Thromboelastometry-
The New Coagulation Measurement

Andrew Bernard, MD
Associate Professor of Surgery
Trauma Center Medical Director
UK Healthcare
Objectives

1. Understand how thromboelastometry works
2. Describe the published literature on efficacy of TEM/TEG
3. Interpret typical thromboelastograms
Hypothesis:

Pre-ICU MTP (FFP after 6 units PRBC) is inadequate for correcting coagulopathy.
The Ratio of Blood Products Transfused Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital

Matthew A. Borgman, MD, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Kurt W. Grathwohl, MD, Thomas Repine, MD, Alec C. Beekley, MD, James Sebesta, MD, Donald Jenkins, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Reappraising the concept of massive transfusion in trauma

Simon J Stanworth¹, Timothy P Morris², Christine Gaarder³, J Carel Goslings⁴, Marc Maegele⁵, Mitchell J Cohen⁶, Thomas C König⁷, Ross A Davenport⁷, Jean-Francois Pittet⁸, Pär I Johansson⁹, Shubha Allard¹⁰, Tony Johnson²¹¹, Karim Brohi⁷
**Improved Survival After Hemostatic Resuscitation: Does the Emperor Have No Clothes?**

*Louis J. Magnotti, MD, Ben L. Zarzaur, MD, MPH, Peter E. Fischer, MD, MS, Regan F. Williams, MD, Adrienne L. Myers, MD, Eric H. Bradburn, DO, Timothy C. Fabian, MD, and Martin A. Croce, MD*

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**TABLE 4.** Extended Cox Proportional Regression Hazards Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion ratio</td>
<td>0.558</td>
<td>0.279–1.114</td>
<td>0.098</td>
</tr>
<tr>
<td>Blunt injury</td>
<td>2.456</td>
<td>1.080–5.584</td>
<td>0.032</td>
</tr>
<tr>
<td>Admission GCS score</td>
<td>0.925</td>
<td>0.842–1.017</td>
<td>0.106</td>
</tr>
<tr>
<td>Age</td>
<td>1.017</td>
<td>0.999–1.036</td>
<td>0.069</td>
</tr>
<tr>
<td>Admission BE</td>
<td>0.948</td>
<td>0.905–0.992</td>
<td>0.021</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
Coagulopathy of trauma is dynamic.

Pro-thrombotic State
DVT / PE
(Majority)

Hemorrhagic State
Bleeding
Ongoing hypotension
CONTACT       

TISSUE       

COMMON PATHWAY       

THROMBIN / FIBRINOGEN

Intrinsic Pathway
PK HK
XII XIIa HK
Ca^{2+} Xla
IX IXa Ca^{2+}
VIIa/Tissue Factor
Ca^{2+}
PL
VII

Extrinsic Pathway
PK HK
XII XIIa HK

X a Ca^{2+}

PL

Prothrombin Thrombin

Fibrinogen

Fibrin Monomer XIIIa

Fibrin Polymer

Cross-Linked Fibrin Polymer

PK Prekallikrein
HK High Molecular Weight Kininogen
PL Phospholipids
Thromboelastography

- Functional assay
- Global assessment (from initiation of protein coagulation through clot lysis)
- Factor Deficiencies
- Fibrinogen Function
- Platelet Function
- Clot Strength
- Lysis
Thromboelastography Technology

TEG

ROTEM Delta
Thromboelastography Technology

TEG

ROTEM Delta

Cup

Pin

.36 ml whole blood (Clotted)

4°45'
Hemostasis profile:

- R time
- α Angle
- MA
- LY

Fibrin strands → clot kinetics → strength/elasticity → dissolution
R (reaction) time
- Coagulation factors

K (clotting) time
- Interaction of factors, fibrin & platelets

Alpha angle
- Fibrin & platelets

Maximal Amplitude (MA)
- Platelet function

Lysis 30/60 (LY30/60)
- Fibrinolysis
Typical TEG Tracings

**Normal**
- R; K; MA; Angle = Normal

**Hypercoagulation**
- R; K = Decreased;
- MA; Angle = Increased

**D.I.C**
- **Stage 1**
  - Hypercoagulable state with secondary fibrinolysis
- **Stage 2**
  - Hypocoagulable state

**Platelet Blockers**
- Thrombocytopenia/
- Thrombocytopathy
- R = Normal; K = Prolonged;
- MA = Decreased
Graphic Result

$Started \@ 07:24 \ 1 \ Nov \ 04$

Sample: 10/31/2004 08:22:29 PM - 09:49:14 PM

Click on a tracing to show details
Sample placement to amplitude of 2mm

Clotting factor activity
R time → amplitude of 20 mm

Time to reach level of clot strength

Clotting factors, fibrinogen, and platelet function
- Slope from R-time to K-time
- Speed of clot strengthening
- Clotting factors, fibrinogen, and platelet function
- Greatest vertical amplitude of tracing
- Clot strength
- Platelet number and function
Rate of amplitude reduction @ 30 min after MA

Measure of clot stability

Increased rate indicates hyperfibrinolysis
Rectal, Small Bowel, Sacral, & Open Femur Fx

Arrived in Class IV Shock

GSW to Pelvis & RLE
Same Patient

- Intra-op after 11 PRBC, 2 Plt, 4 Cryo, 6 FFP, 3 WB, & 1 Factor VIIa

- Post-op after 19 PRBC, 2 Plt, 4 Cryo, 6 FFP, 6 WB, & 1 Factor VIIa
Patient 2

- L parietal GSW requiring emergent craniotomy

- POD 1: Hypercoagulable
GSW to Left Flank

- Sigmoid Colon, Small Bowel, and Abdominal Wall Injury
- 2 PRBC given intra-op
• Post-op TEG shows early fibrinolysis

• TEG after Amicar infusion
The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

The CRASH-2 collaborators*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>All causes of death</th>
<th>Bleeding death</th>
<th>Non-bleeding death</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>20127</td>
<td>0.91 (0.85–0.97); p=0.0035</td>
<td>0.85 (0.76–0.96); p=0.0077</td>
<td>0.94 (0.86–1.02); p=0.13</td>
</tr>
<tr>
<td>Time to treatment (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>7451</td>
<td>0.87 (0.76–0.97)</td>
<td>0.68 (0.57–0.82)</td>
<td>1.04 (0.89–1.21)</td>
</tr>
<tr>
<td>&gt;1–3</td>
<td>6033</td>
<td>0.87 (0.77–0.97)</td>
<td>0.79 (0.64–0.97)</td>
<td>0.91 (0.78–1.05)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>6634</td>
<td>1.00 (0.90–1.13)</td>
<td>1.44 (1.12–1.84)</td>
<td>0.89 (0.78–1.02)</td>
</tr>
<tr>
<td>χ² test of homogeneity</td>
<td></td>
<td>4.411 (p=0.11)</td>
<td>23.516 (p=0.0000)</td>
<td>2.537 (p=0.28)</td>
</tr>
</tbody>
</table>

*Table 1: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment
ORIGINAL ARTICLE
Use of rotation thromboelastometry (ROTEM®) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate

H. Schöchl,¹ L. Forster,¹ R. Woidke,² C. Solomon³ and W. Voelckel⁴

¹ Staff Anaesthetist, 4 Head of Department, Department of Anaesthesiology and Critical Care Medicine, AUVA Trauma Centre, Salzburg, Austria, 2 Trauma Surgeon, Department of Trauma Surgery, AUVA Trauma Centre, Salzburg, Austria,
3 Staff Anaesthetist, Department of Anaesthesiology and Critical Care Medicine, Hannover Medical School, Hannover, Germany
Postinjury Coagulopathy Management
Goal Directed Resuscitation via POC Thrombelastography

Jeffry L. Kashuk, MD,* Ernest E. Moore, MD,* Michael Sawyer, MD,† Tuan Le, MD,‡ Jeffrey Johnson, MD,* Walter L. Biffi, MD,* C. Clay Cohren, MD,* Carlton Barnett, MD,* Philip Stahel, MD,§ Christopher C. Sillman, MD, PhD,‖ Angela Sautaia, MD, PhD,‖ and Anirban Banerjee, PhD‖

Annals of Surgery • Volume 251, Number 4, April 2010
Guideline for Blood Product Use

**Abnormal TEG**

**Prolonged R time**
- Transfuse 4 units FFP
- Decrease Maximum Amplitude
- Transfuse 2-4 units Whole Blood

**Prolonged K time or Decrease a-Angle**
- Transfuse 4 units FFP then 4 units Cryoprecipitate
- Consider rVIIa if abnml after above

**Increase LY30**
- Amicar 5gm IV load over 1 hour then 1 gm/hr until LY normal
Hemorrhage is the enemy (early)

Hypercoagulability is the enemy (late)

Diagnosis: time consuming and confusing

ROTEM Delta and TEG

“Whole blood coagulation measurement”

Fast

One test

Easily repeatable

It’s what you want—clot measurement
ROTEM delta

- Proven technology - 1400 clinical units
  50 countries - 400 publications

- Integrated system on-board computer, Touchscreen & LIS protocols

- Electronic programmed Pipette & on screen step by step directions

- LQC once a week, EQC automatic, CLIA Option 2

- Remote viewing in real time

- Global Intrinsic & Extrinsic with specific Fibrinogen test
Surgical Hemostasis Webinar
4pm EDT Oct 20
Dr. Klaus Goerlinger
Schochl, Cotton et al. Unpublished data.
1) “Turnaround time”

2) “Obviation of other coag tests”

3) “Opportunity to return to POC (that we used to have with TEG in OR but had to abandon because of difficulty with instrumentation maintenance and QC)”

4) “Opportunity to use fewer units of clotting factors, thus improving outcome while saving money”

5) “As above, especially for platelet function (in future) so that not every patient on anti-platelet drugs has to get empiric platelets”

6) “Cost vs TEG”
Why United States last launch for Rotem?

FDA

Lawyers

Rotem had to be Significantly better
Why Thromboelastometry?

Target directed Transfusions

Rapid reaction to coagulopathies

Reduce Transfusion Costs… both Economic & Adverse Effects
Coagulation monitoring / management during liver transplantation

14th ALEXAIC 2010, 28th-30th September, 2010

Klaus Görlinger
Universitätsklinikum Essen
Germany
klaus@goerlinger.net
“Blood is the most dangerous medication that a physician ever prescribes”

Louis Wadsworth
November 2006
The University of British Columbia
The Centre for Blood Research
Intraoperative usage of blood products per year in visceral surgery and liver transplantation at University Hospital Essen, Germany
Intraoperative usage of coagulation factor concentrates per year in visceral surgery and liver transplantation at University Hospital Essen, Germany

No off-label-use of rFVIIa!
Cumulative cost saving compared to 1999 in visceral surgery and liver transplantation at University Hospital Essen, Germany

\[ \Sigma = 1,765,280.-- \text{ Euro} \]
“An audit of red cell and blood product use after the institution of thromboelastometry in a cardiac intensive care unit”

L. Anderson,* I. Quasim,* R. Soutar,† M. Steven,* A. Macfie* and W. Korte‡

*Department of Anaesthesia, †Department of Haematology, Western Infirmary, Glasgow, UK, and ‡Institute for Clinical Chemistry and Haematology, Kantonsspital, St Gallen, Switzerland

Received 7 July 2005; accepted for publication 31 August 2005
A retrospective analysis of data from 990 patients was performed which covered a period 6 months prior to the introduction of ROTEM thromboelastometry and 6 months after its introduction.
In the 6 months prior 
red cells were used in 60% of patients and 
fresh frozen plasma (FFP) and platelets used in 17 
and 16% of patients, respectively.

In the following 6 months 
red cell use had fallen to 53% and 
FFP and platelets to 12 and 11%, respectively (P < 005).

Introduction of thromboelastometry has significantly 
decreased our use of red cells and blood products.
Annual treatment costs of all cardio surgical patients were analyzed before 729 patients after 693 patients implementation of ‘bedside’ ROTEM.
Cost reduction of perioperative coagulation management in cardiac surgery: value of ‘bedside’ thrombelastography (ROTEM)

Grit J. Spalding a, Martin Hartrumpf a, Tobias Sierig b, Nils Oesberg b, Christian Günther Kirschke b, Johannes M. Albes a,* Department of Cardiovascular Surgery, Heart Center Brandenburg, Bernau/Berlin, Germany Department of Anesthesiology, Heart Center Brandenburg, Bernau/Berlin, Germany

Received 27 September 2006; received in revised form 26 February 2007; accepted 27 February 2007

Please cite this article in press as: Spalding GJ, et al., Cost reduction of perioperative coagulation management in cardiac surgery: value of ‘bedside’ thrombelastography (ROTEM), Eur J Cardio-thorac Surg (2007), doi:10.1016/j.ejcts.2007.02.022
After Rotem

- Red Blood Cell Units < 25%
- Platelet Concentrates < 50%
- FFP unchanged
- Pooled coagulation concentrates & Factor XIII < 80%
- Factor VIIA omitted
- Fibrinogen > two fold
- Avg. Monthly costs all blood products < 32%
- Coagulation factor monthly costs 50%
- Combined Savings 44%
ROTEM vs. TEG – Tests

**ROTEM**
- IN-tem (intrinsic)
- HEP-tem (heparinase)
- Extem (extrinsic)
- FIBtem (Fibrinogen)
- Aptem (Hyperfibrinolysis)

**TEG**
- Koalin (intrinsic)
- Heparinase cup
<table>
<thead>
<tr>
<th><strong>ROTEM® Parameters</strong></th>
<th><strong>TEG® Parameters</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CT – Clotting Time (seconds)</td>
<td>R – Reaction Time (minutes)</td>
</tr>
<tr>
<td>CFT – Clot Formation Time (seconds)</td>
<td>K – Coagulation Time (minutes)</td>
</tr>
<tr>
<td>α Alpha Angle (°)</td>
<td>α Alpha Angle (°)</td>
</tr>
<tr>
<td>A (x) – Amplitude at a time point. 10/15/20/25/30 mm (minutes)</td>
<td>No equivalent parameter</td>
</tr>
<tr>
<td>MCF – Maximum Clot Firmness (mm)</td>
<td>MA – Maximum Amplitude (mm)</td>
</tr>
</tbody>
</table>
Thromboelastometry:

- Based on whole blood analysis
- Typical reaction curves
- Numerical data for many phases of hemostasis
- Abnormal results clearly indicated
- Clot firmness = Quality of clot
TEG – Pin suspended by gravity on torsion wire

TEG detection by Professor Hartert (1948)

Motion of the pin

Torsion wire

Continuous registration

Blood clot

4.75°

Thromboelastogram
Stable Function Principle of ROTEM® III

The rotating axis, stabilized and guided by a high precision ball bearing, carries the sensor.

The cuvette is stationary.

Clotting or lysis leads to a change of torque which is detected by a CCD chip.

The patent protected opto-mechanical detection system is very robust and less susceptible to mechanical shocks or vibrations.
Rotem advantages vs TEG

- Eliminates Vibration/Stability issues
- Greatly Improves ease of use
- Significantly easier to stay in compliance
- Advanced targeted diagnostics for Coagulopathy
- Test data in about 15 minutes
- 24/7/365 – TEG - $60,000 Rotem - $11,000
Ease of Use

- Integrated touch screen – step by step directions
- Electronic preprogrammed push button pipette – “pipetting for dummies”
- Mobile – No balancing issues, “put it where you need it”, Rotem is Whole Hospital Near patient Blood Management System.
- Citrated samples used immediately or up to 6 hours, (no need to wait 30 mins, like TEG)
- Rotem = 4 testing channels vs TEG’s 2 testing channels
Easier Compliance for Laboratory & Less Costs

- Operator ID required
- Pt ID required
- Sample ID required
- Automatic daily EQC – Daily verification in menu.
- Automatic Channel shut down if out of spec
- Once a week LQC – CLIA option 2

Rotem 24/7/365 LQC = $11,000 per year

TEG 24/7/365 LQC = $60,000 per year
Rotem Differential Guided Diagnosis

- **INTEM** – Intrinsic Pathway activator – Ellagic Acic
- **HEPTEM** – Heparinase – Run with Intem
- **EXTEM** – Extrinsic pathway activator – Tissue factor
- **FIBTEM** – Platelet inhibitor, Fibrinogen graph, excludes platelet contribution to clot formation (Cytochalasin D)
- **APTEM** – Antifibrynolitic, Hyperfibrinolysis confirmation (aprotinin)
FIBTEM as an Indicator for Fibrinogen Substitution

Use of fibrin-based thromboelastometry for cryoprecipitate transfusion in cardiac surgery involving deep hypothermic circulatory arrest during cardiopulmonary bypass
Sang Hyun Lee, Sangmin M. Lee, Chung Su Kim, Hyun Sung Cho, Gaab Soo Kim, Mi Sook Gwak, Choo Hoon Chang and Kiick Sung

Blood Coagulation and Fibrinolysis 2010, 21:000–000

This study showed that fibrinogen level reflected in FIBTEM values during pump can be used to estimate FIBTEM after PR_{eversal} and the amount of cryoprecipitate needed for replacing mainly the fibrinogen could be predicted with high sensitivity and specificity.
Advantages of Rotem in Trauma

Transfusion in trauma: why and how should we change our current practice?

O.M. Theusinger, D.R Spahn and M.T. Ganter

Institute of Anesthesiology, University Hospital and University of Zurich, Zurich, Switzerland

Correspondence to Oliver M. Theusinger, MD, Resident, Institute of Anesthesiology, University Hospital and University of Zurich, Ra¨ mistrasse 100.

Current Opinion in Anaesthesiology 2009,22:305–312
“Hemorrhage is known to be a major cause of early death after injury and has been shown to be responsible for 30–40% of trauma mortalities.” [1–3].

“Furthermore, hemorrhage with consecutive multiple transfusions has been shown to significantly worsen clinical outcomes” [4,5].
Transfusion in trauma: why and how should we change our current practice?
O.M. Theusinger, D.R Spahn and M.T. Ganter

“Traditionally, acute traumatic coagulopathy has been thought to be due to consumption of coagulation factors, dilution from intravenous fluid therapy, hypothermia and metabolic acidosis.”

“It has recently been shown, however, that none of these factors is initially responsible for the acute traumatic coagulopathy. These factors become significant only in the later phase of traumatic coagulopathy.” [Brohi,12, 13]

This study confirms that acute coagulopathy of trauma is associated with systemic hypoperfusion and is characterized by anticoagulation and hyperfibrinolysis. Thrombin binding to thrombomodulin activates protein C thereby inhibiting factor Va/VIIla and consuming PAI-1 (derepression of fibrinolysis).


The pathogenesis and problems of acute trauma bleeding including transfusion requirements, organ dysfunction and mortality are reviewed. Early treatment and recognition of coagulopathy has implications for the care of shocked patients and the management of massive transfusion.
Transfusion in trauma: why and how should we change our current practice?
O.M. Theusinger, D.R Spahn and M.T. Ganter

Studies by Brohi et al. [11–14] have described an early and previously unknown acute traumatic coagulopathy before any of the above-mentioned traditional causes of traumatic coagulopathy were present. It has been shown that tissue injury and hypoperfusion followed by the activation of the anticoagulation thrombomodulin protein C pathway plays the central role in the pathogenesis of acute traumatic coagulopathy. As a result of overt activation of protein C, acute traumatic coagulopathy is characterized by coagulopathy in conjunction with hyperfibrinolysis.

This study shows for the first time that tissue injury and hypoperfusion followed by the activation of the anticoagulation thrombomodulin protein C pathway plays the central role in the pathogenesis of acute traumatic coagulopathy.


The study shows that TBI alone does not cause early coagulopathy, but must be coupled with hypoperfusion to lead to coagulation derangements, associated with the activation of the protein C pathway. This finding has implications for the treatment of coagulopathy after severe TBI.
“The activation of the thrombomodulin protein C pathway has clinical significance; high thrombomodulin and low protein C plasma levels were associated with increased mortality, blood transfusion requirements, acute renal injury, and reduced ventilator-free days early after trauma” [11–14].
“Factor XIII is the key coagulation factor to stabilize the clot. Schroeder et al. [54] and Nielsen et al. [55,56] have proven a relation between decreased factor XIII activity and reduced clot firmness” (maximal amplitude [TEG]/ maximum clot firmness [Rotem]) by computerized TEG.

“Trauma and major hemorrhage is known to be a cause of acquired factor XIII deficiency [57]. It seems reasonable to substitute factor XIII early, thereby improving clot firmness, reducing bleeding and minimizing the use of blood products [58–60].”
“Bruce and Nokes [66] recently demonstrated that the use of PCCs in trauma patients leads to a considerable reduction in the use of blood products (FFP, RBCs and cryoprecipitate) and that survival improved and bleeding stopped earlier.”

“Therefore, PCCs might have a place in control of trauma related bleeding, although this indication is currently off label.”
This study emphasizes the value of PCC in reversing the effects of oral anticoagulant therapy in bleeding patients. It also demonstrates the potential value of PCC in controlling the bleeding in patients undergoing cardiac and other surgical procedures.
Algorithms – reduce blood products

“algorithm incorporates information obtained from the patient’s history, clinical presentation and routine coagulation laboratory and bedside viscoelastic coagulation tests.”

“in the first 6 months after implementation of the algorithm, the use of FFP dropped by approximately 50% and RBCs as well as platelet administration decreased by approximately 20% each.”
Conclusion - Theusinger

“Modern and future transfusion strategies are based on online bedside coagulation monitoring with specific goal-directed administration of antifibrinolytics, coagulation factors, RBCs, FFP and platelets to optimize coagulation early.

This improves the patient’s outcome, minimizes the patient’s exposure to blood products and reduces costs.”

Time for changing coagulation management in trauma-related massive bleeding

Dietmar Fries\textsuperscript{a}, Petra Innerhofer\textsuperscript{b} and Wolfgang Schobersberger\textsuperscript{c}


Department of General and Surgical Critical Care Medicine, Innsbruck Medical University, Department of Anaesthesiology and Critical Care Medicine, Medical University Innsbruck and cInstitute for Sports Medicine, Alpine Medicine and Health Tourism (ISAG), Innsbruck and Hall, Innsbruck, Austria
Recent Findings

- Trauma – aPC Pathway leads to Fibrinolytic Potential
- Widespread use of Viscoelastic devices, (Rotem) highlights importance of Fibrinogen contribution to Clot Firmness
- Clot Firmness a precondition to cessation of bleeding
- Growing evidence – Targeted therapy, coagulation factor concentrates, guided by Viscoelastic measurements, (Rotem)
- Enables effective correction of Severe Coagulopathy
Dietmar Fries

“In simple terms, to achieve clot formation and thus stop bleeding, sufficient amounts of thrombin and substrate are required.”

In addition to activated platelets, on whose surface most of the thrombin is formed during propagation and amplification of coagulation, fibrinogen can be regarded as the primary substrate of coagulation [5,6].
(Traditional Lab), “tests have never been validated for the prediction of hemorrhagic tendency, as they reflect only the small amount of thrombin formed during initiation of coagulation and are unable to show the activity of factor XIII or TAFI.:

[Thrombin-Activable Fibrinolysis Inhibitor]

“In severely injured patients, impaired tissue perfusion triggers increased expression of thrombomodulin and thus activity of protein C, resulting in systemic anticoagulation and increased fibrinolysis through consumption of plasminogen activator inhibitor and low concentrations of TAFI [17–19].”
“The gold standard for reliable detection of acute hyperfibrinolysis is TEG/ROTEM [8–10], and their increasing use might expand our knowledge about the frequency of and conditions favoring hyperfibrinolysis.”
“ROTEM/TEG measurements of clot firmness in relation to fibrinogen polymerization can provide valuable information, as strong fibrin polymerization can compensate for the decrease in platelet contribution to clot firmness [51].”
“Clinical data from gynecology, neurology and cardiac surgery show that blood loss is increased when fibrinogen levels are below 150–200 mg/dl [61,62,63,64].

Because of the methodological shortcomings and the unavoidable time delay in plasma fibrinogen measurements, authors prefer to rely on functional thresholds (FIBTEM 7–10mm refers to fibrinogen concentration of about 150–200 mg/dl) for substituting fibrinogen.
“Until now data have been limited to small case series findings from experimental studies and in-vitro studies, whereas large randomized, placebo-controlled studies have been claimed to show clear benefit. Because of the ethical and methodological difficulties in conducting such studies in severely injured patients, it seems questionable whether such results will be available in the near future. However, available data indicate that it might be time to change coagulation management in trauma patients.”
Coagulation management in trauma patients
Dietmar Fries, Petra Innerhofer and Wolfgang Schobersberger

Department of Anesthesia and Intensive Care Medicine, University of Innsbruck, Austria
Correspondence to Dietmar Fries, MD, Department of Anesthesia and Intensive Care Medicine, University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria
Tel: +43 512 504; fax: +43 512 504 2749; e-mail: dietmar.fries@uibk.ac.at
Current Opinion in Anaesthesiology 2002, 15:217±223
“The critical concentration of 1.0 g/l was reached in a study by Hiippala et al., when blood loss exceeded 142% of the calculated blood volume despite substitution of FFP [50]. However, it is impossible to determine the definitive critical level of Fibrinogen, because clinical circumstances vary and coinciding deficits of other hemostatic factors may also alter hemostatic competence. To increase the plasma fibrinogen level in a 70-kg subject by 100 mg/dl, a bolus of 3 g fibrinogen is needed, equivalent to 900 ml FFP.
Parameter: Clotting Time

- **CT - Clotting Time (seconds)** – The time from the start of the test until first significant levels of a clot are detected. This measurement is initiated by adding a clot activator until an amplitude of 2 mm is reached.

- **Description: CT - Clotting Time (seconds)** – The CT describes how rapid fibrin formation starts. This parameter is related to, but not identical to the clotting time in a standard coagulation test for plasma.

  \[ \text{CT (clotting time)}: \Rightarrow \text{initiation of clotting, thrombin formation, start of clot polymerization} \]

- **Clinical Application:** The CT parameter facilitates the decision to substitute clotting factors (e.g. FFP, Thawed Plasma or Anticoagulant antidotes such as Protamine)
Parameter: Clot Formation Time

- **CFT - Clot Formation Time** (seconds) – The time from the measurement of CT until a fixed level of clot firmness. The CFT is the time between 2 mm amplitude and the 20 mm amplitude of the clotting signal.

- **Description:** CFT - Clot Formation Time (seconds) – The CFT describes the rate of initial clot formation mediated by thrombin-activated platelets, fibrin and activated factor XIII (FXIIIa).

- **CFT** (clot formation time): $\Rightarrow$ fibrin polymerization, stabilization of the clot with Platelets and F XIII

- **Clinical Application:** The CFT parameter facilitates the decision to substitute with Platelet Concentrate, or Fibrinogen Containing Products, such as FFP or Cryoprecipitate or both. A shortened CFT may be observed in a hypercoaguable state.
Parameter: α Angle

- **α Angle** - (°) - The angle between the baseline and a tangent to the clotting curve through the 2mm CT point.

- **Description**: α Angle - Describes the kinetics of clotting. Therefore, a larger alpha angle reflects the rapid clot formation mediated by thrombin-activated platelets, fibrin and activated factor XIII (FXIIIa); CFT becomes shorter as the alpha angle becomes larger.

  α Angle → the faster the clot builds increases the amplitude which is indicative of increased clot stability.

- **Clinical Application**: This parameter correlates to the parameter, CFT. Smaller α Angles typically suggest thrombocytopenia or hypofibrinogenemia. Whereas, a large α Angle may be observed in hypercoagulable states.
Parameter: A20

- **A20** – (mm) – The clot firmness at the amplitude time point of minutes after CT.

- **Description**: A20 – (mm) – Amplitude 20 represents the clot firmness at 20 minutes after CT.

- **Clinical Application**: directly relates to the MCF. Often it facilitates a decision to use Platelet Concentrate or Fibrinogen containing components when the amplitude/value is below established reference ranges.
Parameter: Maximum Clot Firmness

- **MCF** – (mm) – The **MCF - Maximum Clot Firmness** measures clot firmness, thus, overall clot stability.

- **Description:** **MCF** is the maximum amplitude that is reached prior to clot being dissolved by fibrinolysis.

- **Clinical Application:** A low **MCF** suggests decreased clot firmness. Whereas, an elevated **MCF** may indicate a hypercoagulable state. **MCF** correlates to **A20**.
Parameter: Maximum Lysis

- **ML - (%) – Maximum Lysis** is a parameter that describes the degree of fibrinolysis relative to the MCF achieved during the measurement. (Percent reduction of clot firmness after MCF in relation to MCF).

- **Description**: A **ML** of 5% means that during a selected period of observation, the **MCF** decreased by 5%.
  
  **ML (Maximum Lysis)**: ⇒ is not calculated at any fixed time, rather it is defined as the % of lysis at the end of the measurement.

- **Consider**: Total run time and the time after **MCF**.

- **Clinical Application**: **ML (maximum lysis)**: Evaluate in conjunction with **Lysis Index**.
  
  **ML** ⇒ stability of the clot (ML < 15%) or fibrinolysis (ML > 15% within 1h)
### Expected Values

#### INTEM

<table>
<thead>
<tr>
<th>CT (sec)</th>
<th>CFT (sec)</th>
<th>$\alpha$ –angle ($^\circ$)</th>
<th>A20 (mm)</th>
<th>MCF (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>122-208</td>
<td>45-110</td>
<td>70-81</td>
<td>51-72</td>
<td>51-72</td>
</tr>
</tbody>
</table>

#### HEPTEM

Comparison with INTEM.
A better clot quality in HEPTEM as compared to INTEM indicates the presence of heparin in the sample.

The above reference ranges for INTEM were established in 3 US centers on a reference sample group of healthy blood donors. (n=149)
A

- INTEM
  - CT normal
    - END
  - CT prolonged
    - HEPTEM
      - HEPTEM normal
        - Heparin/LMWH
          - Option: Protamine
      - HEPTEM prolonged
        - Factor deficiency?
          - Option: FFP

B

- INTEM
  - CFT and MCF Normal
    - END
  - CFT and MCF Abnormal
    - FIBTEM
      - MCF > 6 mm
        - Intact fibrin network
          - Option: Platelets
      - MCF < 6 mm
        - No intact fibrin network
          - Option: FFP/Cryoprecipitate
Platelet Function Testing
TEG’s Platelet Mapping

TEG claims: With the Platelet Mapping Assay, TEG can detect Plavix and ASS

- There are 2 recent articles (Alström et al, Scharbert et al) showing that the PMA is not useful for patient assessment

- Platelet Mapping Assay – 1 hour, $140, 4 separate test each with a margin of error of 5%. Calculated Platelet function

- “A novel modification of the Thrombelastograph assay, isolating platelet function, correlates with optical platelet aggregation”

  ROBERT M. CRAFT, JACK J. CHAVEZ, STUART J. BRESEE, DALE C. WORTHAM, ELI COHEN, and ROGER C. CARROLL, TENNESSEE, and NILES, ILLINOIS

- This article was funded by Haemoscope – Eli Cohen was CEO of Haemoscope
Regular Article

Platelet inhibition assessed with VerifyNow, flow cytometry and PlateletMapping in patients undergoing heart surgery

Ulrica Alström a,*, Fredrik Granath b, Jonas Oldgren c, Elisabeth Ståhle a, Hans Tydén d, Agneta Siegbahn e

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b Centre for Pharmacoepidemiology, Karolinska Institute, Sweden
c Department of Cardiology, Uppsala University Hospital, Sweden
d Department of Cardiac and Thoracic Anesthesia and Surgery, Örebro University Hospital, Sweden
e Department of Clinical Chemistry, Uppsala University Hospital, Sweden

Article Info

PlateletMapping is an instrument for monitoring the effect of clopidogrel and aspirin [16]. In the present study, three-quarters of the patients had ADP-receptor blockade as measured by PlateletMapping-MA ADP within the reference range for untreated patients, despite dual anti-platelet treatment. As this test correlated neither to the other platelet function tests nor to the clinical parameters, this test was not considered useful in the present clinical setting.

Conclusion: We found a modest agreement between the methods for preoperative platelet inhibition, though not for PlateletMapping-MA ADP. There was a correlation between preoperative platelet inhibition measured by VerifyNowP2Y12 and surgical blood loss or transfusion requirements. However, for the individual patient, preoperative use of VerifyNowP2Y12 as an instrument to decide bleeding and transfusion risk does not seem helpful.
Material and Methods: Sixty patients were included. Platelet inhibition was analyzed with flow cytometry including phosphorylation status of the vasodilator-stimulated phosphoprotein (VASP-assay) and two bedside analyzers, VerifyNow-System and PlateletMapping, a modified thrombelastograph.

Please cite this article as: Alström U, et al, Platelet inhibition assessed with VerifyNow, flow cytometry and PlateletMapping in patients undergoing heart surgery, Thromb Res (2009), doi:10.1016/j.thromres.2009.06.024
“the value of these tests in identifying patients with increased risk for bleeding during heart surgery appears limited.”

PlateletMapping-MAADP and MAAA did not correlate to any of the above flow cytometry variables, nor to VASP-assay, VerifyNowP2Y12

Please cite this article as: Alström U, et al, Platelet inhibition assessed with VerifyNow, flow cytometry and PlateletMapping in patients undergoing heart surgery, Thromb Res (2009), doi:10.1016/j.thromres.2009.06.024
Conclusion: “We found a modest agreement between the methods for preoperative platelet inhibition, though not for PlateletMapping-MAADP. There was a correlation between preoperative platelet inhibition measured by VerifyNowP2Y12 and surgical blood loss or transfusion requirements. However, for the individual patient, preoperative use of VerifyNowP2Y12 as an instrument to decide bleeding and transfusion risk does not seem helpful”
Evaluation of the Platelet Mapping T"1 Assay on rotational thromboelastometry ROTEM®

G. SCHARBERT, A. AUER, & S. KOZEK-LANGENECKER

Department of Special Anesthesia and Pain Management, Medical University of Vienna,
Guuw I 8-20, 1090-Vienna, Austria

(Received 6 November 2008; revised December 2008; accepted 2 December 2008)
“Whole blood was drawn from 22 adult volunteers and patients with and without antiplatelet medication. Platelet aggregability was determined in three whole blood assays:
The Platelet Mapping Assay using both activators arachidonic assay (AA) and adenosine diphosphate (ADP) on TEG, it’s adapted version on Rotem, and the multiple electrode impedance aggregometer Multiplate.”
“Specificity of the AA- and ADP-activated Platelet Mapping™ Assay in the TEG® was lower than the respective tests in the ROTEM® and Multiplate® analysis.”

“Thus limited correlation between various test modalities seems to be an inherent problem in platelet function monitoring.”

“The Platelet Mapping TM Assay is currently recommended in a number of publications for antiplatelet drug monitoring with its correlation to clinical outcome (23). Our experiments, however, showed a high number of false positive and false negative results”
“In our experiment, specificity was higher for ROTEM® (40%) compared with TEG® (30%)”

due to the overall unreliable test results obtained with the Platelet Mapping™ Assay we have decided not to implement this test in our hospital's everyday clinical routine.”
“Comparison of four tests to assess inhibition of platelet function by clopidogrel in stable coronary artery disease patients”
Marie Lordkipanidze´ 1,2,3†, Chantal Pharand1,2,3†, Thuy Anh Nguyen1,3, Erick Schampaert2,4,5, Donald A. Palisaitis2,4,5, and Jean G. Diodati2,4,5*
“pre-specified sub study of a randomized, double-blind trial included 116 patients with stable coronary artery disease requiring diagnostic angiography. Patients received clopidogrel for 1 (300 or 600 mg) or 7 days (300 or 75 or 150 mg daily) before the procedure. Blood samples obtained before clopidogrel initiation and before diagnostic coronary angiography were assayed using light transmission aggregometry [adenosine diphosphosphate (ADP) 5 and 20 mM as the agonist], whole-blood aggregometry (ADP 5 and 20 mM), PFA-100w (Collagen-ADP cartridge), and VerifyNoww P2Y12.”
Conclusion:

“At present, no platelet function assay can be acclaimed as optimal for quantifying the inhibition of platelet aggregation by clopidogrel.”
Value of PMA

- This is also reflected in evaluations of the assay
- Good results in few evaluation articles using “normal donors”

Original clinical investigation

**Evaluation of the TEG® platelet mapping™ assay in blood donors**

Louise Bochsen*¹, Bo Wiinberg², Mads Kjelgaard-Hansen², Daniel A Steinbrüchel³ and Pär I Johansson¹

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Email: Louise Bochsen* - louise.bochsen@rh.regionh.dk; Bo Wiinberg - bwi@life.ku.dk; Mads Kjelgaard-Hansen - mjkh@life.ku.dk; Daniel A Steinbrüchel - daniel.steinbruchel@rh.regionh.dk; Pär I Johansson - per.johansson@rh.regionh.dk

* Corresponding author

**Table 2: Analytical (CVₐ) and inter-individual (CVₑ) variation of the TEG® Platelet Mapping™ assay variables (see text) in blood donors.**

<table>
<thead>
<tr>
<th></th>
<th>MA₈amin</th>
<th>MA₈amin</th>
<th>MA₈oF</th>
<th>MA₈t</th>
<th>MA₈p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVₑ (%)</td>
<td>3.5</td>
<td>5.2</td>
<td>6.6</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>CVₑ (%)</td>
<td>2.8</td>
<td>4.7</td>
<td>26.2</td>
<td>6.6</td>
<td></td>
</tr>
</tbody>
</table>
TEG PMA Principle

Final result is calculated by the following formula:

$$100 - \left\{ \frac{MA_p - MA_{fibrin}}{MA_{thrombin} - MA_{fibrin}} \right\} \times 100$$

Depending on the single values results which are 55 as a mean can also be 77 or 69 depending on the combination if errors

Assay accuracy is questionable
A novel modification of the Thrombelastograph assay, isolating platelet function, correlates with optical platelet aggregation

ROBERT M. CRAFT, JACK J. CHAVEZ, STUART J. BRESEE, DALE C. WORTHAM, ELI COHEN, (CEO Heamoscope)
and ROGER C. CARROLL
KNOXVILLE, TENNESSEE, and NILES, ILLINOIS
From the Departments of Anesthesiology and Medicine, University of Tennessee Graduate School of Medicine; and Haemoscope Corp. **Supported by** the University of Tennessee Anesthesiology Research Fund and the Physicians’ Medical Education and Research Foundation, **as well as Haemoscope Corp**, of which **Dr Cohen is chief executive officer. Haemoscope Corp may benefit from these studies.** Submitted for publication November 4, 2003; revision submitted January 20, 2004; accepted for publication January 28, 2004.


TEG’s “functional fibrinogen” & “rapid teg”

- Both tests are significantly more expensive than respective ROTEM tests.
- Both tests are less convenient (require more pipetting steps).
- Both tests use crimp cap vials.
- (danger of injury, while working with potentially infective materials)
- FF test is Reopro (does not block platelets completely (Lang 2003/2004))

Referent: msc
Rapid TEG
Rapid TEG assay is faster than Kaolin and even more useful in trauma (J. of Trauma, 2009)

In a recent publication (J Trauma, 2009), RapidTEG has been advertised as giving faster results than Kaolin (mean 19.2 min vs 29.9 min).

The publication says that for RapidTEG r time (CT) may not be evaluated (only k (CFT), alpha and MA (MCF))

This is related to the fact that CT is immeasurable short in this assay.
EXtem is faster and proven in clinical studies

Referent: msc
Algorithms
Sample times

1. Anaesthesia

2. CPB

3. Protamine

Optional¹

either INTEM or EXTEM

30 min before coming off bypass

Optional²

1. Baseline testing left to clinician preference - may be helpful for comparison with subsequent tests.
2. EXTEM useful to guide PCC or FFP use in some centres. Monitor EXTEM if using aprotinin which prolongs CTTEM.
## Transfusion Algorithm

<table>
<thead>
<tr>
<th>Condition / Coagulation Values</th>
<th>Action to be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
</tr>
<tr>
<td>Patient's history, Routine Coag, ROTEM</td>
<td></td>
</tr>
<tr>
<td>• Acquired coagulation disorders (e.g. medication, HIT II)</td>
<td></td>
</tr>
<tr>
<td>• Hereditary coagulation disorders</td>
<td></td>
</tr>
<tr>
<td>• Routine lab, coags: Hb, Hct, PT/INR, aPTT, TT, Fibrinogen, Platelets</td>
<td></td>
</tr>
<tr>
<td>• EX-, IN-, FIB-, APTEM</td>
<td></td>
</tr>
</tbody>
</table>

**Blood loss ≥ 50% of EBV (Estimated Blood Volume) and Diffuse Microvascular Bleeding**

<table>
<thead>
<tr>
<th>Condition / Coagulation Values</th>
<th>Action to be Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROTEM EX-, IN-, FIB-, APTEM, HEPTEM in cardiac and vascular surgery</td>
<td></td>
</tr>
<tr>
<td>• FIBTEM MCF ≤ 7 mm</td>
<td></td>
</tr>
<tr>
<td>• INTEM CT and CFT prolonged, HEPTEM normal and/or ACT prolonged, Heparinase-ACT normal</td>
<td></td>
</tr>
<tr>
<td>• EX-, INTEM decline of MCF after maximum plus APTEM normal (Hyperfibrinolysis)</td>
<td></td>
</tr>
</tbody>
</table>

| Correct and treat (aim): | |
| • Hypothermia (T ≥ 35°C) | |
| • Hypocalcemia | |
| • Acidosis | |
| • Anemia (Hct ≥ 21%) | |
| • Hypertension (MAP 55 - 65 mmHg) (except TBI), MAP 80 - 90 mmHg | |

| Volume replacement: | |
| • Cristalloids and colloids | |

| Fibrinogen 2 - 6 g IV, after a total of 6 g Fibrinogen - FXIII (Fibrogammin®) | |

| Protamine sulfate | |

| Ongoing haemorrhage | |
| • ROTEM EX-, IN-, FIB-, APTEM | |
| • Coags including FXIII | |

**Blood loss ≥ 200% of EBV (Estimated Blood Volume) and Diffuse Microvascular Bleeding**

<table>
<thead>
<tr>
<th>EXTEM CT, CFT and MCF abnormal</th>
<th>Factors II, VII, IX, X-concentrate (Boriplex® P/N 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tranexamic acid (Cyklokapron®)</td>
<td>500 - 2000 IU IV depending on BW, INR</td>
</tr>
<tr>
<td>• Bolus: 15 mg/kg BW IV</td>
<td></td>
</tr>
<tr>
<td>• Followed by 1 - 2 mg/kg/h</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ongoing massive haemorrhage and diffuse microvascular bleeding</th>
<th>Recombinant factor VIII (NovoSeven®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No acidosis, no hypothermia, no hypocalcemia, no DIC</td>
<td></td>
</tr>
<tr>
<td>• Fibrinogen substituted, Hct ≥ 21%</td>
<td></td>
</tr>
<tr>
<td>• Platelets ≥ 50 000/μl (≥ 100 000/μl cardiac surgery and TBI)</td>
<td></td>
</tr>
</tbody>
</table>

**Blood loss ≥ 60% of EBV (Estimated Blood Volume) and Diffuse Microvascular Bleeding**

| ROTEM EX-, IN-, FIB-, APTEM, HEPTEM in cardiac and vascular surgery | |
| • EX-, INTEM CT normal, MCF < 40 mm | |
| • FIBTEM MCF ≤ 7 mm | |
| • No heparin rebound | |
| • Hct ≥ 21% | |

| Coags including FXIII before/after substitution of FXIII | |

| Volume replacement: | |
| • Cristalloids and colloids | |

| Keep FXIII ≥ 60% | |
| FXIII ≤ 40%, then | |
| Fibrogammin® 20 IU/kg BW IV | |
| FXIII ≤ 50%, then | |
| Fibrogammin® 15 IU/kg BW IV | |

| Platelet concentrate | |

| Fresh frozen plasma | |
| 15 ml/kg body weight (i.e., 2 - 4 bags) | |

---

**Examples**

Correlation FF or fib-TEM with Clauss

100 normals and patients with various underlying conditions were analysed for Fibrinogen (Clauss) and for FIBTEM. No patient received plasma expanders.

The correlation between Fibrinogen Clauss and Fibtem is good ($r^2 = 0.867$). This suggests that the clot firmness correlates well with the available fibrinogen and that in FIBTEM platelets are blocked (almost) completely.
FIBTEM as a Indicator for Fibrinogen Substitution

FIBTEM correlates well to fibrinogen levels

100 normals and patients with various underlying conditions were analysed for Fibrinogen (Clauss) and for FIBTEM. No patient received plasma expanders.

The correlation between Fibrinogen Clauss and Fibtem is good ($r^2 = 0.867$). This suggests that the clot firmness correlates well with the available fibrinogen and that in FIBTEM platelets are blocked (almost) completely.