Use of ROTEM from the Laboratory Perspective

A/Prof David Roxby
SA Pathology
What’s the Problem?

- Constant changes in treatment recommendations
- Lack of good evidence to guide practice
- Variations in clinical practice
- Inappropriate use of labile blood components
- Exposing patients to risk with poor evidence for benefit
Importance of Peri-operative Coagulation Monitoring

- Diagnose potential causes of haemorrhage
- Predict risk of bleeding
- Guide appropriate haemostatic therapy
  - Blood products associated with increased
    - LOS
    - Infections & sepsis
    - MOF
    - Morbidity & mortality
    - TRALI
    - TACO
Laboratory & Clinical Issues

Before surgery
- Is there a coagulopathy

During surgery
- What coagulopathy is developing

After surgery
- If patient is bleeding, is it due to
  - Surgical problems
  - Excess heparin
  - Coagulopathy
WHAT IS A ROTEM?

• A modified version of thromboelastography [TEG] developed in 1948 by Hartert

Courtesy Dr Roger Browning, Dept Anaesthesia and Pain Medicine, King Edward Memorial Hospital
Rotational Thromboelastometry (ROTEM)

- Real-time measurement of visco-elastic properties of clot kinetics
  
  Determination of the physical changes in blood when a force (shear) is applied over specific time interval

- Results dependent on both concentration & activity of circulating clotting elements

- High negative predictive value
  
  - normal results → bleeding highly unlikely due to significant coagulopathy

- Graphical & numerical displays

- Use algorithm guided replacement therapy
**Principle of thromboelastometry [ROTEM®]**

Citrated whole blood – test within 4 hours

4 channels

Assay Time = 5-10 mins
Rotational Thromboelastometry

- Different activators & additives
- Detect & differentiate specific haemostatic defects
  - Assess broader picture of haemostasis
  - Identify mechanisms of blood loss & trauma-associated coagulopathy
    - Hyperfibrinolysis
    - Heparin & protamine effects
    - Hypofibrinogenemia
    - Fibrin polymerisation disorders
    - Coagulation factor deficiency & thrombocytopenia
# Tests

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>Activator Inhibitor</th>
<th>Information provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTEM</td>
<td>Tissue factor activation</td>
<td>Assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway (rTF)</td>
</tr>
<tr>
<td>INTEM</td>
<td>Contact activation</td>
<td>Assessment of clot formation, fibrin polymerisation and fibrinolysis via the intrinsic pathway (ellagic acid)</td>
</tr>
<tr>
<td>FIBTEM</td>
<td>Tissue factor activation and platelet inhibition</td>
<td>Analysis without platelets (cytochalasin D): Qualitative assessment of fibrinogen status</td>
</tr>
</tbody>
</table>
# Tests

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>Activator Inhibitor</th>
<th>Information provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTEM</td>
<td>Tissue factor activation + Aprotinin</td>
<td>In-vitro fibrinolysis inhibition: Fast detection of lysis when compared to EXTEM</td>
</tr>
<tr>
<td>HEPTEM</td>
<td>Contact activation + Heparinase</td>
<td>Analysis without heparin influence: Specific detection of heparin (compared to INTEM), assessment of clot formation in heparinised patients</td>
</tr>
</tbody>
</table>
Within OT – Networked to Theatre, ICU, Lab

Within Lab – Networked to Theatre, ICU, ED
Why Don’t We Just Stick With The Traditional Coag Profiles?

Traditional coagulation tests include: INR, aPTT, Fgn & Plt count

1. Speed
   - Traditional coags take 30 – 60 minutes Vs 10-15 min for useful information from the ROTEM → Avoid results becoming historical

2. Traditional coagulation tests give no information on:
   - Clot strength
   - Hyperfibrinolysis
   - Interaction between the various components of haemostasis
   - No information of platelet function
Why Don’t We Just Stick With The Traditional Coag Profiles?

3. **ROTEM - whole blood (not plasma)**
   - Information regarding *overall haemostasis* which may be adequate despite an abnormality in one component (e.g. low platelet count compensated by a high fibrinogen level)

4. **INR & aPTT**
   - Designed to assess the effect of coumadins and heparin / haemophilia
   - Never intended for use in assessing the multifactorial coagulopathies in major haemorrhage or surgery
   - Never designed to be predictive of bleeding
What do all these lines / squiggles mean?

CT, α, CFT, Aₓ, MCF, LIₓ, ML

✔ Are there adequate clotting factors or are they inhibited?
  ✔ CT / Clotting time
✔ Is the clot strength deficient?
  ✔ Fgn, plts & FXIII
    ✔ Assessed by amplitude A₅/ A₁₀ or MCF (maximum clot firmness)
    ✔ Advantage A₁₀ allows decision before MCF
✔ Is there excessive fibrinolysis?
  ✔ Clot degrades over time (Lix/ML)
EXTEM / INTEM Trace

CT Clotting Time [sec] From 0mm – 2mm

Reference ranges: 137-246 sec
42-74 sec
EXTEM / INTEM Trace

CFT  Clot Formation Time [sec]

Reference ranges: 40-100 sec
46-148 sec

From 2mm – 20mm
EXTEM / INTEM Trace

Alpha angle [°]

Reference ranges:  
70-83 °  
63-83 °
EXTEM / INTEM Trace

A10  Clot Firmness [mm]

Reference ranges:  44-66 mm
                   43-65 mm
EXTEM / INTEM Trace

MCF  Maximum Clot Firmness [mm]

Reference ranges:  50-72 mm
                  49-71 mm
EXTEM / INTEM Trace

ML  Maximum Lysis [%]
LI  Lysis Index [%]

Reference ranges:  ML<15 %  LI(30) 94-100%
                  ML<15 %  LI(30) 94-100%
FIBTEM Tests

A10  Clot Firmness [mm]

Reference ranges: 7-23 mm
FIBTEM Tests

MCF  Maximum Clot Firmness [mm]

Reference ranges:  9-25 mm
How Do I Interpret the Results?

- Results should not be interpreted in isolation; the clinical condition must always be considered.
- Pattern recognition plays an important role.
  - Shape of the curve may provide more information than measured values.

Important for lab:
- Minimise waste (FFP & cryo).

Curr Opin Crit Care 2013; 19:605-612
How Do I Interpret the Results?

- Platelet contribution
- Coagulation factors
- Fibrin(-ogen) polymerisation

- Fibrinolysis
- Anticoagulant management

SPECIFIC THERAPY
How Do I Interpret the Results?

In most cases you need to ask 5 simple questions

1. Is the patient still bleeding (or at high risk of recurrent or concealed bleeding)?
2. Should I replace fibrinogen?
3. Should I replace clotting factors?
4. Is there evidence of fibrinolysis?
5. Should I give platelets?

Do not forget:
- Hypothermia
- Ionised Ca
- Hb 70g/L
Parameters

- CT EXTEM > 80s correlates with fall in FII, FVII & FX to < 35% of normal
- FIBTEM MCF correlates well with fibrin level: < 7 mm correlates with fibrin < 1.5 g/L
- A5 & 10 accurately predict MCF for EXTEM & FIBTEM:
  - $R^2 = 0.735, p < 0.001$
  - $R^2 = 0.982, p < 0.001$
Is the patient still bleeding (or at high risk of recurrent or concealed bleeding)?

- **YES**
  - Should I replace fibrinogen?
    - **YES**
      - Is EXTEM A10<40mm & FIBTEM A10<10mm?
        - Give 10 apheresis cryo
    - **NO**
      - Consider doing nothing even if results abnormal

- **NO**
  - Consider doing nothing even if results abnormal
**INTEM**
- CT: 236s
- CFT: 220s
- A10: 33mm
- MCF: 42mm
- ML: - %
- 2006-12-15 13:46
- \(\alpha\): 55°

**EXTEM**
- CT: 109s
- CFT: 263s
- A10: 31mm
- MCF: 38mm
- ML: - %
- 2006-12-15 13:50
- \(\alpha\): 48°

**FIBTEM**
- CT: 185s
- CFT: - s
- A10: 3mm
- MCF: 3mm
- ML: - %
- 2006-12-15 13:58
- \(\alpha\): - °

**APTEM**
- CT: 98s
- CFT: 276s
- A10: 31mm
- MCF: 40mm
- ML: - %
- 2006-12-15 13:59
- \(\alpha\): 46°

**INTEM & EXTEM**
- Borderline amplitude
- Suggests: platelet and/or fibrinogen deficiency

**EXTEM**
- Slightly prolonged CT
- Suggests: minor factor deficiency

**FIBTEM**
- Very low amplitude
- Suggests: fibrinogen deficiency

**APTEM**
- Suggests: no hyperfibrinolysis
How Do I Interpret the Results?

Should I replace clotting factors?

Is EXTEM CT > 140s

Give 2-4 units FFP

Is EXTEM CT 100-140s & FIBTEM A10 < 10mm?

If FIBTEM A10 is low correct first as cryo will correct mildly prolonged EXTEM CT

Is INTEM CT > 240s?

Does HEPTEM CT correct?

Yes – heparin affect

No – coag factor deficiency or protamine affect
INTEM
Prolonged CT
low amplitude

HEPTEMV
Normal CT
normal amplitude

Suggests:
heparin influence

INTEM

<table>
<thead>
<tr>
<th>CT:</th>
<th>1501s</th>
<th>CFT:</th>
<th>442s</th>
<th>α:</th>
<th>32°</th>
</tr>
</thead>
<tbody>
<tr>
<td>A10:</td>
<td>25mm</td>
<td>MCF:</td>
<td>41mm</td>
<td>ML:</td>
<td>-%</td>
</tr>
</tbody>
</table>

HEPTEMV

<table>
<thead>
<tr>
<th>CT:</th>
<th>138s</th>
<th>CFT:</th>
<th>71s</th>
<th>α:</th>
<th>77°</th>
</tr>
</thead>
<tbody>
<tr>
<td>A10:</td>
<td>49mm</td>
<td>MCF:</td>
<td>53mm</td>
<td>ML:</td>
<td>14%</td>
</tr>
</tbody>
</table>
How Do I Interpret the Results?

<table>
<thead>
<tr>
<th>EXTEM</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: 57s</td>
<td>444s</td>
<td>α: 90°</td>
<td></td>
</tr>
<tr>
<td>A10: 23mm</td>
<td>MCF: 35mm</td>
<td>ML: -%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTEM</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: 200s</td>
<td>449s</td>
<td>α: 72°</td>
<td></td>
</tr>
<tr>
<td>A10: 23mm</td>
<td>MCF: 32mm</td>
<td>ML: -%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FIBTEM</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: 67s</td>
<td>-s</td>
<td>α: -°</td>
<td></td>
</tr>
<tr>
<td>A10: 15mm</td>
<td>MCF: 16mm</td>
<td>ML: -%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APTEM</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CT: 52s</td>
<td>398s</td>
<td>α: 90°</td>
<td></td>
</tr>
<tr>
<td>A10: 25mm</td>
<td>MCF: 35mm</td>
<td>ML: -%</td>
<td></td>
</tr>
</tbody>
</table>

Normal Ranges

**EXTEM**
- **CT**: 38 - 79 sec
- **CFT**: 34 - 159 sec
- **A10**: 43 - 65 mm
- **MCF**: 50 - 72 mm
- **ML**: 0 - 15 %

**INTEM**
- **CT**: 100 - 240 sec
- **CFT**: 30 - 110 sec
- **A10**: 44 - 66 mm
- **MCF**: 50 - 72 mm
- **ML**: 0 - 15 %

**FIBTEM**
- **A10**: 7 - 23 mm
- **MCF**: 9 - 25 mm

**CT** (clotting time)
*Green display 0 - 2 mm*
*Time in seconds from start of measurement until initiation of clotting, initiation of clotting, thrombin generation & start of clot polymerisation*

**CFT** (clot formation time)
*Pink display 2 - 20 mm*
*Time in seconds from initiation of clotting until clot firmness of 20 mm is detected. Fibrin polymerisation, stabilisation of the clot with platelets & FXIII*

**A10** (amplitude in mm)
*Blue display if >20 mm*
*Otherwise stays pink*
*Early assessment of clot firmness; increasing stabilisation of the clot by the polymerised fibrin, platelets as well as FXIII*

Physiological Targets:
- **Temp**: > 36°C
- **pH**: > 7.2
- **iCa**: > 1 mmol/L
- **Hb**: > 70 g/L

**EXTEM A10 < 40 mm**
**FIBTEM A10 < 10 mm**
**LOW FIBRINOGEN**
**CRYOPRECIPITATE 15 UNITS**

**EXTEM A10 < 40 mm**
**FIBTEM A10 > 10 mm**
**POOR PLATELET CONTRIBUTION**
**PLATELETS 1 DOSE**

**EXTEM CT > 90 sec OR APTEM CT > 90 sec**
**LOW COAGULATION FACTORS**
**FFP 2 units**
**PCC 12.5 units/kg**

**LYSIS INDEX**
**EXTEM ML > 15%**
**APTEN ML < 15%**
**HYPERFIBRINOLYSIS**
**TRANEXAMIC ACID 1 gm**

**NORMAL RESULTS**

If heparin is on board from Cell Saver red cell infusion

**EXTEM CT < 80 sec AND EXTEM A10 > 50 mm AND FIBTEM A10 > 15 mm**
**IF ONGOING BLEEDING**
**CONSIDER SURGICAL HAEMOSTASIS**

**INTEM CT > 240 sec AND HEPTEN CT < 240 sec**
**HEPARIN EFFECT**
**PROTAMINE 25 mg**

Repeat ROTEM tests 10 mins after therapy
Quality Control

- Plasma based lyophilized controls
  - Control values: Normal & abnormal
  - May be used as precision or accuracy controls
  - *External QAP - NEQAS*

- Pipette

- Maintenance

- Specimen delivery systems
  - Manual
  - Pneumatic tube

- Training & competency
Reliability

- EXTEM, INTEM & FIBTEM reproducible & stable over time (0-240 min after blood withdrawal)

- High reproducibility: coefficient of variation (CV) <6% in all assays

Theusinger, Eur J Cardiothorac Surg 2009
Limitations of ROTEM

...The typical assays are not responsive to the effect of von Willebrand factor or platelet antagonists such as aspirin or thienopyridines (e.g. clopidogrel)...
Blood Product Use – Liver Transplant

- Generally empiric & not guided by lab tests due to delay in coag results
- Complexity of treatment intra-operatively may result in sub-optimal transfusion therapy
Intra-operative Laboratory Testing: Non-ROTEM

- Admission FBE & coags
- Intra-operative (TAT<5 mins)
  - Blood gases
    - Hourly
    - 30 mins: anhepatic / reperfusion
- FBE & coags (TAT~40-60 mins)
  - Baseline
  - 1 – 2 hourly
Intra-operative Testing: ROTEM

- Admission FBE & coags
  - No intra-op coag tests
- Intra-op blood gases
- ROTEM [TAT~12 mins]
  - Immediately after anaesthesia
    - Address abnormalities
      - Cryo
      - Plts
      - FFP/PBX
  - Anhepatic phase
  - Reperfusion
  - Skin closure
  - More frequently if required – diffuse bleeding
### Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Non-ROTEM (n= 96)</th>
<th>ROTEM (n= 96)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median [IQR])</td>
<td>51 (45-57)</td>
<td>52 (44-59)</td>
<td>0.94</td>
</tr>
<tr>
<td>Male/Female</td>
<td>67/29</td>
<td>64/32</td>
<td>0.54</td>
</tr>
<tr>
<td>MELD Score (Median [IQR])</td>
<td>16 (12-22)</td>
<td>19 (14-26)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
## Turn-around Times

<table>
<thead>
<tr>
<th>Specimen Delivery</th>
<th>Theatre</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen Delivery</td>
<td>Specimen Delivery</td>
<td>2 min</td>
</tr>
<tr>
<td>Specimen Processing</td>
<td>Specimen Processing</td>
<td>3 mins</td>
</tr>
<tr>
<td>CT</td>
<td>CT</td>
<td>60 secs [60-77]</td>
</tr>
<tr>
<td>CFT</td>
<td>CFT</td>
<td>152 secs [126-197]</td>
</tr>
<tr>
<td>A10</td>
<td>A10</td>
<td>10 mins</td>
</tr>
<tr>
<td>MCF</td>
<td>MCF</td>
<td>Not measured</td>
</tr>
<tr>
<td>Coagulation Screen</td>
<td>Coagulation Screen</td>
<td>42 mins [35-54]</td>
</tr>
<tr>
<td>FBE</td>
<td>FBE</td>
<td>22 mins [14-34]</td>
</tr>
</tbody>
</table>
### Total blood products used

<table>
<thead>
<tr>
<th></th>
<th>Non-ROTEM (n=107)</th>
<th>ROTEM (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>533</td>
<td>557</td>
</tr>
<tr>
<td>FFP</td>
<td>577</td>
<td>420</td>
</tr>
<tr>
<td>Plt</td>
<td>111</td>
<td>193</td>
</tr>
<tr>
<td>Cryo</td>
<td>70</td>
<td>295</td>
</tr>
<tr>
<td>Scavenged RCs</td>
<td>1407</td>
<td>981</td>
</tr>
</tbody>
</table>

(Scavenged RCs (Av mls))
## Products Used

<table>
<thead>
<tr>
<th></th>
<th>Non-ROTEM Median [IQR]</th>
<th>ROTEM Median [IQR]</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>4 (2-7)</td>
<td>4 (2-7)</td>
<td>0.95</td>
</tr>
<tr>
<td>FFP</td>
<td>5 (3-8)</td>
<td>2 (0-6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Plt</td>
<td>1 (0-2)</td>
<td>2 (1-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cryo</td>
<td>0 (0-2)</td>
<td>2 (1-4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
TOTAL COAGULATION PROTEINS

Fibrinogen
## Comparison of FFP use during various phases of OLT

<table>
<thead>
<tr>
<th></th>
<th>Non-ROTEM (Median [IQR])</th>
<th>ROTEM (Median [IQR])</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-anhepatic</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.98</td>
</tr>
<tr>
<td>Anhepatic</td>
<td>1 (0-3)</td>
<td>0 (0-2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>3 (2-4)</td>
<td>2 (0-3)</td>
<td>0.008</td>
</tr>
</tbody>
</table>
## LOS & Post-op Ventilator Support

<table>
<thead>
<tr>
<th></th>
<th>Non-ROTEM (Median [IQR])</th>
<th>ROTEM (Median [IQR])</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation hrs</td>
<td>29 (25-52)</td>
<td>25 (18-36)</td>
<td>0.003</td>
</tr>
<tr>
<td>ICU LOS (hours)</td>
<td>73 (50-156)</td>
<td>72 (44-117)</td>
<td>0.32</td>
</tr>
<tr>
<td>HOS LOS (hours)</td>
<td>542 (399-795)</td>
<td>387 (299-595)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
But the PT was normal...
## Case 1 - Baseline ROTEM Scoliosis Surgery

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>8.7 g/dL</td>
</tr>
<tr>
<td>Plts</td>
<td>112 G/L</td>
</tr>
<tr>
<td>INR</td>
<td>1.3</td>
</tr>
<tr>
<td>aPTT</td>
<td>31 sec</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.5 g/L</td>
</tr>
</tbody>
</table>
Diffuse Bleeding after 3 hours
Which diagnosis can be made based on ROTEM changes?

1. Hyperfibrinolysis
2. Disturbed platelet function
3. Hypofibrinogenaemia
4. Disturbed thrombin generation
5. Heparin effect
Case 2

What might be the underlying problem?

1. Dilutional coagulopathy
2. Low platelet count
3. Coumarin therapy
4. Hyperfibrinolysis
5. Heparin effect
Heparin Effect!
Case 3 Which diagnosis can be made based on ROTEM changes?

1. Hyperfibrinolysis
2. Disturbed platelet function/low count
3. Hypofibrinogenaemia
4. Disturbed thrombin generation
5. Heparin effect
6. Coumarin therapy
7. Heparin effect

What is the next step?

1. Administration of TXA
2. Transfusion of FFP
3. Transfusion of cryo
4. Administration of protamine
5. Transfusion of platelets

Hb 85  INR 2.2  pH 7.05  Ca++ 1.15
Plts 119  Fgn 1.0
AAA repair
Case 4 Which diagnosis can be made based on ROTEM changes?

1. Hyperfibrinolysis
2. Disturbed platelet function/low count
3. Hypofibrinogenaemia
4. Disturbed thrombin generation
5. Heparin effect
6. Coumarin therapy
7. Heparin effect

What is the next step?

1. Administration of TXA
2. Transfusion of FFP
3. Transfusion of cryo
generation
4. Administration of protamine
5. Heparin effect
6. Transfusion of platelets
7. Heparin effect
**Case 5** Which diagnosis can be made based on ROTEM changes?

1. Hyperfibrinolysis
2. Disturbed platelet function/low count
3. Hypofibrinogenaemia
4. Disturbed thrombin generation
5. Heparin effect
6. Coumarin therapy
7. Heparin effect

**What is the next step?**
1. Administration of TXA
2. Transfusion of FFP
3. Transfusion of cryo...
1. Hyperfibrinolysis
2. Disturbed platelet function/low count
3. Hypofibrinogenaemia
4. Disturbed thrombin generation
5. Heparin effect
6. Coumarin therapy
7. Heparin effect

What is the next step?
1. Administration of TXA
2. Transfusion of FFP
3. Transfusion of cryo generation
4. Administration of protamine generation
5. Heparin effect
6. Transfusion of platelets
7. Heparin effect
Conclusion

- Useful tool for global assessment of haemostasis
- Results rapidly available to lab & clinical area & interpreted within minutes
- Improved clinical & laboratory guidance for use of blood & products
- Review of MTPs
  - Guidelines
  - Ratios