be a sign of hyperfibrinolysis.

a dose-dependent correlation between AUC values and blood concentration of GPIIb/IIIa receptor inhibitors within the whole therapeutic range [82]. Multiplate can also be used for monitoring of the reversing effect of DDAVP on COX 1-induced platelet inhibition [102].

Whereas up to now a simple and reliable method for ex vivo examination of platelet function in PC was not available, the Multiplate analyzer seems to be a helpful tool for this indication [27, 103]. Furthermore, Rahe-Meyer et al. [96, 97] could demonstrate the predictive value of Multiplate analysis regarding transfusion requirements during and after cardiac surgery. Moreover, the study of Poston et al. [104] provides evidence that thrombelastography and whole blood aggregometry is predictive for both bleeding complications and thrombosis after off-pump coronary artery bypass surgery. Therefore, Poston et al. [104] postulate that titration of perioperative platelet function, according to thrombelastography and whole blood aggregometry results, may minimize the risk of thrombosis without increase in bleeding complications.

Limitations

There are only few data concerning the sensitivity of the Multiplate analyzer to von Willebrand syndrome [105]. Furthermore, it has to be kept in mind, that determination of von Willebrand factor in RISTOtest takes place under low shear

stress conditions and the artificial addition of ristocetin. Moreover, other methods – like PFA-100 – are more specific and sensitive for diagnosis of von Willebrand syndrome type I and type II [98].

Results of Multiplate analysis correlate significantly with platelet count and reflect interactions between platelets, erythrocytes and leucocytes. This explains differences between the results of whole blood impedance aggregometry (Multiplate) and platelet function analyzers using platelet-rich plasma [99]. Since the Multiplate analyzer is a very new device, only limited data exist about its diagnostic power. Therefore, the clinical significance of whole blood impedance aggregometry using the Multiplate system remains to be determined in further studies on patients with abnormalities of primary haemostasis.

Conclusions

In addition to the high sensitivity towards the effects of platelet inhibitors (including ASA, clopidogrel, and GPIIb/IIIa receptor inhibitors), the Multiplate analyzer – especially in combination with thrombelastometry (ROTEM) – is predictive for both bleeding complications and thrombosis. This may allow titration of perioperative platelet function to minimize the risk of bleeding *and* thrombosis. Therefore, the combined use of these two tools may be optimal for POC coagulation management during cardiac surgery [7, 106].

Fig. 1. ROTEM analysis in a patient with petechia and mucosal bleeding without thrombocytopenia (platelet count 260/nl): MCF_{EX} = 9 mm and MCF_{FIB} = 7 mm. Conventional laboratory tests: fibrinogen 1.9 g/l; Quick (PT in %) 72%; aPTT 32.7 s; TT >60 s; antithrombin 115%; D-dimers > 6,400 µg/l.

Fig. 2. ROTEM analysis in a patient with severe thrombocytopenia (platelet count 22/nl) without spontaneous bleeding: MCF_{EX} = 46 mm and MCF_{FIB} = 19 mm. Conventional laboratory tests: fibrinogen 4.2 g/l; Quick (PT in %) 76%; aPTT 29.8 s; antithrombin 48%.

Rotational Thrombelastometry (ROTEM)

Blood Samples and Measuring Method

ROTEM analysis uses 300 µl of citrated whole blood for each measurement. It allows the evaluation of the coagulation system as an holistic dynamic process. The principle of rotational thromboelastometry (ROTEM) is related to, but in some aspects different from, classical thromboelastography, which was first described by Hartert in 1948 [107, 108]. In contrast to classical thrombelastography (TEG®, Haemoscope, Niles, IL, USA) the cup is fixed in a temperature-controlled cup holder, and the pin rotates back and forth through an angle of 4.75 ° with a cycle time 10/min. The movement of the pin is driven by an elastic spring and is guided by a high precision ball bearing system. The exact position of the pin axis is detected by the reflection of light by a small mirror which is attached to the shaft. The loss of the elasticity upon clotting of the sample leads to a change in rotation of the pin. This is detected by a CCD array, and the data are automatically analysed by computer [109, 110]. The stabilisation of the pin by a ball bearing system and the opto-mechanical detection method provides a good protection against the impact of vibrations and mechanical shocks. This allows the usage of the ROTEM system as a mobile unit, which can be transported easily to the operation theatre for POC coagulation management.

The ROTEM® system comes with four independent channels which enable the performance of four independent tests at the same time. The use of an automatic electronic pipette and computer-assisted operation procedures and analysis of the data make the ROTEM system easy to use.

ROTEM tests are started by re-calcification and accelerated by adding an activator of the extrinsic or intrinsic coagulation pathway. Thromboplastin (tissue factor) from rabbit brain is used for activation of the extrinsic pathway in ExTEM, FibTEM and ApTEM (for explanation of abbreviations see footnote of table 1). FibTEM contains additional cytochalasin

D in order to inhibit platelet activation [111, 112]. ApTEM includes aprotinin in order to block hyperfibrinolysis. All extrinsic activated tests include an heparin inhibitor which is able to eliminate the effect of up to 6 IU heparin per ml blood. In InTEM (intrinsic pathway clotting time) test coagulation is activated by partial thromboplastin (phospholipids) and ellagic acid. HepTEM is an InTEM test with additional heparinase in order to eliminate the heparin effect [110].

ROTEM Parameters and Reference Range

Unlike conventional clotting assays, ROTEM determines not only the clotting time (in s), but also the dynamics of clot formation (CFT = clot formation time in s), the mechanical clot stability (A5, A10, A15 = amplitude at 5, 10 or 15 min in mm; MCF = maximum clot firmness in mm) and its lysis over the time (ML = maximum lysis in % = reduction of clot firmness in relation to MCF within the complete measurement period; CLI30, CLI45, CLI60 = clot lysis index at 30, 45 or 60 min in % = remaining clot firmness at fixed test timepoints in relation to MCF) [110]. By using activated tests ROTEM results can be interpreted after 10–15 min. Clot firmness achieves its maximum normally after 20–30 min. To detect a late hyperfibrinolysis, ROTEM tests have to be monitored for up to 60 min [22]. For reference values see table 3.

Indications

ROTEM analysis allows reliable detection of hyperfibrinolysis, fibrinogen deficiency and fibrinogen polymerisation disorders, thrombocytopenia and platelet function disorders, coagulation factor deficiencies and heparin effects [114–116] (fig. 1, 2). Clot firmness (A10 or MCF) in ExTEM and FibTEM have to be compared to differentiate between fibrinogen deficiency/polymerisation disorders and thrombocytopenia/platelet function disorders [111, 110, 117]. Heparin effects as well as a protamine overdosage can be detected or excluded by comparing the clotting times of InTEM and

Fig. 3. Algorithm for ROTEM- and Multiplate-based POC coagulation management in cardiac surgery; part 1 – management before weaning from cardiopulmonary bypass [106, 121].

HepTEM [22, 116, 118]. Cho et al. [119] demonstrated in their study that residual heparin effects can be detected more sensitively by TEG/heparinase-TEG than by activated clotting time (ACT) / heparinase-ACT. Furthermore, the use of heparinase enables monitoring of haemostasis even in completely heparinised patients during cardiopulmonary bypass [78, 110, 118, 120, 121]. As the ROTEM system allows mea-

surement at a large temperature range (30–40 °C), the effects of hypo- and hyperthermia on the coagulation system can be verified [22, 122]. Finally, diagnostic or therapeutic additives (e.g. aprotinin, heparinase, ecarin, recombinant factor VIIa, factor VIII or factor XIII) can be used for in vitro testing in order to predict the efficiency of a risky or expensive therapy in vivo [22].

Fig. 4. Algorithm for ROTEM- and Multiplate-based POC coagulation management in cardiac surgery; part 2 – management after weaning from cardiopulmonary bypass [106, 121].

Limitations

In order to avoid incorrect interpretations of ROTEM results, the following limitations have to be considered [22, 110, 123]:

- Diagnosis of von Willebrand syndrome is not possible with ROTEM.

- The effects of antiplatelet drugs – like ASA or ADP antagonists (clopidogrel, ticlopidine) – cannot be detected because activation of platelets by thrombin overrules the effects of platelet aggregation inhibitors.
- GPIIb/IIIa receptor antagonists in normal therapeutic

Fig. 5. **a** Multiplate analysis in a ASA and clopidogrel responder ($AUC_{COL} < 300 \text{ AU} \times \text{min}$; $AUC_{ADP} < 500 \text{ AU} \times \text{min}$). **b** Multiplate analysis in a ASA and clopidogrel 'nonresponder' ($AUC_{COL} > 300 \text{ AU} \times \text{min}$; $AUC_{ADP} > 500 \text{ AU} \times \text{min}$).

dosage or mild Glanzmann's disease do not necessarily reduce MCF measured in ROTEM.

- There is a minor correlation between CT in ExTEM and PT. Therefore, determination of PT in addition to ROTEM tests can be helpful for calculation of the therapeutic dose of PCC.

Conclusions

Compared to PFA-100 and conventional coagulation tests, including ACT, TEG/ROTEM is superior in predicting blood loss during and after cardiac surgery [76, 124]. The best predictors of increased bleeding tendency in ROTEM analysis are the CFT or the MCF in HepTEM and the MCF in FibTEM [76, 125, 126]. Recent studies have shown that, compared to conventional coagulation management, TEG/ROTEM-based POC coagulation management enables reduction of transfusion requirements and costs in cardiac and liver surgery [7, 30, 33, 34, 127, 128]. Furthermore, TEG/ROTEM may be helpful to identify patients with elevated risk of post-operative thrombotic complications including myocardial infarction [78, 129].

However, it must be considered that impaired primary haemostasis because of von Willebrand syndrome or the effect of antiplatelet drugs – like ASA or clopidogrel – cannot be detected by ROTEM analysis. Therefore, in cases in which primary haemostasis may be affected – especially in cardiac surgery – a combined use of ROTEM and platelet function analysis (PFA-100 or Multiplate) should be preferred for POC coagulation management [106, 121].

POC Coagulation Management in Cardiac Surgery

After implementation of a ROTEM-based POC coagulation management in the field of visceral and transplantation

surgery in 2000, the overall intraoperative use of blood components could be reduced by 56% until 2006 (PRBC by 30%, FFP by 73%, and PC by 69%) [7]. A reduction of perioperative blood loss and transfusion requirements in cardiosurgical patients by the use of POC tests could also be demonstrated by other authors [30–34, 130]. Based on our experience in ROTEM-based POC coagulation management in liver transplantation and multiple trauma patients we started with ROTEM diagnostics in thoracic and cardiovascular surgery in April 2004 and with Multiplate analysis in December 2005.

Treatment of Platelet Function Disorders in Cardiac Surgery

Many patients in cardiac surgery are pretreated with antiplatelet drugs. Furthermore, extracorporeal circulation is responsible for multifactorial platelet function disorders. The platelets are damaged mechanically by the pump and are activated by contact with the artificial surface of the cardiopulmonary bypass circuit. Hypothermia also induces platelet function disorders [24, 122, 131, 132]. In addition, heparin can cause an unspecific activation and therefore a consumption of platelets [133]. Routinely POC platelet function analysis is so far not established everywhere. Impedance aggregometry with the Multiplate analyzer may close this gap in the future, but more evaluation studies are necessary [96]. The critical value for platelet substitution in cardiac surgery given by the Bundesärztekammer is 100/nl. In case of bleeding, the administration of platelets should be considered independently from platelet count if there is any suspicion for severe platelet function disorders (e.g. in context with clopidogrel pretreatment or cardiopulmonary bypass time of more than 3 h). Furthermore, a haemoglobin level of 8–10 mg/dl or a haematocrit of 24–30% is needed to marginate platelets to the vessel wall and to enable an interaction with subendothelial collagen in the area of vascular lesions [134, 135]. ROTEM and Multiplate analysis allow an evaluation of platelet function independent of the number of platelets [96].

Algorithm for POC Coagulation Management in Cardiac Surgery

As it has been demonstrated by other authors [6, 31–33, 130, 136, 137], experience-based diagnostic and therapeutic algorithms are able to reduce perioperative blood loss and transfusion requirements in cardiac surgery. This could already be proven for POC coagulation management during liver transplantation in our clinic in Essen [7]. Based on our experience with POC coagulation management, we developed – in cooperation with our colleagues from the university clinics of Frankfurt/M. and Hannover – an algorithm for ROTEM and Multiplate based coagulation management in cardiac surgery which was first presented at the Deutscher Anästhesie-Con-

Fig. 6. a Multiplate analysis at the beginning of cardiopulmonary bypass – 4 h after termination of eptifibatide infusion (co-medication with ASA and clopidogrel) in a patient with acute coronary syndrome: diffuse bleeding after the first cut. **b** Multiplate analysis in the same patients after weaning from cardiopulmonary bypass and heparin reversal with protamine (6 h after termination of eptifibatide infusion): normalisation of AUC in ASPItest and TRAPtest and no platelet transfusion required.

gress 2007 in Hamburg [22, 96, 106, 117, 121, 138, 139] (fig. 3, 4). This algorithm considers the following points:

- standardized questionnaire for bleeding and drug history,
- Multiplate analysis for evaluation of preoperative platelet function in case of clopidogrel pretreatment within the last 10 days (fig. 5, 6),
- prophylactic or therapeutic application of antifibrinolytics (fig. 7),
- ROTEM analysis after declamping of the aorta in order to predict the risk of bleeding even after protamine administration,
- optimizing the basic conditions for haemostasis (body temperature, pH, haemoglobin level, ionised calcium concentration) before weaning from cardiopulmonary bypass [122, 131],
- optimizing of heparin reversal with protamine under consideration of ACT and ROTEM analysis [118, 119],
- ROTEM- and Multiplate-based coagulation management in case of diffuse bleeding even after protamine administration (fig. 8),

Cut-off values for therapeutic interventions recommended in this algorithm corresponds with the clinical experience of the participating clinics and are furthermore based on the results of the Multiplate study carried out by Rahe-Meyer et al. [96] in Hannover.

ROTEM Triggers for Cardiac Surgery

Based on our experience with ROTEM-based coagulation management in cardiac surgery we recommend the following cut-off values as triggers for therapeutic interventions in patients with diffuse bleeding [22, 106, 121]:

- $CLI60_{EX} < 85\%$ → aprotinin or tranexamic acid,

- $CT_{IN} > 240$ s and $CT_{HEP}/CT_{IN} < 0.8$ → protamine,
- $CT_{EX} > 90$ s or $CT_{HEP} > 280$ s → PCC or FFP,
- $MCF_{EX} \leq 50$ mm and $MCF_{FIB} \leq 12$ mm → fibrinogen concentrate (or cryoprecipitate),
- $MCF_{EX} \leq 50$ mm and $MCF_{FIB} > 12$ mm → platelet transfusion,
- $MCF_{EX} > 50$ mm and $MCF_{FIB} > 12$ mm → check Multiplate! (Cave: Effects of antiplatelet drugs – like ASA and clopidogrel – cannot be detected by ROTEM analysis! Therefore, in these patients an additional Multiplate analysis should be performed),
- $CLI60_{EX} < 88\%$ and $CLI60_{AP} < 92\%$ and $CLI60_{XIII} \geq 95\%$ → factor XIII concentrate,
- $CT_{EX} < 80$ s and $MCF_{EX} > 60$ mm and $MCF_{FIB} > 16$ mm → consider administration of DDAVP, von Willebrand factor / factor VIII concentrate or rFVIIa.

Multiplate Triggers for Platelet Transfusion in Cardiac Surgery

In case of diffuse bleeding and ROTEM values within the normal range ($CT_{EX} \leq 90$ s and $CT_{HEP} \leq 280$ s and $MCF_{FIB} > 12$ mm and $MCF_{EX} > 50$ mm) platelet function disorders have to be taken into account, particularly in regard to preoperative antiplatelet therapy or a cardiopulmonary bypass time of more than 3 h. Therefore, in these patients an additional Multiplate analysis should be performed in order to appreciate the need for platelet transfusion. Under these conditions transfusion of platelets normally is indicated if Multiplate parameters fall below the following cut-off values [12, 96, 106] (table 2):

- $AUC_{ASPI} < 200$ AU × min or
- $AUC_{COL} < 200$ AU × min or
- $AUC_{ADP} < 300$ AU × min or
- $AUC_{TRAP} < 500$ AU × min.

Fig. 7. Detection of fulminant hyperfibrinolysis ($CLI30_{EX} = 0\%$) and subsequent hypofibrinogenemia ($MCF_{FIB} = 5\text{ mm}$) in ROTEM analysis during cardiopulmonary bypass.

Fig. 8. Secondary bleeding at ICU after aortocoronary bypass grafting in a patient with clopidogrel pretreatment. Identification of hypofibrinogenemia in ROTEM analysis ($MCF_{FIB} = 5\text{ mm}$) as the cause of bleeding. After substitution with 4 g fibrinogen concentrate bleeding stopped and no re-exploration was required.

Impact of the ROTEM- and Multiplate-Based Coagulation Management on the Intraoperative Usage of Blood Components in the Cardiac Surgery of the University Clinic of Essen

In context with our POC coagulation management the overall intraoperative usage of blood components in cardiac surgery could be reduced by 34% within 2 years (from 2004 to 2006). Regarding the several blood components the reduction is distributed as follows:

- PRBC: reduction from 3,276 to 2,599 transfused units (–21%),
- FFP: reduction from 1,986 to 613 transfused units (–69%),
- PC: increase from 336 to 485 transfused units (+44%).

In contrast to our results in liver transplantation, a reduction in usage of PC could not be realised in cardiac surgery [7]. The increase in PC consumption probably is induced by a growing number of patients with a combined ASA and clopidogrel therapy [60, 63, 64, 68].

Overall the reduction in transfusion requirements in cardiac surgery resulted in cost saving of EUR 110,913.00 per year. However, these economy savings were in part balanced by an increase in costs for fibrinogen concentrate. A remarkable increase in the usage of PCC concentrate could not be noticed in context with this new strategy. An exact analysis of the efficiency and economy of a ROTEM- and Multiplate-based POC coagulation management in cardiac surgery is the subject of a projected pharmaco-economic study. In this context, inherent consequential costs shall be taken into account, e.g. TRALI, TACO, sepsis, ventilation time and stay at intensive care unit (ICU) and at hospital. In a pilot study including 10 patients with aortic arch replacement because of acute type A

aortic dissection, a significant reduction in postoperative FFP usage and perioperative costs for blood components and coagulation factor concentrates could be demonstrated. Furthermore, a trend to a reduced postoperative ventilation time and a shortened stay at the ICU and hospital could be shown in this small population [120, 127, 128].

In summary, POC coagulation management based on the combined use of thrombelastometry (ROTEM) and platelet function analyzers (PFA-100 and/or Multiplate) is helpful in predicting bleeding complications in cardiac surgery. Furthermore, this combination may be applicable for risk estimation for postoperative thromboembolic events. Moreover, coupled with therapeutic algorithms for control of platelet transfusion and therapy with rapidly available and highly effective coagulation factor concentrates, they provide the possibility to reduce transfusion requirements and costs.

Conflict of Interest

The authors point at associations with the following companies: Dr. Görlinger held scientific lectures on fee basis for Pentapharm GmbH (Munich, Germany), Instrumentation Laboratory (Kirchheim, Germany), Diagnostica Stago (Asnières sur Seine, France), and CLS Behring GmbH (Marburg, Germany).

Ethical and Legal Prerequisites

All studies carried out in Essen and Hannover involved in this paper have been approved by an ethical committee and thus meets the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996.

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