The Thrombelastograph™ (TEG®) in 2016: Cardiac surgery, Liver Transplant, Trauma and Beyond

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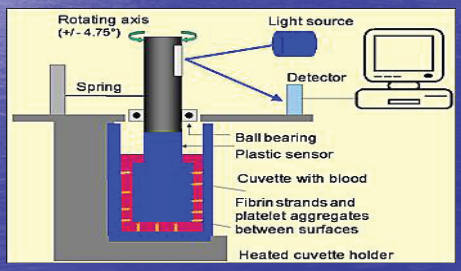
ROTEM® (Rotational Thrombelastometry, Pentapharm)

- Automated
- Similar principle to TEG



Outline

- Point-of-Care coagulation monitoring - TEG®
  - Principle (including newer modifications)
    - Platelet Mapping
    - Tissue factor activation (rapid TEG)
    - Functional fibrinogen
  - Applications/Evidence
    - Liver transplant, cardiac surgery
    - Trauma
    - Other (OB, NS, Pharmacologics)
    - Algorithms

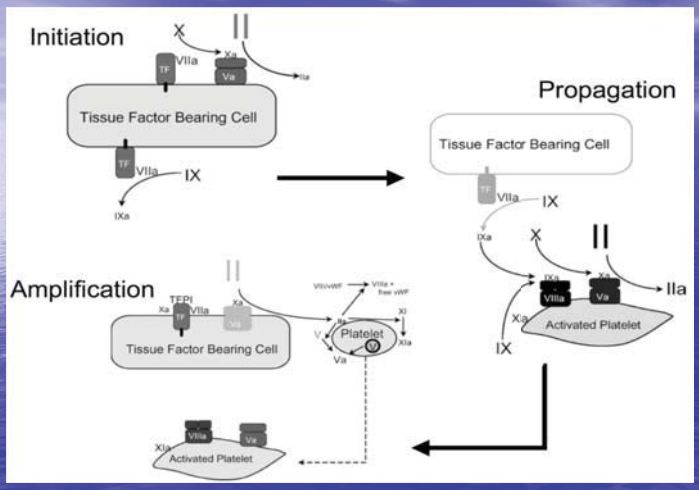
- Europe → USA 2011
- Disposable pin fixed - tip rotating axis
- Axis rotates on ball bearing system, connected spring → measure elasticity, detected reflection of light on mirror
- Changes elasticity → change axis rotation
- Much initial data European

Ideal POC Coagulation Monitor

- Can it be a 'life-saving tool' to assist clinical judgment?
- Rapid results
- Predict bleeding/cause
- NOT necessarily expect to correlate traditional labs
- NOT exclusive – needs included in Rx algorithms

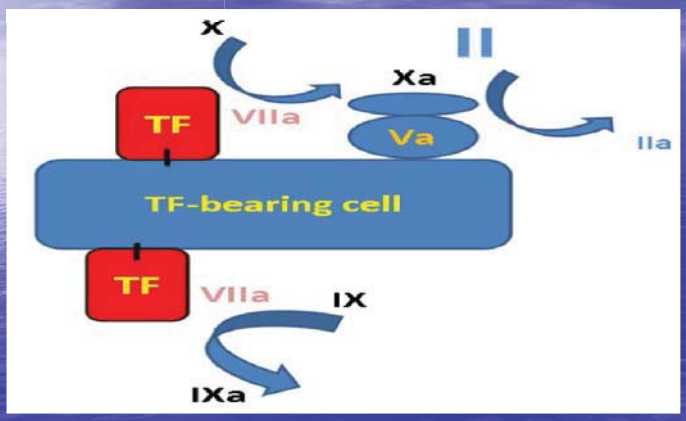
Traditional TEG® (Haemonetics)

New TEG^R 6



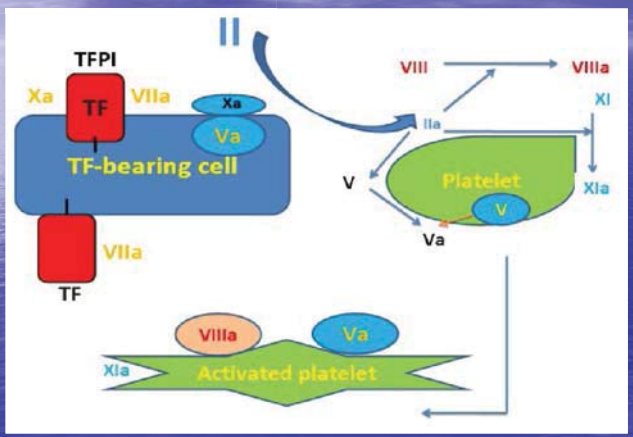
- Measure clot viscoelasticity via resonance
- Sample exposed fixed vibration frequency. With LED, detector measures up/down motion blood meniscus
- Stronger clots - higher resonant frequencies - higher TEG^R readouts
- Automatically loaded microfluidic cartridges - simultaneous multiple assays
- No pipetting/prior manipulation reagents

Initiation

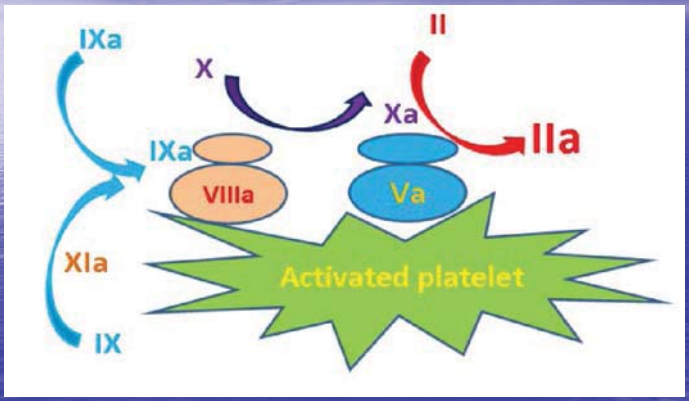


- Global 'visco-elastic' whole blood monitor
- Fits physiology 'cell-based theory' coagulation
- Follows dynamic blood clot formation
  - Initial fibrin formation
  - Fibrin-platelet interaction
  - Clot strength/platelet function
  - Fibrinolysis

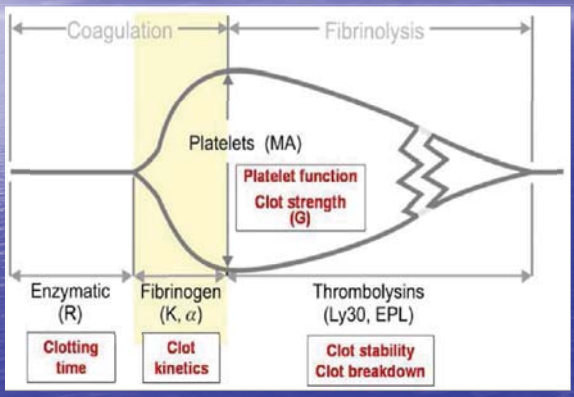
Amplification

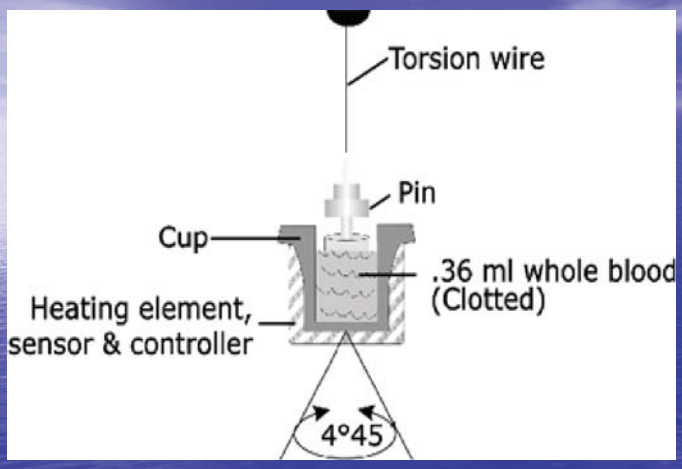


Propagation

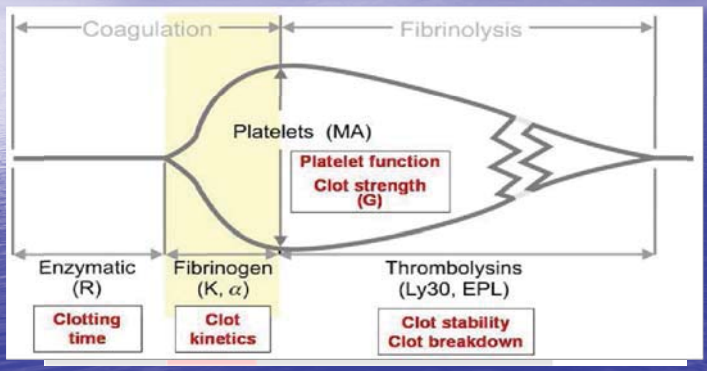


K time (min): coagulation time 2 → 20 mm
Angle (degrees): slope curve from R → K

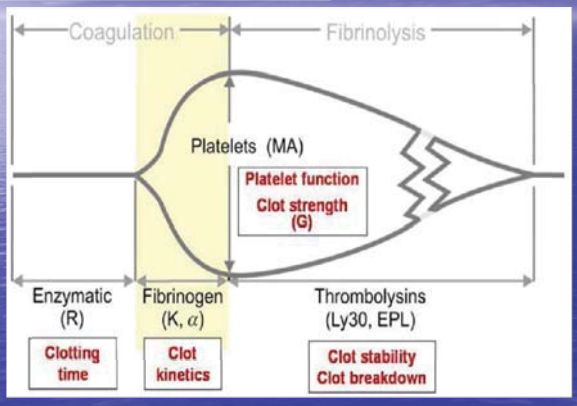




MA (mm): Max width
G (dynes/sec): clot strength
EPL (%)



R time (min): Reaction time → set clot formation (2 mm width)



R time

- Initial fibrin (clot) formation
- Where traditional laboratory tests (PT/PTT) end
- Prolonged:
  - Factor deficiencies (e.g., liver disease, isolated - hemophilia)
  - Factor inhibitors (e.g. hemophilia after long Rx VIII)
  - Anticoagulants (IV, oral, ? DOAC)

K time and Angle

- Rate elasticity increases (fibrin build-up/cross linking)
- Prolonged K/↓ angle (together):
  - Significant abnormalities R time
  - Problems with fibrinogen (e.g., liver disease)
  - Problems platelet count or function

Options

- Native blood (0.36 ml)
  - Too slow
- Celite activation (1 ml)
  - Aprotinin interference (no longer used in USA)
- Kaolin activation (1 ml)
  - Current standard in OR
- Citrated sample with added Ca^{2+}
  - Off-site monitoring
  - Blue–top with liquid
  - Research: wait > 60 mins (Camenzind 2000)

MA and G

- Maximum elastic shear depends contributors to clot strength (direct measure):
  - Platelet function (60%)
  - Fibrinogen (40%)
- $G = \frac{5{,}000 \times MA}{100 - MA}$
- Derived measure

- Heparinase
  - Bacterial derived enzyme
  - Simultaneous regular + heparinase samples
  - Cardio-pulmonary bypass, liver transplant reperfusion, heparin contamination (sampling)
- Tissue Factor
  - Rapid TEG^{R} (kaolin + TF) – trauma/ER at MHH - TMC
  - R/K times very short
  - Replaced by Activated Clotting Time (ACT)
    - Similar limitations to ACT in cardiac surgery

Estimated % Lysis (EPL)

- Rapidity of clot breakdown
- > 7.5%
- Relevant - applications Tranexamic Acid (TXA)
  - Orthopedic
  - Cardiac
  - Liver Transplant
  - Trauma
  - OB

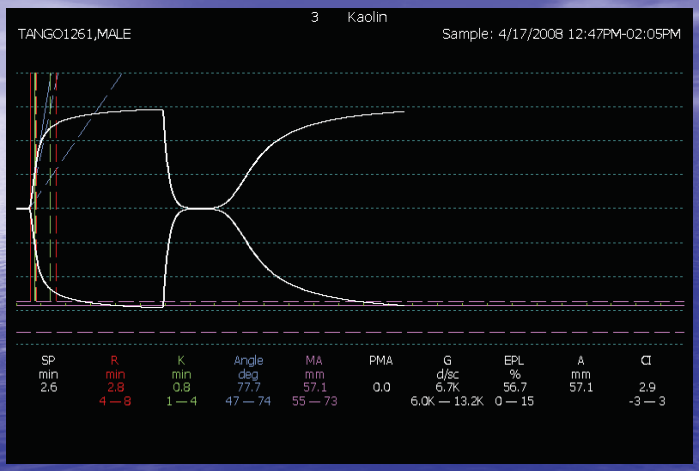
Potential limitations

- Standardization, quality control (Chitlur 2011)
  - International working group (9 labs)
  - Pooled normal plasma (not WB like usual)
  - Repeat readings, pretty wide variation:
    - R: 8 - 17%
    - K: 31- 59%
    - Angle: 3-47%
    - MA: 14-21%
    - G: 21-33%
    - Does this make a clinical difference? Probably not
- Blood collection
  - Tissue trauma, contamination heparin flush

- Sample analysis
  - Operator influence
  - Anesthesia residents/faculty, technicians vs. credentialed lab personnel?
    - Pressure from laboratory services
- Device maintenance
  - Federal CLIA requirements (> manufacturer's)
  - Dedicated anesthesia tech daily QC's
  - Associated cost

Running Sample

- Prepare cuvette well, piston cover, machine
- ≥ 1 ml blood (< 2 minutes, or blue top – anticoagulated, mix with CaCl)
- Mix 1 ml in plastic kaolin vial (purple top)
- Withdraw 0.36 ml (pipette)
- Add to plastic cuvette
- Lower piston and mix
- Slide lever to right to start
- Press start - computer



MHH-TMC set-up

Main OR

- 3 devices (6 channels), 'off laboratory grid'
- Mini-lab next to trauma, transplant ORs
- Service non-cardiac ORs
- Remote view - computer screen trauma, transplant ORs (22,23)
- Kaolin, heparinase
- Platelet Mapping
- Functional Fibrinogen

ER Trauma Lab

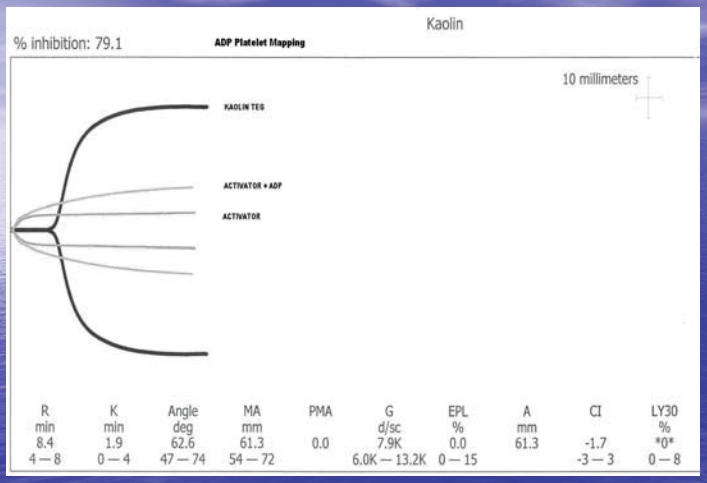
- Rapid TEG^R (trauma surgeon preference)
- Numerical results loaded hospital EMR
- Screen view in trauma ORs
- No FF, PM yet

Main lab

- Kaolin, rapid, heparinase TEG^R
- Citrated and recalcified
- No PM, FF yet

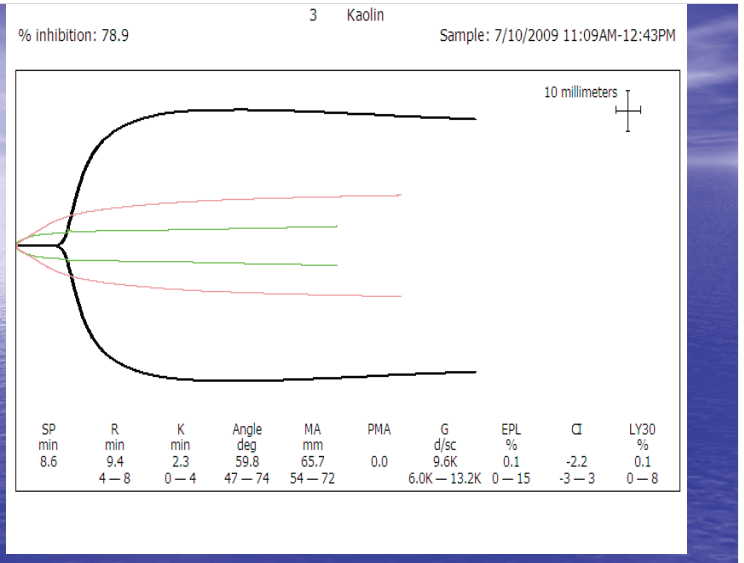
Rapid TEG

- Key role Tissue Factor (TF) in injury
- Low [TF] → accelerates coagulation in TEG
- R, K too short to be useful
- Replaced ACT (< 118 secs)
- Shorter time to MA/G/lysis (bang for $)
- Trauma
  - 5 (R, K, ACT) - 15 (MA/G) mins vs. 48 (Cotton 11)
  - R-TEG^{R} replaced laboratory tests (Cotton 12)
  - G, MRTG, TTG ∞ survival (Kashuk 12)



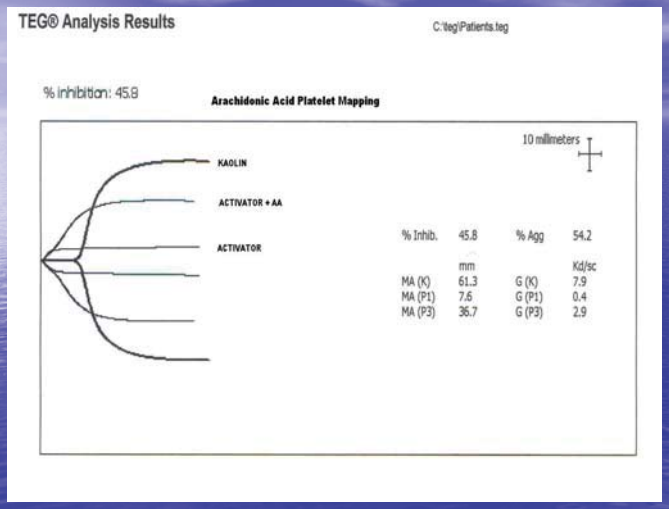
Platelet Mapping^{TM}

- Problem: Aspirin, Plavix^{R} (+ newer generation) anti-platelet Rx
- TEG^{R} 'global' measure
- Multiple activators platelets (AA, ADP, collagen, epinephrine - thrombin dominates)
- MAY not detect isolated effect one activator/inhibitor pathways compared to thrombin effect



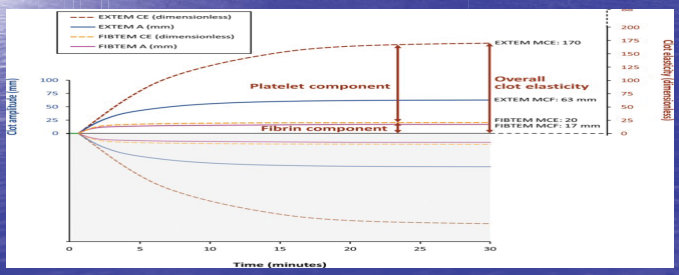
Need to inhibit thrombin: Add heparin (green top)

1. Regular kaolin sample (total MA)
2. Heparin sample + activator (reptilase, XIII) – otherwise straight line (fibrin-MA)
3. Hep sample + activator + either ADP (Plavix^{R}, Effient^{R})/AA (aspirin) (ADP/AA – MA)
4. % inhibition MA/G



- Perioperative data:
  - Can make informed decisions interruption therapy for elective surgery?
  - Correlates blood loss after CPB (Carroll 06)
  - Assess effect before cardiac surgery (Hobson 06)
  - Preop patients:
    - ASA - 90% agreement plt aggregometry (lab std)
    - Clopidogrel – 70% agreement (Agarwal 06)

- Assessing methodology for calculating plt contribution to clot strength in TEG/ROTEM (Solomon C, Anesth Analg 15)
  - Plt component of clot strength
  - Platelet inhibitors
  - Clot elasticity (force which blood resists rotation)
  - Non-liner relationship clot amplitude/elasticity



- Collyer – preop pts (BJA 09)

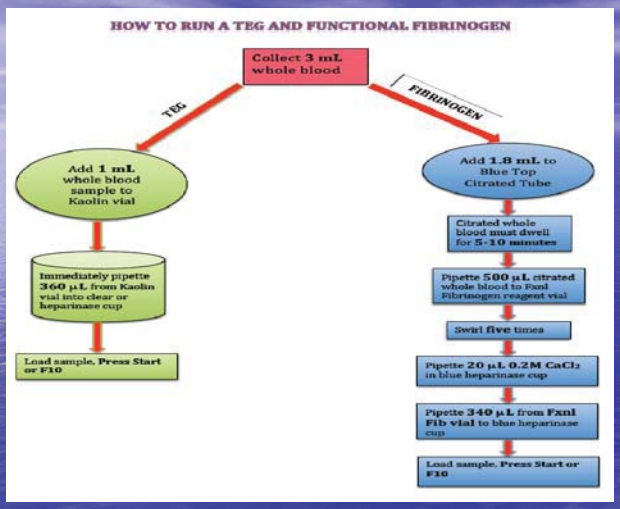
	AA inhibition (%)	ADP inhibition (%)
Control (20)	17	48
Aspirin (18)	52	53
Clopidogrel (21)	32	72

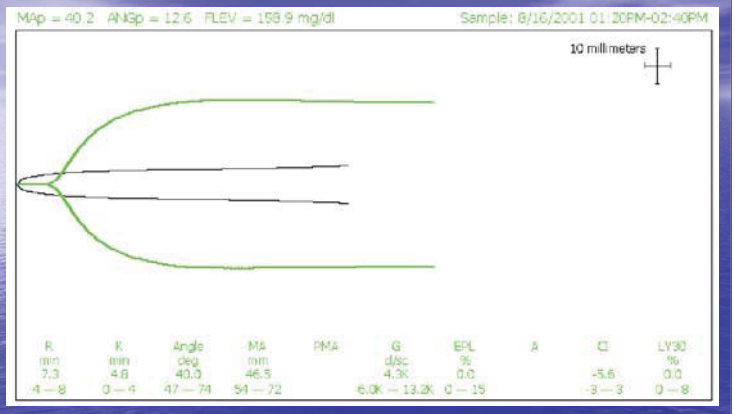
- Clopidogrel changes over time:
  - Day 3 (67%), day 5 (49%), day 7 (36%)
- Useful trends, significant overlap
- Each patient may be different (duh!)

Functional Fibrinogen

- Address limitation TEG^R 'mono-analysis'
  - Criticism from ROTEM^R users
- Recall: fibrinogen + platelet = clot strength
- Abciximab (plt inhibitor cardiologists used in cath lab) - inhibits plt contribution, leaves fibrinogen contribution clot strength

- Cattano – observational (J Thromb Thrombolysis 13)
  - Preop clinic ON Rx (57)
  - Baseline 53% (AA), 44% (ADP)
  - Significant 20% < post-op inhibition in PACU
  - Suggested stratification < 3, 3-7, > 7 days
  - Individualized Rx and interruption?
    - Thus far, data disappointing





- Johansson – collaborator Holcomb/Cotton trauma (182)(Transfusion 13)
- Predictors Massive Transfusion:
  - *Kaolin*: MA, Ly 30: *Rapid*: MA, G, Ly 30: FF
- Predictors Mortality:
  - *Kaolin*: MA: *Rapid*: MA, G, Ly 30: FF
- Goal-directed Rx
  - MA_{FF} (14-24) – Rx FFP/cryo/fibrinogen if < 14

Manufacturer Normal Range

Non-citrated Blood

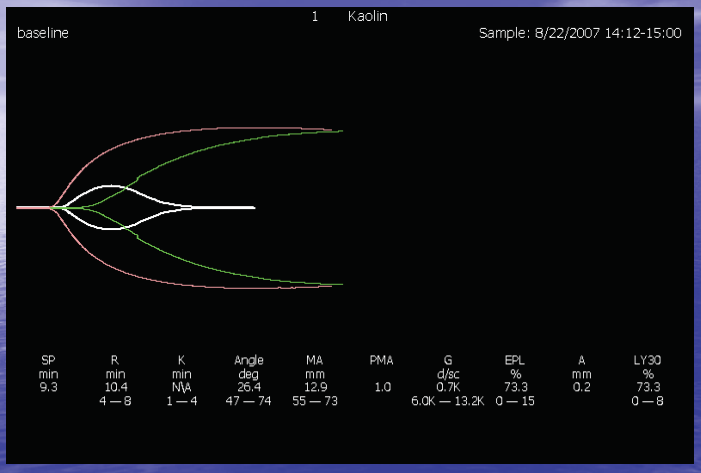
- MA_{FF} 18.3 ± 4.6 (9.1 - 27.6)
- FLEV 335.0 ± 83.0 (169 – 501)

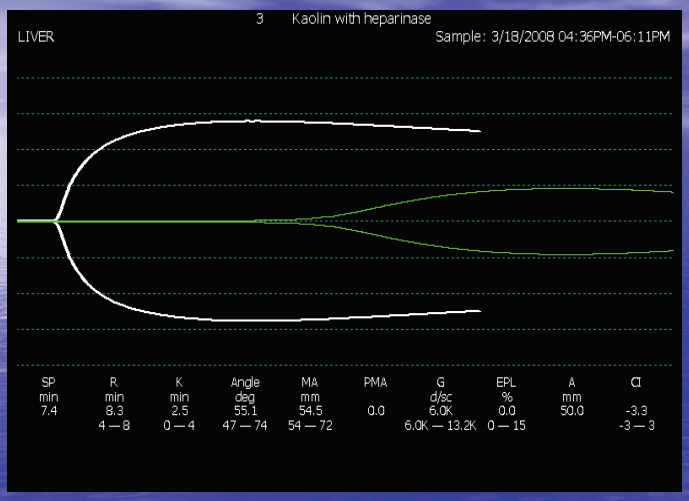
Applications/Evidence

Liver Transplantation

- Multiple risks bleeding and thrombosis
- Reperfusion - heparin-like activity (donor or recipient)(Kettner 98, Pivalizza 98)
- Fibrinolysis – too aggressive clot breakdown (Kang 87, Porte 89, Grosse 91, Steib 94, Avidan 01)
- Only 62% LT centers routinely (Schumann 13)
- Upper GI hemorrhage cirrhotic patients

- Trauma data (Shock 12)
  - Yes it works (68 pts)
  - FF correlated usual lab value (R^2 = 0.87)
  - Lab (R^2 = 0.75) and FLEV (R^2 = 0.80) correlated overall clot strength (MA)
    - Exactly what we would expect
  - Fibrinogen contribution clot strength 30%
    - What we predicted earlier
  - Fib > 200 = normal clot strength (plateau 500)





- RCT high-risk (60): 3 x < FFP/plts hTEG (= EBL) (Royston 01) *
- RCT – bleeding post-CPB (92): ↓ non-RBC products, blood loss, re-exploration (Nuttall 2001) *
- PRCT - ↓ MA predicted EBL after OPCAB (Poston 05)
- PRCT kaolin TEG vs conventional (224): ↓ FFP, plts, total products (Ak 09) *
- PRCT (69): ↓ total BP use > 50% (not SS) (Westbrook 09) *

Liver Transplantation

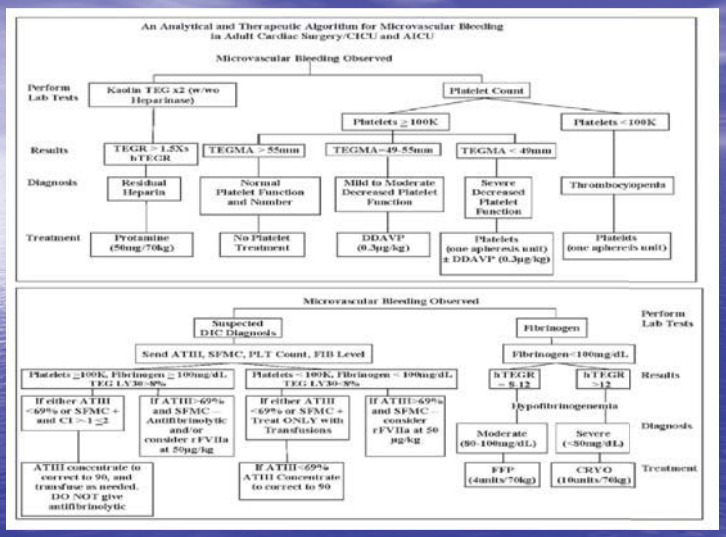
- Multiple reports TEG^R use
- Increasingly incorporated algorithms USA:
  - Pre-anhepatic: MA < 45
  - New liver:
    - R 2 x > heparinase, MA < 45, Lysis > 8%
- Little level I evidence
- Role functional fibrinogen? – limited data
  - Useful baseline, less accurate after reperfusion (Yang 14)

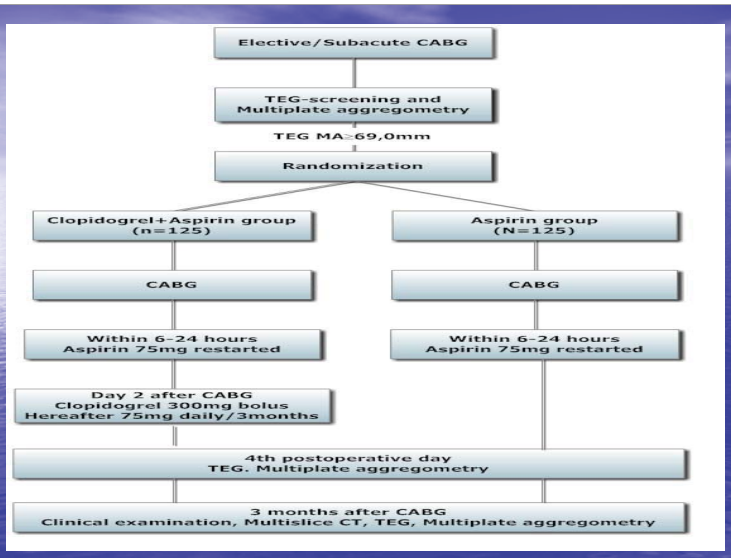
- Cochrane Review: 'Absence evidence TEG/ROTEM guided transfusion ↓ bleeding. Unclear implications clinical condition pt (Afshari 11)
  - Meta-analysis 8 cardiac surgery (6 TEG *, 2 ROTEM) + 1 LT
  - Only 1 low risk bias (S-L) **
  - EBL all < 1 L (776) – NOT Massive Transfusion!
  - ↓ EBL TEG group (85 ml, CI > 30)
  - ↓ proportion receiving FFP/plts (RR 0.39)
  - No change mortality, total transfusion

Cardiac Surgery

- Targeted Rx for ↓ MA (clot strength)
  - Negative predictor blood loss (proved DON'T need BT if TEG^R normal)
- ↓ transfusion (12.5%), re-exploration (4 fold), retrospective, single-center > 1,000 pts (Spiess 95)
- High-risk (105): ↓ postop/overall FFP/plts - TEG group. No change post-op drainage (Lesserson 99) **

- Systematic review – 12 (7,000 pts) - ↓ RBC, FFP, plt transfusions (30-50%), re-exploration (OR 0.34) (Bolliger 13)
  - PBM based transfusion triggers TEG/ROTEM more restrictive CCTs
  - Evidence improved clinical outcome still limited
- NICE (National Institute Health Care Excellence): recommended TEG^R/ROTEM^R – more effective, less costly std lab tests (UK 14)
  - PRCTs proving improved outcome still lacking





Guide for Heart Failure Transfusion Medicine Support – Hematopathology - MHH

- Protamine: TEG-R > 1.5 hTEG-R
- Plts: Plt < 100, MA < 45 (EPL<15, LY30<8)
- FFP: hTEG-R > 10 (PT > 20, PTT > 45)
- Cryo: Fib < 200, Angle < 45 (MA normal)
- EACA: EPL >15, LY30 > 8 (MA < 50, CI < 1) or Fib < 100, D-Dimer > 5
- 'Adequate': Angle > 45, MA > 45

Cardiac Surgery

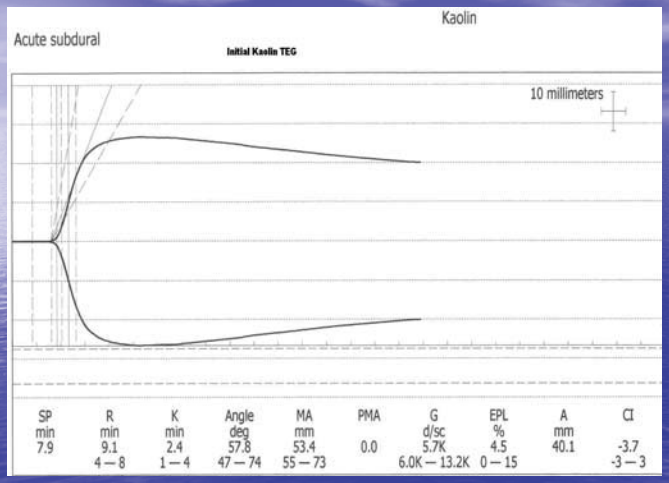
- Multiple reports, increasing PRCTs
- Best if used as part of algorithm
- ↓ blood products (primarily FFP/plts) 3-8 fold
- Fewer differences *actual* EBL
- Role FF?
  - Pedi/adult cardiac studies ongoing (Gautam 14)

- PM - predicts postoperative CT drainage in pts undergoing CABG (Chowdury 14)
  - Significantly associated plt transfusion
- Comparison 3 POC testing devices adult elective cardiac surgery (Espinosa 14)
  - Significant changes all TEG^R variables after surgery
  - Significant post-op correlations with [fibrinogen]

Trauma

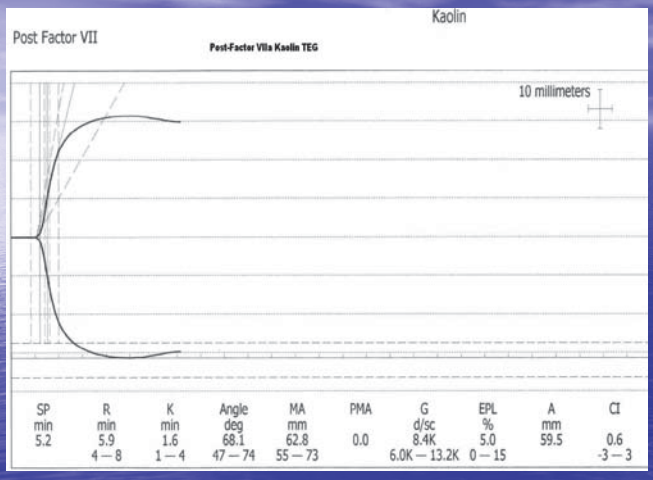
- 'Plasma based lab tests inappropriate monitor/Dx, recommend TEG^R/$ROTEM^R$' (Gando 11)
- RCT: TEG^R predict early transfusion (Kaufmann 97)
- Level 1 trauma: – ve predictor transfusion, ↑ survival (45% hypercoagulable) (Johannson 2007)
- > predictor bleeding PT/INR (Kheirabadi 07)
- Early post-injury hypercoagulability (Schreiber 05)
- Military > predict bleeding PT/PTT (Plotkin 08)

- Multiple small observational studies: robust agreement - low clot strength admission predicts BP use/mortality
- Admission rapid TEG^R predicts PE
  - MA > 65 (even stronger for MA > 72 (Cotton 12)
- Rapid TEG^R – predict early transfusion (Cotton 11)
- Early MA predicts orthopedic trauma patients at increased VTE risk (Gary 16)
  - Admission MA > 65 (OR 3.66), > 72 (OR 6.7)



Algorithms (Johannson 13)

- R > 10 (10-20 ml/kg FFP), > 14 (30 ml/kg)
- Heparinase R 3 mins less (protamine)
- Angle < 52 (20-30 ml/kg FFP)
- MA_{FF} < 14 (FFP [20-30 ml/kg], cryo [3-5 ml/kg] or fibrinogen [1-2G])
- M < 45 (2 plt concentrates), 46-49 (1)
- Lysis > 8% (TxA 1-2 G)
  - Other centers using > 3% (Cotton 12)

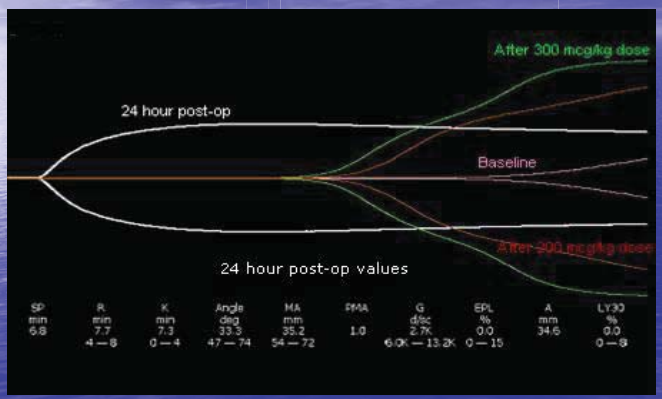


Neurosurgery

- Primary ICH/TBI(traumatic brain injury) (78)
  - 8 hypocoagulable (R, angle, MA) predicted 30-day mortality, only 2 detected conventional tests (Windelov 11)
- Correlation TEG – hematoma enlargement ICH (Kawano-Castillo 14)
- Hypercoagulability - acute ischemic stroke (AIS). ↓ R, K, ↑ angle = worse outcome
- NOT predict response to anti-fibrinolytic tPA, e.g., dose modification (Elliot 15, McDonald 15)
- ↑ delta predict hemorrhagic transformation

Inherited coagulation disorders

- Case reports - hemophilia, vWD (Pivalizza 03)



Perioperative Hypercoagulability

- MA predicts post-op thrombotic complications (inc MI) (McCrath 05)
- Abdominal surgery - ↑ MA (10%), G (50%) → day 7 (Mahla 01, Arcelus 95)
- Preop TEG predicts post-CABG thrombotic events (not grafts)(Zacho 13)
- Goal-directed thrombotic prevention?
- TEG^R not sensitive low-dose SC heparin/LMWH (∞ preservation thrombin effect)

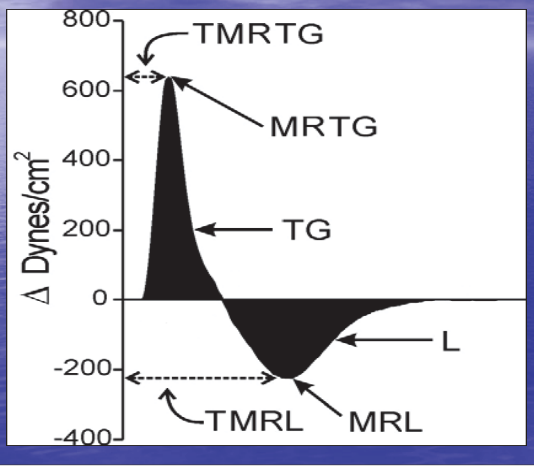
Velocity curve thrombin generation

- 1st derivative TEG^R profile transforms numerical data → velocity curve
- Clot growth/disintegration ∞ change amp (A)/elastic modulus (G) over time
- Dynamic velocity profile ∞ thrombin generation curve (TGAs)
- Cell based model hemostasis: function ∞ thrombin activity

Obstetrics

- Case reports, small studies emerging
  - Physiologic changes, reference ranges DIFFERENT (Steer 93, Macafee 12)
  - Eclamspia (Sharma 97, Liu 00)
  - Hyperfibrinolysis (Whitta 95)
  - Abruption (Steer 94)
  - Fibrinogen (Gottumukkala 99)
  - Predicts blood loss (weakly) (Butwick 11)

TEG^R Thrombus generation velocity profile



PPH (SSC/ISTH)

- Recommended monitor Europe (Ekelund 15)
  - 'May be potentially pivotal'
  - Dilutional coagulopathy
  - Localized consumption (uterus, placental bed)
  - DIC (AFE, abruption, eclampsia)
  - ↑Fibrinolysis
- POCTs with Rx algorithm: ↓ bleeding, transfusion (Levi 09, Mallaiah 15)

- TMRTG: Time MRTG (sec) – time initiation + max rate clot strength
- MRTG: Max rate thrombus generation, (mm/min)
- TG: Thrombus generated (mm/min) – AUC, total clot strength
- TMRL: Time max rate clot lysis (sec) - clot stability
- MRL: Max rate of lysis (mm/min)
- L: Area clot lysis (mm/min) - extent clot strength reduction due clot lysis or retraction

- Initial data: hematology/hemophilia
- Predicted clinical bleeding (Sorensen 04)
- Sensitive anticoagulants (Nielsen 06)
- Limited data since …..

TEG^R Billing/CPT codes

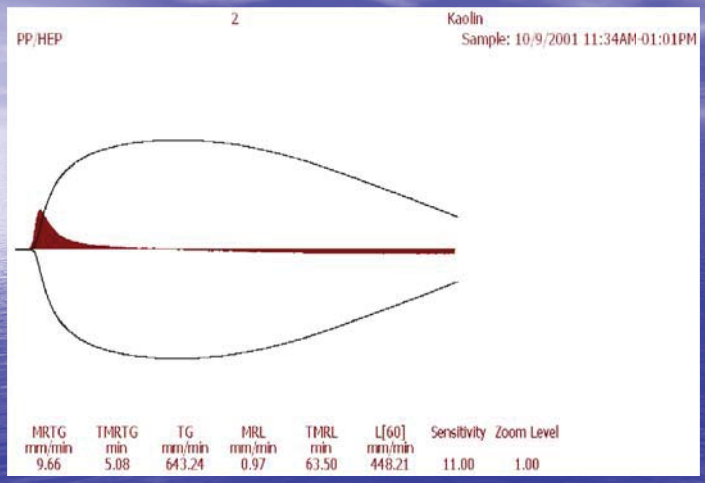
- 85396 – global coag/lysis test (includes interpretation/report) – only 1/day

Technical components:

- 85347 – coagulation time (R time - $ 5.88)
- 85576 – plt aggregation (MA - $ 29.69)
  - Report total # for PM
- 85384 – fibrinogen activity (K, angle -$ 11.74)
- 85390 – fibrinolysis (% EPL -$ 7.13)

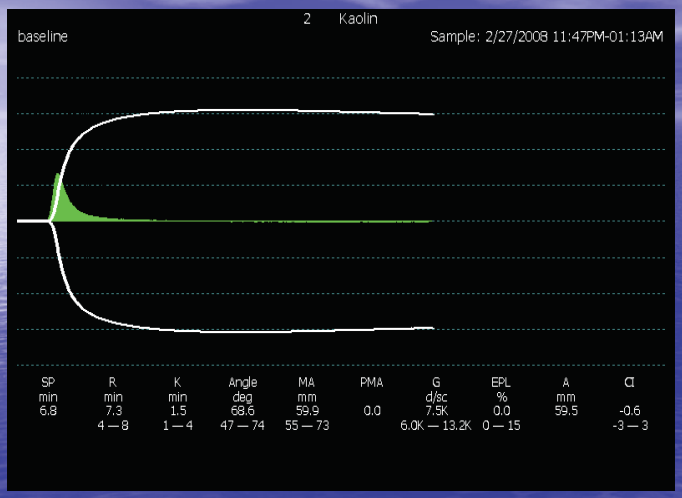
Professional component:

- Medicare pays for pathologist/independent lab. Less successful for us - generate signed report and submit …..



Summary: TEG^R in 2016?

- Less level I evidence than we'd like
  - PRCTs ongoing, increasing
- Accept advantages/limitations POC device
  - Better with TEG^R 6 and ROTEM^R
- Tool to assist decision making → translate ↓ bleeding/transfusion
- PM, FF added to 'mono-analysis'
- Benefits related incorporation algorithm(s) cardiac, liver transplant, trauma



Recent References

- Coagulation monitoring – Ganter (Anesth Analg 08)
- Thrombelastography/thrombelastometry – Luddington (Clin Lab Haem 05)
- Monitoring Plt Function – Shore-Lesserson (Hematol Oncol Clin N Am 07)
- TEG/ROTEM to monitor haemotherapy with MT – Afshari (Cochrane Database Systemic Reviews 11)
- Critical appraisal of POC coagulation testing in critically ill pts – Levi (J Thromb Hemost 15)
- Assessing methodology for calculating platelet contribution to clot strength in TEG/ROTEM - Solomon C (Anesth Analg 15)

Liver references

- Karakoc – Effect hepatectomy on coagulation (TEG). Euro J Gastro (10)
- Coakley – J CT Vasc Anesth (06)
- Hannaman - Anesthesia care for LT. Transplantation Reviews (11)
- Mallett - Clinical utility viscoelastic tests (TEG/ROTEM) in pts liver disease and LT. Semin Thromb Hemost (15)
-

Trauma references

- Admission rTEG can replace CCTs in ED - Holcomb (Annals Surg 12)
- Admission rTEG predicts PE in trauma pts – Cotton (JTACS 12)
- Can TEG predict VTE events in pts with severe extremity trauma? – Gary (JOT 16)

Cardiac surgery

- Review transfusion/management cardiac surgery - Despotis (Transfusion 08)
- Reduced RBC use with blood salvage strategy – Weltert (Transfusion 13)
- Critical appraisal POC coagulation testing critically ill patients – Levi (J Thromb Haemost 15)

General References

- Haemostatic monitoring PPH – Solomon (BJA 12)
- Hemostatic resuscitation PPH – supplement to surgery – Ekelund (Acta Obst Gynecol Scand 16)
- TEG and ROTEM: technology and clinical applications – Whiting (Am J Hematol 14)
- Monitoring pts at risk MT – Wikkelsoe (Acta Anaesth Scand 11)
- Level 1 trauma (Denmark) – Johansson (Transfusion 13)
- POC coagulation testing and transfusion algorithms – Enriquez (BJA 09)

Neurosurgery/Neurology references

- TEG predicts possible coagulation disturbances in pts with ICH (Kawano-Castillo, Stroke 15)
- Prognostic role of TEG in identifying NS pts with worse prognosis (Windelv, Blood Coag Fibrinolysis 11)
- TEG does not predict clinical response to rtPA for AIS (McDonald – J Thromb Thrombolysis 15)