THROMBOELASTOMETRY IN THE BLEEDING PATIENT

BEN DEATON, MD
DISCLOSURES

- None
BACKGROUND

- Bleeding and coagulopathy in critical care environments can be a source of significant morbidity and mortality.
- Coagulopathy complex
- Exposure to allogenic blood products carry important associated morbidity.
COAGULOPATHY

- Can result from numerous conditions
  - Liver failure
  - Sepsis
  - Trauma
  - Transfusions themselves
  - Hypothermia
- Strategies to evaluate and correct coagulopathy are evolving
- One such strategy has been the increasing use of TEG and ROTEM
• What is TEG?
  • Thromboelastography
• What is ROTEM?
  • Thromboelastogram

• Viscoelastic coagulation testing
  • Sometimes called VHAs (Viscoelastic Hemostatic Assays)
• Developed in 1948 By Dr. Hartert in Germany
ROTEM SCHEMATIC

- Rotating pin: +/- 4.75°
- Diode
- Light
- Detector
- Blood in disposable cup
- Heating/cooling device
cerca 1995

TEG system wired to monitors in the OR, ICU, and Lab.
- Amplitude in mm (Firmness)
- Time in min

Key:
- CT: Clotting time
- CFT: Clot formation time
- alpha: Alpha-angle
- A10: Amplitude 10 min after CT
- MCF: Maximum clot firmness
- LI30: Lysis index 30 min after CT
- ML: Maximum lysis

Graph features:
- Alpha (α) angle
- A10
- MCF
- LI30
- ML
- CT
REPORTED BENEFITS

• Purported benefits of TEG and ROTEM over routine screening coagulation?
  • RSCTs are performed in plasma
  • TEG/ROTEM performed in whole blood with cellular components (particularly platelets)
LIMITATIONS OF STANDARD COAGS

- INR
- Fibrinogen concentration
- aPTT
- ACT
- Platelet count
- Bleeding time
- Platelet function assay
BENEFITS

- The idea is TEG/ROTEM can/will:
  - Diagnose/assess coagulopathy in bleeding patient
    • Including hypercoagulability and hyperfibrinolysis
  - Guide transfusion strategy
  - Prediction and/or Reduction in mortality
OTHER BENEFITS

• Other benefits:
  • Rapid turnaround time
  • Reduced Factor concentrates, fresh frozen plasma, cryoprecipitate, platelet concentrates
  • Antifibrinolytic drugs, other drugs
  • Surgery time and patient time in the ICU
  • Total time in the hospital and for recovery

• What it is not:
  • Pre-procedure coagulation testing
BRIEF REVIEW OF HEMOSTASIS

• **Primary hemostasis** – damage to vascular wall ➔ exposure of injured collagen ➔ binding of vWF ➔ plt plug formation

• **Secondary hemostasis** – Coagulation cascade and fibrin mesh
BRIEF REVIEW OF PLATELETS

Thrombin also mediates platelet activation via the PAR 1 receptor.

ADP and TxA2 further activate other platelets via their respective receptors. Platelet activation also leads to expression of GP IIb/IIIa receptor on the platelet surface and its subsequent activation (GP IIb/IIIa*), thus enhancing its affinity for fibrinogen.

Fibrinogen mediates platelet-to-platelet cross-linkage via activated GP IIb/IIIa receptors.
ROTEM PARAMETERS

- There are MANY!
- It is difficult to try to understand them all.
- Review a practical guide to using ROTEM in a bleeding patient.
# Table of ROTEM® delta Parameters

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Parameter</th>
<th>Definition</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Coagulation Time (synonym r)</td>
<td>The time from test start until an amplitude of 2 mm is reached.</td>
<td>s</td>
</tr>
<tr>
<td>CFT</td>
<td>Clot Formation Time (synonym k)</td>
<td>The time between 2 mm amplitude and 20 mm amplitude.</td>
<td>s</td>
</tr>
<tr>
<td>α</td>
<td>α-Angle</td>
<td>Angle between the baseline and a tangent to the clotting curve through the 2 mm point.</td>
<td>degree (°)</td>
</tr>
<tr>
<td>CFR</td>
<td>Clot Formation Rate</td>
<td>Angle between the baseline and the tangent at the maximum slope.</td>
<td>degree (°)</td>
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<tr>
<td>MCF</td>
<td>Maximum Clot Firmness (synonym MA)</td>
<td>The maximum amplitude reached during the test.</td>
<td>mm</td>
</tr>
<tr>
<td>MCF-t</td>
<td>MCF Time</td>
<td>The time from CT until MCF is reached.</td>
<td>s</td>
</tr>
<tr>
<td>ACF</td>
<td>Actual Clot Firmness or Last Clot Firmness</td>
<td>Clot firmness at the actual time point after reaction start. ACF is not a parameter in its classical sense, but it is for orientation to judge the clot firmness at the actual time point.</td>
<td>mm</td>
</tr>
<tr>
<td>A(x)</td>
<td>Amplitude (firmness) at time x</td>
<td>Clot firmness (in mm amplitude) at the respective time point after CT.</td>
<td>mm</td>
</tr>
<tr>
<td>A5</td>
<td>Firmness at time 5 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A15</td>
<td>Firmness at time 15 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5</td>
<td>Firmness at time 15 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A25</td>
<td>Firmness at time 20 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A25</td>
<td>Firmness at time 25 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5</td>
<td>Firmness at time 30 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCE</td>
<td>Maximum Clot Elasticity E=100*MCF/(100-A)</td>
<td>MCE is a parameter calculated from MCF. The spreading (suction) of this parameter at high amplitudes is better as compared to the MCF.</td>
<td></td>
</tr>
</tbody>
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<tr>
<td>ML</td>
<td>Maximum Lysis</td>
<td>Maximum lysis detected during the run time, described as the difference between MCF and the lowest amplitude after MCF, described in % of MCF</td>
<td>%</td>
</tr>
<tr>
<td>L(x)</td>
<td>Lysis Index at time x minutes</td>
<td>Ratio of the amplitude and MCF at a given time point after CT.</td>
<td>%</td>
</tr>
<tr>
<td>L150</td>
<td>Lysis Index at time 150 minutes</td>
<td>L150 at CT + 150 min calculated A/MCF*100</td>
<td>%</td>
</tr>
<tr>
<td>L45</td>
<td>Lysis Index at time 45 minutes</td>
<td>L45 at CT + 45 min calculated A/MCF*100</td>
<td>%</td>
</tr>
<tr>
<td>L60</td>
<td>Lysis Index at time 60 minutes</td>
<td>L60 at CT + 60 min calculated A/MCF*100</td>
<td>%</td>
</tr>
<tr>
<td>LOT</td>
<td>Lysis Onset Time</td>
<td>The time span from CT to the start of significant lysis in % . Significant lysis is defined as a decrease of the amplitude of 15% as compared to MCF.</td>
<td>s</td>
</tr>
<tr>
<td>LT</td>
<td>Lysis Time</td>
<td>The time from CT until the clot firmness is decreased to 10% of the MCF during fibrinolysis.</td>
<td>%</td>
</tr>
<tr>
<td>CLR</td>
<td>Clot Lysis Rate</td>
<td>The strongest lysis, described by the angle between the baseline and the tangent to the declining firmness curve at the minimum of the 1st derivative.</td>
<td>degree (°)</td>
</tr>
</tbody>
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<tr>
<td>G</td>
<td>G = 5000MCF/(100 - MCF)</td>
<td>Shear Elastic Modulus Strength</td>
<td>%</td>
</tr>
<tr>
<td>TPI</td>
<td>Thrombodynamic Potential Index TPI = EMX/K EMX = (100*MCF)/(100-MCF)</td>
<td>According to Raby 1975, the Thrombodynamic Potential Index describes the patient’s global coagulation</td>
<td>%</td>
</tr>
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<tr>
<td>maxV</td>
<td>Maximum velocity</td>
<td>The maximum of the 1st derivative of the curve</td>
<td>mm/min</td>
</tr>
<tr>
<td>maxV-1</td>
<td>Time to maximum velocity</td>
<td>Time from reaction start until the maximum of the 1st derivative of the curve is reached.</td>
<td>s</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under 1st derivative curve</td>
<td>Area under the 1st derivative curve from start of the derivative curve until MCF is reached.</td>
<td>mm x 100</td>
</tr>
</tbody>
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</thead>
<tbody>
<tr>
<td>AR(x)</td>
<td>Area under the curve at time x</td>
<td>The area under the curve from CT to the respective time point.</td>
<td>mm²</td>
</tr>
<tr>
<td>AR5</td>
<td>Area until time 5 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR10</td>
<td>Area until time 10 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR15</td>
<td>Area until time 15 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR20</td>
<td>Area until time 20 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR25</td>
<td>Area until time 25 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR30</td>
<td>Area until time 30 minutes</td>
<td></td>
<td></td>
</tr>
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</table>

*Important routine parameters are shaded grey*
Example of a reaction curve ("TEMogram")
The most important parameters which can be derived from the curve are shown
## ROTEM PARAMETERS

- **CT** = Clotting Time
- **CFT** = Clot Formation Time
- **α-Angle**
- **MCF** = Maximum Clot Firmness
- **A10** = Amplitude at 10 min
- **LI30** = Lysis Index at 30 min
- **ML** = Maximum lysis

**NOTE:** A sample algorithm will be used for general principles in this presentation. However, normal values can vary between institutions and machines. Please use appropriate local values and algorithms for clinical use.
CLOTTING TIME

• Clotting Time is a measure of how well the clotting cascade is working.
• Measured in Seconds

• $C_{T_{\text{EXTEM}}} \leq 85\text{s}$ is normal

• If $C_{T_{\text{EXTEM}}} > 85\text{s}$, give Plasma
  • Or consider PCC when wishing to restrict volume infusion.
    • PCC = Prothrombin Complex Concentrate, aka K-Centra
• Next look at the $A10_{\text{EXTEM}}$
  • $A10 = \text{Amplitude @ 10minutes}$
    • $A10 = \text{CT + 10 min}$

• We expect $A10_{\text{EXTEM}} \geq 45\text{mm}$

• If $A10_{\text{EXTEM}} < 45\text{mm}$ suggests a problem with fibrinogen or platelet function.
  • We need to distinguish which so that we can give the correct product (either cryoprecipitate, platelets or both.)
A10

- Assume $A_{10}^{\text{EXTEM}} < 45\text{mm}$
- Now look at $A_{10}^{\text{FIBTEM}}$

- When enough Fibrinogen is present, $A_{10}^{\text{FIBTEM}} \geq 10\text{mm}$

- So, if $A_{10}^{\text{EXTEM}} < 45\text{mm}$ and $A_{10}^{\text{FIBTEM}} \geq 10\text{mm}$
  - $\Rightarrow$ Give platelets

- Or, if $A_{10}^{\text{EXTEM}} < 45\text{mm}$ and $A_{10}^{\text{FIBTEM}} < 10\text{mm}$
  - $\Rightarrow$ Give cryoprecipitate
The diagram illustrates various parameters in a graph that measures amplitude in mm (firmness) against time in minutes. Key parameters include:

- **CT**: Clotting time
- **CFT**: Clot formation time
- **alpha**: Alpha-angle
- **A10**: Amplitude 10 min after CT
- **MCF**: Maximum clot firmness
- **LI30**: Lysis index 30 min after CT
- **ML**: Maximum lysis

The graph shows a typical waveform with labeled points and terms that indicate the dynamics of clotting and lysis processes.
HYPERFIBRINOLYSIS

• Who gets hyperfibrinolysis?
  • Trauma patients
  • CT surg patients
  • tPA
  • Malignancy
  • Labor

• Evidence of Hyperfibrinolysis on ROTEM
  • ML = Maximum Lysis (at any given point in time)
    • Percentage of clot lost in relation to MCF
    • ML ≥ 15% is consistent with hyperfibrinolysis
EXTEM Graph above; INTEM, FIBTEM, APTEM all below
FIBRINOLYSIS

- If evidence of fibrinolysis ➔
  - Tranexamic Acid
  - Amicar (Aminocaproic Acid)
ONGOING BLEEDING?

- Draw another ROTEM in 10-15 minutes
**TYPICAL BLOOD PRODUCTS**

- **FFP**
  - Clotting factors
  - Protein C, S, Z
  - vWF

- **RBCs**
  - All at UNM are leukoreduced
  - Most pts should get non-irradiated cells
  - Some immunocompromised pts should get irradiated to reduce the risk of GvH disease (graft vs host.)
CRYOPRECIPITATE

- Fibrinogen
- Factor XIII (aka fibrin stabilizing factor)
  - Factor XIIIa is a primary component for cross linking fibrin.
  - Note: Factor XIIIa requires Ca$^{2+}$ as a co-factor
- Factor VIII
- von Willebrand Factor
PCC (aka K-CENTRA)

• Trade name for PCC
  • PCC = Prothrombin Complex Concentrate

• Contains II, VII, IX, X, protein C, protein S

• Contraindications:
  • Heparin-Induced Thrombocytopenia (HIT)
  • Disseminated Intravascular Coagulaiton (DIC)

• Adverse Reactions:
  • MI, VTE, arterial thrombosis, DIC
  • Higher thromboembolic risk than plasma
  • Pt’s with VTE, MI, CVA, TIA in last 3 months were excluded from trials.

• http://www.kcentra.com/professional/presentations/dr-blind.png (video 22:33)
EXTEM

ST: 08:26:14
RT: 01:00:12
CT: 76 s
[0043 -- 0082]
CFT: 109 s
[0048 -- 0127]
α: 69 *
[0065 -- 0080]
A10: 43 mm
A20: 46 mm
[0050 -- 0070]
MCF: 46 mm
[0052 -- 0070]
ML: * 12 %

INTEM

ST: 08:26:49
RT: 01:00:14
CT: 172 s
[0122 -- 0208]
CFT: 97 s
[0045 -- 0110]
α: 72 *
[0070 -- 0081]
A10: 42 mm
A20: 44 mm
[0051 -- 0072]
MCF: 43 mm
[0051 -- 0072]
ML: * 8 %

FIBTEM

ST: 08:27:38
RT: 01:00:12
CT: 68 s
CFT: ---
α: 65 *
A10: 11 mm
A20: 12 mm
[0007 -- 0024]
MCF: 12 mm
[0007 -- 0024]
ML: * 0 %

APTEM

ST: 08:28:50
RT: 00:59:12
CT: 77 s
CFT: 107 s
α: 69 *
A10: 44 mm
A20: 46 mm
A20: 46 mm
MCF: 46 mm
ML: * 9 %

Temperature: 37.0°C
WHAT’S THE EVIDENCE?

• Well.....

• Justify the cost of replacing in-place technology

• Let’s take a look
TURN AROUND TIME


• 50 surgical pediatric patients

• Timing of Results of Standard Coags vs ROTEM A10

• Median 53 min (IQR 45–63min) vs 23 min (IQR 21–24min)
REDUCED TRANSFUSIONS

• Spiess et al, J Cardiothorac Vasc Anesth, 1995

• Retrospective Analysis
• Before and After Institution of TEG-based Transfusion Algorithm
• 1079 sequential patients undergoing major cardiac surgery (CABG ± open ventricular procedures)
• Group 1 – 488 patients
• Group 2 – 591 patients
REDUCED TRANSFUSIONS

• Significantly lower incidence of transfusions
  • 78.5% vs 86.3%, during hospitalization, p=0.001
• Lower median donor exposure
  • 6 (IQR 11) in Group 2 vs. 8 (IQR 15) in Group 1, p=0.001
• Mediastinal re-exploration
  • 1.5% in Group 2 vs. 5.7% in Group 1, p=0.0001

• Use of TEG monitoring before re-exploration has decreased the cost and potential risk for patients undergoing CABG surgery.
RCT OF ROTEM IN CARDIAC SURG

- RCT of 100 cardiac surg patients
- Randomized to monitor Conventional Coags vs POC ROTEM
- Used algorithm for transfusion strategies
- Primary outcomes were blood loss and transfusion requirements
RCT OF ROTEM IN CARDIAC SURG - 2012

- Trial stopped early
- Conventional 5un RBC (IQR 4-9) vs POC 3un RBC (IQR 2-6), p<0.001
- Reduced plasma and plt exposure
- Reduced post-op mechanical ventilation
- Decreased ICU LOS
- Decreased hemostatic therapy costs
- Decreased 6-month mortality
MORTALITY IN TRAUMA

• Rourke, et al. 2012

• Prospective cohort trial
• 517 major trauma patients
• What about fibrinogen?
• Low fibrinogen was independent predictor of 24h and 28d mortality
• Administration of high dose Cryo improved survival
• TEG/ROTEM in coagulopathy, transfusion and mortality in trauma
• 55 studies (12,489 patients)
  • TEG/ROTEM were SN and SP for early detection/prediction of:
    • Hypocoagulability
    • Transfusion needs
    • Mortality
  • 1 observational study suggested ROTEM-based algorithm reduces transfusion needs
  • No clear mortality reduction
• **Evidence is low quality**
  • No RCTs
  • Limited observational data
  • More research needed
• No clear evidence that TEG or ROTEM improve survival in adult cardiac surg and liver transplant patients.

• However, reduced bleeding and fewer patients requiring both Plt and FFP.

• More research needed
COCHRANE REVIEW TRAUMA - 2015


- Primarily focused on A5, A10, A15 for diagnosis of TIC.

- Only 3 studies → major limitation of this review.

- More research needed
LIMITATIONS OF TEG TESTING

• Warfarin not detected with TEG
  • No data on Warfarin detection with ROTEM
• Direct oral anticoagulants (DOACs)
  • No data for either TEG or ROTEM

CT VS CFT FOR PT/PTT

• CT often used as a marker of clotting cascade function with success
  • Similar to PT or PTT
  • Our algorithm, Teaching from TEM intl, Algorithm in Cardiac surgery stdy (Weber, et al.)

• However some studies suggest CFT or $\alpha$-Angle may be better
  • Haas, et al. 2012
    • 50 Ped Surg patients
    • 30 pts undergoing orthotopic liver transplant
MEASURE OF FIBRINOGEN

- $A_{10_{\text{FIBTEM}}}$ is a good test for fibrin activity as compared to Fibrinogen level determined by Clauss method.
  - $A_{5_{\text{FIBTEM}}}$

- In trauma, low fibrinogen correlated with mortality
- And, reversal with improved survival
• Response to blood products
• GI bleeding
• Coagulopathic pts in sepsis/septic shock
• Pre-operative coagulation status
• Hemolytic conditions (DIC, TTP, etc.)
• Use in obstetrics
• Hypercoagulability
ADVANTAGES

• Advantages
  • Faster turnaround time
  • All steps of coagulation, clot growth, and fibrinolysis
  • Hypofibrinogenemia and when to treat
  • Hyperfibrinolysis
  • Reduced bleeding and transfusion (cardiac surgery)
  • Likely appropriate for response to blood product therapy
DISADVANTAGES

• Disadvantages
  • Interdependent values and variability
  • Lack of standardization & data
    • Variability of reagents
    • Variability between machines
    • Variable algorithms
  • Mostly low quality evidence,
    • Mostly observation data with lack of controls and small studies
BOTTOM LINE

• Surgical evidence has shown some benefits
  • Less bleeding and less transfusion
  • Best RCT thus far also showed improved outcomes
    • But only 1, and only 100 pts. Ties to TEM Intl.
• Level of evidence
  • Moderate in cardiac surgery
  • Low quality in liver transplantation and trauma
  • Poor or none in other areas (sepsis, GI bleeding, obstetrics, etc.)

• In contrast, no significant evidence that standard tests improve important clinical outcomes either.
REFERENCES


REFERENCES

- Hunt H, Stanworth S, Curry N, Woolley, Cooper C, Ukoumunne O, Zhelev Z, Hyde C. Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM®) for Trauma Induced Coagulopathy in Adult Trauma Patients with Bleeding (Review.) The Cochrane Library. 2015. Issue 2.