Thromboelastography (TEG)

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Consequences of blood transfusion

- Cost
- Transmission of infectious diseases
  - Viral, bacterial sepsis...
- Transfusion reactions
  - Allergic reactions, transfusion-related ALI
  - Inflammatory reactions
- Immunomodulation (allogeneic leukocytes)
  - Higher incidence of postoperative surgical infection & cancer recurrence
  - Leucoreduction is beneficial

Blumberg N, Transfusion 2005;45: 33S
De Boer M, Anesth Analg 2008;106: 32
Blood conservation strategies

• Increase preoperative RBC mass
• Autologous blood
• Decrease perioperative bleeding
• Optimize transfusion practices
  – Monitoring of coagulation system
Monitoring of coagulation system
Monitoring of coagulation system: Coagulopathy

• Early correction
  – FFP, cryoprecipitate, platelets
  – Pharmacologic intervention
    » E.g., antifibrinolytic agents
Monitoring of coagulation system: Hypercoagulability

• Too much clot formation
  – Vascular surgery
  – Cardiac surgery (assist devices)
  – Liver transplantation
  – Coronary stenting

• Guides us in the use of anticoagulants
Liver transplantation: hypercoagulability
Need for monitoring of coagulation system

- Traditional coagulation tests
  - PT, PTT, fibrinogen, platelet count
  - Limited view of coagulation system
  - Only slight correlation with blood loss

Need for monitoring of coagulation system

- Alternative tests: thromboelastography (TEG)
  - Overall coagulability of whole blood
  - Interaction between platelets, fibrinogen, and coagulation factors
  - “Hemostasis is a dynamic interplay between platelets, coagulation factors and its inhibitors, and fibrinolytic proteins”
Description of TEG

• Determines viscoelasticity during clot formation

• Developed by Dr. Hellmut Hartert
  – Univ. of Heidelberg (1948)

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Monitoring of coagulation system: TEG

- Torsion wire
- Pin
- Cup
- Heating element, sensor, and controller
- .36 ml whole blood (clotted)
- 4°45'
Monitoring of coagulation system: TEG
Monitoring of coagulation system: TEG

• TEG shows:
  – Kinetics of clot formation and growth
  – Strength and stability of formed clot
Monitoring of coagulation system: TEG

- **Reaction time (R)**
  - Time until initial fibrin formation

- **Coagulation time (K)**
  - From ‘R’ until the amplitude of TEG reaches 20 mm

- **Alpha angle**
  - Represents the acceleration of fibrin build-up and cross-linking

- **MA**
  - Maximum strength of clot

- **A60**
  - Amplitude 60 min after MA
TEG

• Parameters:
  – reaction time (r): 5-15 min
  – coagulation time (k): 3-6 min
  – clot formation rate (α): >45°
  – maximum amplitude (MA): 50-60 mm
  – clot lysis index (CLI) MA/A60: >85%
  – lysis time: >180 min
Initial interpretation of TEG

- R time: reflects coagulation factor levels
- Angle: reflects fibrinogen activity
- MA: reflects platelet function and fibrinogen activity
Systems

• Thromboelastography (TEG)
  – Haemonetics (Haemoscope) Corp (USA)

• ThromboelastoMeter-Autometer (TEM-A)
  – Framer Biomedica (Italy)

• Thromboelastometry (ROTEM)
  – Tem Innovations GmbH (Munich)
Thromboelastography (TEG) (Haemoscope)
ThromboelastoMeter (Autometer) (TEM-A) (Framer)
Monitoring of coagulation system: TEG

- Torsion wire
- Pin
- Cup
- Heating element, sensor, and controller
- 0.36 ml whole blood (clotted)

4°45'
Thromboelastometry (ROTEM) (Tem, Munich)
Thromboelastometry

ROTEM® is derived from "rotational thromboelastometry", a powerful technique for the assessment of blood coagulation disorders.

**Principle:**
- Blood is added into a disposable cuvette (measuring cell) in a heated cuvette holder
- Disposable pin (sensor) is fixed on the tip of a rotating shaft (axis).
- The rotating shaft is stabilized by a high precision ball bearing system
- Shaft rotates back and forth 4.75 degrees
- Shaft is connected to a spring to measure elasticity
- Exact position of the shaft is detected by reflection of light on small mirror on the shaft.
- Data obtained from the reflected light is then computer processed into a graphical output.
Monitoring of coagulation system: TEG & ROTEM
Monitoring of coagulation system: TEG vs. ROTEM

- Overall results are similar but not the same!
  - Main difference: reaction time shorter with ROTEM
- Different technology
  - Plastic composite of the reaction cups & pins
- Celite-activation attenuates the differences

Nielsen V, Blood Coagul Fibrinolysis 2007;18: 247
Assays

• Addition of substances to the cup/blood sample
• These agents have to be added manually (TEG)
• Compare results to native sample
• Improves diagnostic interpretation of TEG/ROTEM
• Only for those with experience!
Example

Larsen O, Anesth 2011;115: 294
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Original “home-made” assays for TEG

- Protamine
- Antifibrinolytic drugs (EACA, TA, aprotinin)
Assays for TEG

- Kaolin (cup with intrinsic pathway activator)
  - Celite (intrinsic pathway activator)
- Heparinase test (cup coated with heparinase)
- Functional Fibrinogen Reagent (FF assay)
- PlateletMapping Assay
- Very rapid “RapidTEG” assay
- (No official antifibrinolytic assay)
Kaolin activated TEG (F XII activator)

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Heparinase TEG

<table>
<thead>
<tr>
<th>r</th>
<th>K</th>
<th>ANG</th>
<th>MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.7</td>
<td>7.9</td>
<td>32.0</td>
<td>35.5</td>
</tr>
<tr>
<td>(15–23)</td>
<td>(5–10)</td>
<td>(22–38)</td>
<td>(47–58)</td>
</tr>
</tbody>
</table>

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Functional Fibrinogen Reagent (FF assay)

- Abciximab (ReoPro) – inhibitor of GP IIb/IIIa
- Eliminates the contribution of plt to clot strength
  - Shows the cause of low MA: plt vs. clotting factors
  - May guide administration of plt vs. fibrinogen
    » Volunteer study

Solomon C, Anesth Analg 2012;114: 721
Functional Fibrinogen Reagent (FF assay)

- With ReoPro:
  - reduced MA
  - straight line
  - reduced MA

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Platelet Mapping Assay

• 4 channels of TEG tracings
  – 1. kaolin-induced TEG
  – 2, 3, 4: Addition of Activator F (reptilase + FXIIIa)
  – 2. Heparin (inhibits thrombin formation)
  – 3. Heparin + Arachidonic acid (TxA2 receptor agonist)
  – 4. Heparin + ADP

Craft R, J Lab Clin Med 2004;143: 301
PlateletMapping Assay

use of reptilase, which generates fibrin through a thrombin-like activity in the absence of platelet activation.\textsuperscript{24} It was also necessary to crosslink this fibrin network with factor XIII\textsubscript{a} to give it sufficient rigidity for us to observe the platelet interaction.\textsuperscript{25}
Platelet Mapping Assay

- 4 channels of TEG tracings
  - 1. kaolin-induced TEG
  - 2,3,4: Addition of Activator F (reptilase + FXIIIa)
  - 2. Heparin (inhibits thrombin formation)
  - 3. Heparin + Arachidonic acid (TxA$_2$ receptor agonist)
  - 4. Heparin + ADP

Craft R, J Lab Clin Med 2004;143: 301

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PlateletMapping Assay

- Allows evaluation of effects of platelet inhibitors
  - Aspirin
  - Clopidogrel (Plavix)

» Blood donor study

- PlateletMapping assay is FDA approved

Bochen L, Thromb J 2007;5: 3
Tantry U, J Am Coll Cardiol 2005;46: 1705
De Wolf A, 2012
RapidTEG assay

• Kaolin AND tissue factor as activators
  – Main advantage: very fast results
  – Predictive of outcome and transfusion requirements in trauma patients

Pezold M, Surgery 2012;151: 48
Cotton B, J Trauma 2011;71: 407

De Wolf A, 2012
**Assays for ROTEM**

<table>
<thead>
<tr>
<th>ROTEM®</th>
<th>EXTEM</th>
<th>INTEM</th>
<th>HEPTEM</th>
<th>FIBTEM</th>
<th>APTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>extrinsic activator (tissue factor); not affected by aprotonin, sensitive to heparin</td>
<td>intrinsic activator; sensitive to heparin</td>
<td>neutralises heparin effects</td>
<td>pharmacological inactivation of platelets; represents the strength of the fibrin clot without the effects of platelets (see text)</td>
<td>inhibition of premature lysis by the addition of APTEM (see text)</td>
</tr>
</tbody>
</table>
FIBTEM

• Addition of cytochalasin D (potent platelet inhibitor
  2° prevention of cytoskeletal reorganization)

• Eliminates the contribution of platelets to clot strength
  – Shows the cause of low MA: ptl vs. clotting factors
  – Could guide administration of ptl vs. fibrinogen

» Volunteer study

Larsen O, Anesth 2011;115: 294

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FIBTEM

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Larsen O, Anesth 2011;115: 294

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Advantages of ROTEM

• More automated system, vibration resistant, self-calibrating

• Automatic pipettes
Monitoring of coagulation system: TEG vs. ROTEM

• Guidance to transfusion practice should be, in my opinion, very similar

• Assays are NOT identical
  – Functional Fibrinogen Assay ≠ FIBTEM
  – Inhibition of platelets through RheoPro (FF assay) vs cytochalasin D (FIBTEM)

Nielsen V, Blood Coagul Fibrinolysis 2007;18: 247
Scharberty G, Platelets 2009;20: 125
Solomon C, Anesth Analg 2012;114: 721
De Wolf A, 2012
Clinical use of TEG/ROTEM

• Benefits of TEG/ROTEM:
  – Rapid, overall evaluation of coagulation system
  – Based on whole blood coagulability
  – Guides blood products
    » Platelets, FFP, cryoprecipitate
  – Guides pharmacologic intervention
    » Protamine, antifibrinolytics, DDAVP, fVIIa
Comparison of TEG/ROTEM and traditional tests

• Very few controlled studies comparing TEG/ROTEM and traditional tests
• There are some correlations with common coagulation tests
• Few correlations: is this worrisome?
• Not really. Different look at coagulation
Comparison of TEG/ROTEM and traditional tests

- Some studies show some correlations
- RapidTEG assay

Cotton B, J Trauma 2011;71: 407
TABLE 3. Spearman’s Correlation of r-TEG Values With CCTs

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th></th>
<th></th>
<th>aPTT</th>
<th></th>
<th></th>
<th>Platelet Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 272)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k-time</td>
<td>0.82</td>
<td>&lt;0.001</td>
<td>0.81</td>
<td>&lt;0.001</td>
<td>-0.26</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>r-value</td>
<td>0.72</td>
<td>&lt;0.001</td>
<td>0.76</td>
<td>&lt;0.001</td>
<td>-0.17</td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td>α-angle</td>
<td>-0.66</td>
<td>&lt;0.001</td>
<td>-0.63</td>
<td>&lt;0.001</td>
<td>0.40</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>-0.65</td>
<td>&lt;0.001</td>
<td>-0.58</td>
<td>&lt;0.001</td>
<td>0.49</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MT patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k-time</td>
<td>0.59</td>
<td>0.015</td>
<td>0.64</td>
<td>0.007</td>
<td>-0.71</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>r-value</td>
<td>0.61</td>
<td>0.012</td>
<td>0.62</td>
<td>0.011</td>
<td>-0.17</td>
<td>0.183</td>
<td></td>
</tr>
<tr>
<td>α-angle</td>
<td>-0.58</td>
<td>0.017</td>
<td>-0.67</td>
<td>0.004</td>
<td>0.71</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>-0.73</td>
<td>0.001</td>
<td>-0.75</td>
<td>&lt;0.001</td>
<td>0.68</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>
Outcome studies based on TEG/ROTEM

• Cardiac surgery:
  – CPB, n = 107
  – Randomized in two groups
    1. Standard coagulation tests (n = 52)
    2. TEG (celite, TF, heparinase) (n = 53)
  – TEG patients received less FFP (4 vs. 16) and platelets (7 vs. 15)

Shore-Lesserson L: Anesth Analg 1999;88: 312
Outcome studies based on TEG/ROTEM

• Cardiac surgery
• Fairly simple, similar TEG criteria
• Similar results

Royston D: Br J Anaesth 2001;86: 57
Welsby I: J Cardiothor Vasc Anesth 2006;20: 531
Nuttall G: Anesth 2001;94: 773
Ak K, J Card Surg 2009;24: 404
Outcome studies based on TEG/ROTEM

- Complex aortic surgery with circulatory arrest (n = 56)
- Randomized in two groups
  1. Standard coagulation tests (n = 29)
  2. ROTEM (celite, TF, heparinase) (n = 27)
    INTEM, HEPTEM, APTEM, FIBTEM
- TEG patients received less FFP (3 vs. 8 U)

Girdauskas E: J Thorac Cardiovasc Surg 2010;140: 1117
<table>
<thead>
<tr>
<th>Finding</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT by HEPTEM &gt;260 s</td>
<td>FFP (15 mL/kg body mass)</td>
</tr>
<tr>
<td>CT by APTEM &gt;120 s</td>
<td>3000 IU PPSB</td>
</tr>
<tr>
<td>MCF by HEPTEM 35–45 mm,</td>
<td>1 platelet concentrate</td>
</tr>
<tr>
<td>MCF by FIBTEM &gt;8 mm</td>
<td></td>
</tr>
<tr>
<td>MCF by HEPTEM &lt;35 mm</td>
<td>1 platelet concentrate</td>
</tr>
<tr>
<td>MCF by FIBTEM &lt;8 mm</td>
<td>2 g fibrinogen</td>
</tr>
<tr>
<td>MCF by APTEM/MCF by HEPTEM &gt;1.5</td>
<td>3 g tranexamic acid</td>
</tr>
<tr>
<td>CT by INTEM/CT by HEPTEM &gt;1.5</td>
<td>5000 IU protamine</td>
</tr>
<tr>
<td>(in any post-CPB analysis)</td>
<td></td>
</tr>
<tr>
<td>Activated clotting time &gt;160 s</td>
<td>5000 IU protamine (1 time)</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>FFP (15 mL/kg body mass)*</td>
</tr>
<tr>
<td>&gt;60 s or INR &gt;1.5</td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;100,000 cells/μL</td>
<td>1 platelet concentrate</td>
</tr>
<tr>
<td>Fibrinogen &lt;1.2 mg/dL</td>
<td>2 g fibrinogen</td>
</tr>
<tr>
<td>α₂-Antiplasmin &lt;80%</td>
<td>3 g tranexamic acid</td>
</tr>
</tbody>
</table>
Outcome studies based on TEG/ROTEM

- Cardiac surgery in patients with recent antiplatelet therapy (n = 59)
- TEG platelet mapping prior to surgery
- TEG platelet mapping could predict excessive chest tube bleeding in first 24 h
  - MAADP < 42.5 mm


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Outcome studies based on TEG/ROTEM

- Patients undergoing PCI (n = 192)
- Aspirin (100%) and/or clopidogrel (84%)
- Correlation between ischemic events and
  - Ptl reactivity to ADP (light transmission aggregometry)
  - MA on TEG (with heparinase)
- Better correlation between MA and events

Gurbel P: J Am Coll Cardiol 2005;46: 1820
De Wolf A, 2012
TEG/ROTEM in Liver Transplantation

• Yoogoo Kang (1985)
  – Native; protamine and EACA TEG assays
• Antifibrinolytic agents
• Guidance for ptl, FFP, cryoprecipitate
• Hypercoagulability
  – Low-dose heparin

Gologorsky E: Liver Transplant 2001;7: 783
Hemostatic changes promoting bleeding

- Thrombocytopenia
  - Platelet function defects
- Enhanced production of nitric oxide and prostacyclin
- Low levels of coagulation factors II, V, VII, IX, X, and XI
- Vitamin K deficiency
- Dysfibrinogenemia
- Low levels of α2-antiplasmin, factor XIII, and TAFI
- Elevated tPA levels

Rebalance

Hemostatic changes promoting thrombosis

- Elevated levels of vWF
  - Decreased levels of ADAMTS-13

Primary hemostasis

Secondary hemostasis

Fibrinolysis

- Elevated levels of FVIII
  - Decreased levels of protein C, protein S, antithrombin, α2-macroglobulin, and heparin cofactor II
- Low levels of plasminogen
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Lisman T, J Hepatol 2010;53: 362
TEG/ROTEM in liver resection

- Liver resection
  - Transient postoperative coag test abnormalities
  - Prolonged PT, aPTT, reduced platelet count
  - Epidural catheter placement/removal?

Siniscalchi A: Liver Transplant 2004;10: 1144
Schuman R: Liver Transplant 2004;10: 363
TEG/ROTEM in liver resection

Cerrutti E: Liver Transplant 2004;10: 289

De Wolf A, 2012
Case report: patient with ITP, urgent CABG

- Preop platelet count 55,000/mm$^3$,
- Preop INTEM, FIBTEM normal
- Post-CPB platelet count 42,000/mm$^3$
- Post-CPB INTEM and FIBTEM normal
- No platelets were transfused

Rossi M: Tex Heart Inst J 2010;37: 361
De Wolf A, 2012
Conclusions

- TEG/ROTEM are more physiologic methods of measuring hemostatic function
- TEG/ROTEM have several advantages
- Limited or no studies with newer assays
- Further prospective studies are warranted
Thank you!