The results of thromboelastography: does it fit laboratory testing ?

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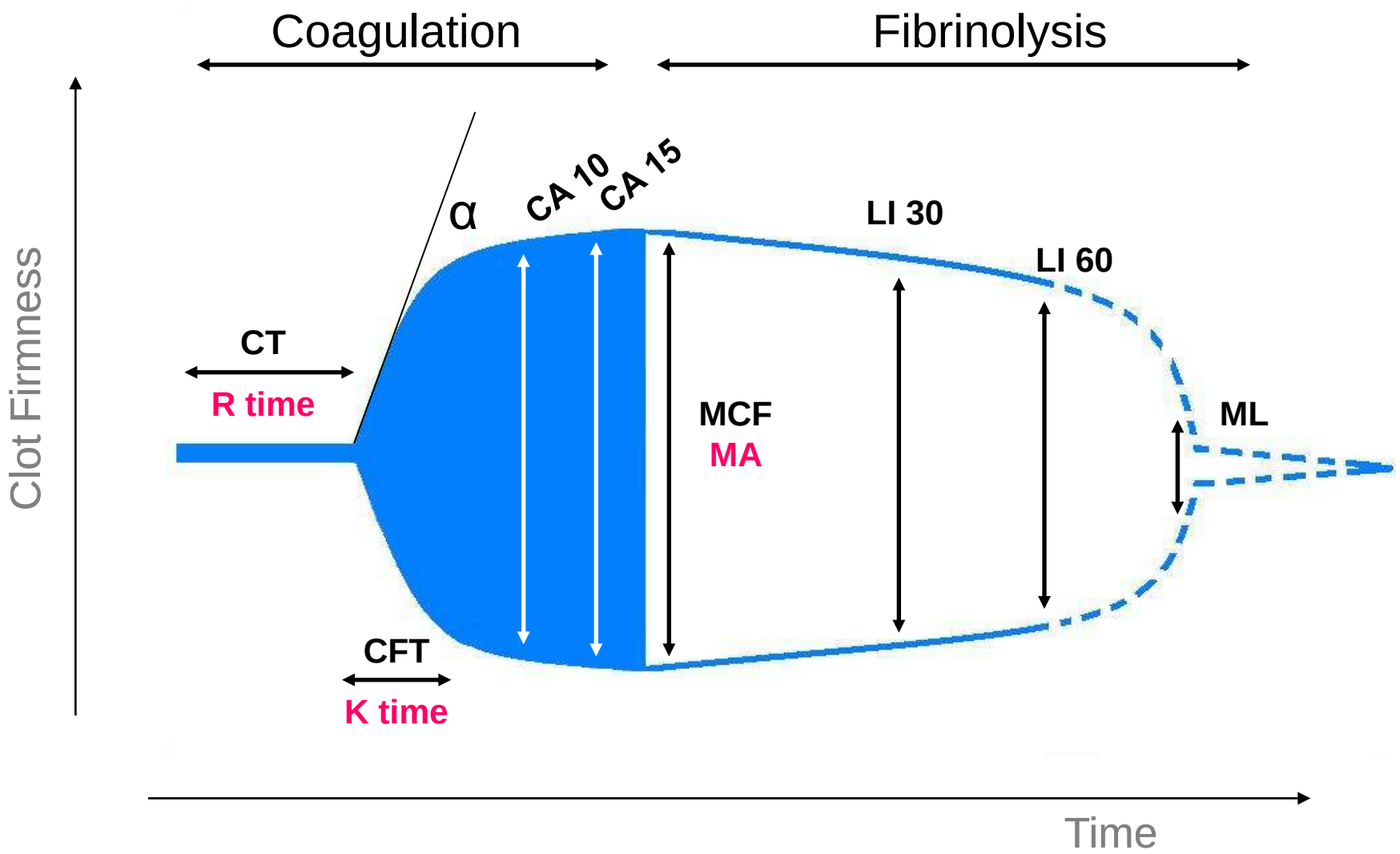
Thromboelastography

- Whole blood method
- Graphical representation of the process of clot initiation, formation and stability
- First described by Hartert in 1948
- Since 1980s, **miniaturization** and use of **standardized reagents** developed for bedside use
  - TEG®: thromboelastograph (Haemoscope Incorporation®, USA)
  - ROTEM ®: rotation thromboelastogram (Pentapharm ®, Germany)

Graphical representation



- Native or citrated whole blood samples
- Various activators
  - Accelerating test times
  - Differential diagnostic information
  - Increased reproducibility
- Using diluted TF, sensitivity increased for detection of bleeding disorders

Assay	Activator/Inhibitor	Indication
TEG		
Kaolin	Kaolin	overall coagulation assessment /platelet function aPTT
Heparinase	Kaolin + Heparinase	specific detection of heparin
Platelet mapping	ADP Arachidonic acid	Monitoring antiplatelet therapy
Native	none	
ROTEM		
ex-TEM	TF	extrinsic pathway asses PT
in-TEM	Ellagic acid	intrinsic pathway assessme aPTT
fib-TEM	TF+ platelet antagonist	qualitative assessment of fibrinogen levels
ap-TEM	TF+ Aprotinin	fibrinolytic pathway
hep-TEM	Ellagic acid + heparinase	specific detection of heparin
tif-TEM	1:1000 TF	

- Heparinase coated cups for evaluation of heparin effect :
  - Heparinase (TEG®)
  - hep-TEM (ROTEM®)
- Adding antifibrinolytic reagent for quick detection of fibrinolysis
  - ap-TEM (ROTEM®)

Bedside use

- Usefulness demonstrated for detection of coagulation abnormalities during surgical procedure and trauma
  - **Liver transplantation :**
    - Detection of enhanced fibrinolysis
    - Heparinase-treated TEG®: contribution of endogenous heparin-like substances in reperfusion coagulopathy
  - **Cardiac surgery :**
    - Heparinase-treated TEG®: assessment of coagulopathy versus heparin effects
  - **Trauma patients:**
    - Detection of early hypocoagulable state
    - Detection of hyperfibrinolysis

Kang et al. Anesth Analg 1985
Ramsay et al. 2004
Ryoston et al. Br J Anesth 2001

Bedside use

- To guide replacement therapy, antifibrinolytic or heparin treatment during surgery
- Cardiac surgery : algorithm based upon a heparinase-treated TEG®
  - 3 x reduction use of haemostatic products
  - cost effective
- Liver transplantation : TEG®-guided transfusion algorithm
- No guidelines
- No clear evidence of the most appropriate thresholds
- Thresholds defined for each technology

Spalding Eur J Cardiothorac Surg 2007

Nielsen et al. Blood Coag Fibrinolysis, 2007

Correlation between TEG parameters and coagulation tests ?

- In trauma patients :
  - Clot firmness (CA15) of ex-TEM and PT (r=0.66)
  - Clot firmness (CA10) of fib-TEM and fibrinogen (r=0.85)
  - Clot Formation Time (CFT) of in-TEM and aPTT (r=0.91)

Rugeri et al. J Thromb Haemost 2007

Correlation between TEG parameters and coagulation tests ?

- Studies shown :
  - Correlation between clot firmness (MA) and fibrinogen in normal population
  - Association between MA and both platelet count and fibrinogen concentration in hypercoagulable state population
  - Correlation between r time and aPTT

Zucherman, et al. Thromb haemos 1981
Kang et al. Anesth Analg 1985

- In trauma patients, which parameters could define
  - hypocoagulable state
  - cutoff values for replacement therapy
    - according to transfusion threshold values based on standard coagulation parameters

- CA15 ex-TEM = 32 mm → PT > 1.5
- CA10 fib-TEM = 5 mm → Fib < 1 g L^{-1}

Rugeri et al. J Thromb Haemost 2007

TEG is useful to detect hyperfibrinolysis

- Occurring during anhepatic stage of liver transplantation and worsening during reperfusion of new organ

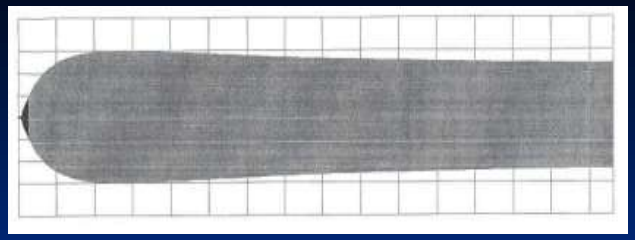
- In trauma patients, early hypocoagulability and hyperfibrinolysis detected using antifibrinolytic containing reagent (ap-TEM)

Kang et al. Anesth Analg 1985

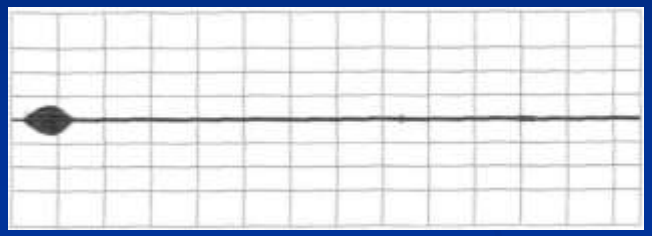
Rugeri et al. J Thromb Haemost 2007

- 25/89 trauma patients presented hypocoagulable state
- For 5 patients, ROTEM showing severe coagulation abnormalities
  - major decrease of clot firmness

  = CA15 ex-TEM < 18mm
  - absence of clot in fib-TEM



ex-TEM Normal trace



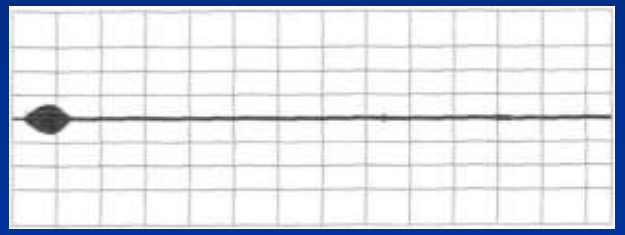
ex-TEM

fib-TEM Normal trace

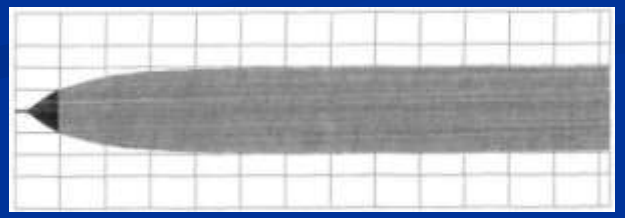
fib-TEM

Rugeri et al. J Thromb Haemost 2007
Levrat et al. Br J Anaesth 2008

- 5 patients with hyperfibrinolysis :
  - LI 30 and LI 60=0
  - Correction of clot firmness in ap-TEM
- Hyperfibrinolysis confirmed: euglobuline lysis test (ELT) = 30-59 minutes



ex-TEM



ap-TEM

Rugeri et al. J Thromb Haemost 2007
Levrat et al. Br J Anaesth 2008

Laboratory setting

- After bedside use, technology applied to areas where conventional testing is inappropriate

- Monitoring of replacement therapy in rare bleeding disorders
  - **FXIII deficiency**
  - **Hemophilia**
  - **Platelet disorders**

Assessment of rare bleeding disorders: FXIII deficiency

- Chromogenic methods for the measurement of plasma FXIII activity restricted linearity and lacked accuracy for low levels < 15 IU/dl

- Usefulness of ROTEM ® for monitoring of FXIII concentrate infusions (Fibrogamin®) in unusual clinical presentation

- Monitoring replacement therapy during pregnancy in a 34 year -old woman with congenital FXIII deficiency and with history of miscarriage bleeding

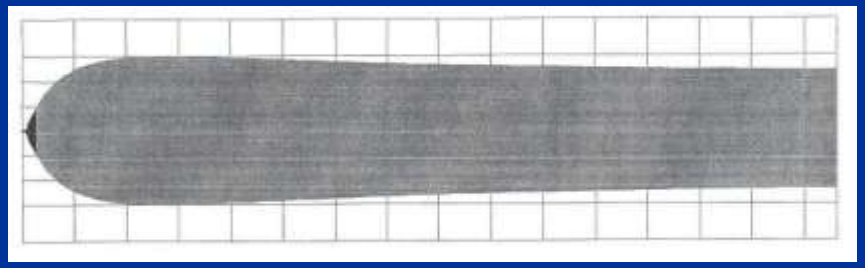
- Measurement of FXIII levels by current method not reliable
  - To adapt prophylactic regimen
  - To determine haemostatic thresholds

Dargaud et al. Blood Coag and Fibrin, 2008

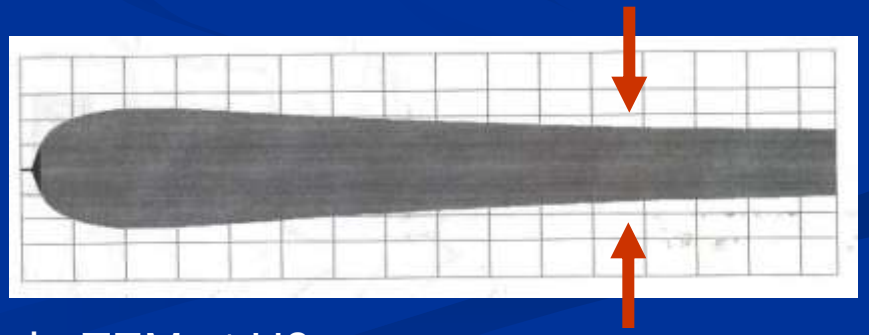
- **During replacement therapy :**

  Ex vivo measurement of ROTEM® parameters at T0, H1 and 3 weeks after Fibrogamin® infusion

  - Baseline trace
    - decrease clot firmness (CA10)
    - decrease clot stability (LI60)
  - FXIII levels <15 IU/dl



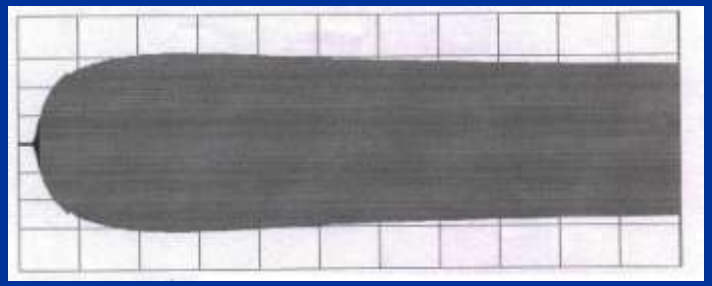
in-TEM normal trace



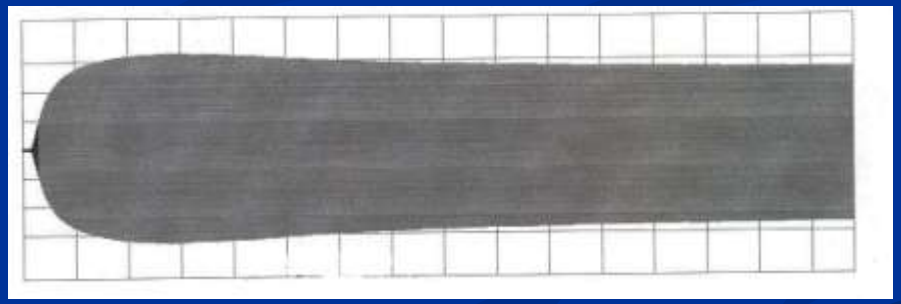
in-TEM at H0

Dargaud et al. Blood Coag and Fibrin, 2008

- Normalisation of ROTEM® trace at H1 and at 3 weeks:
- **FXIII levels**
  - H1 = 45 IU/dl
  - 3 weeks < 15 IU/dl



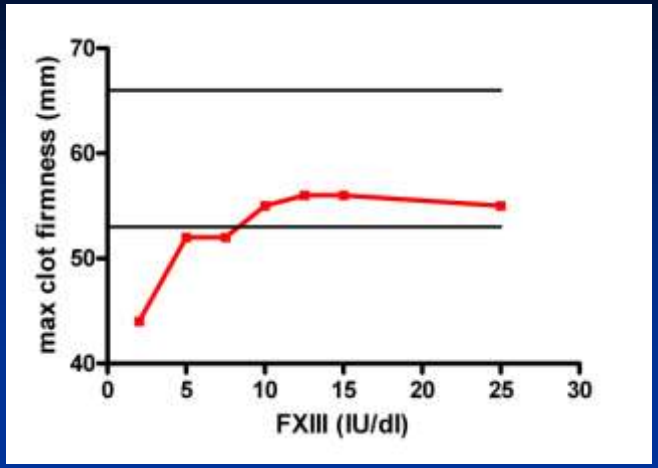
in-TEM at H1



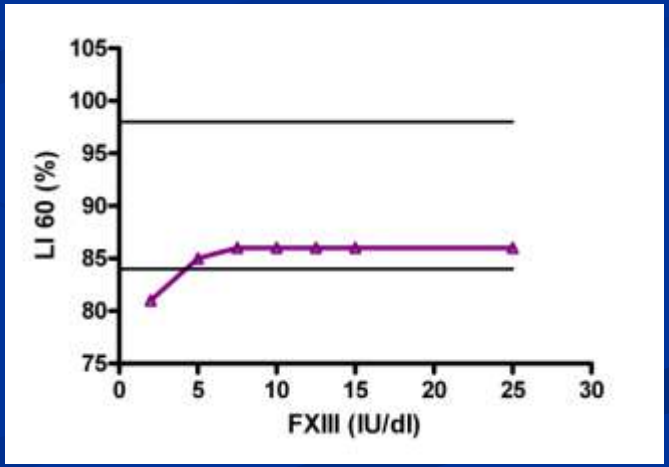
in-TEM at 3W

Dargaud et al. Blood Coag and Fibrin, 2008

- *In vitro*: minimal FXIII concentration able to normalize
  - abnormal clot firmness (CA10 of in-TEM)
  - abnormal stability (LI60 of in-TEM)



- Final concentration of FXIII at 2, 5, 7.5, 10, 12, 15 and 25 IU/dl



- All ROTEM® parameters were normalized at FXIII concentrations above 10 IU/dl

Dargaud et al. Blood Coag and Fibrin, 2008

- ROTEM® able to detect viscoelastic changes of fibrin clot in whole blood samples with low FXIII activities (between 2 and 15 IU/dl)
- ROTEM® quicker and easier in comparison to low-range calibration curve method
- Valuable surrogate marker in patients treated with FXIII concentrates

Assessment of rare bleeding disorders: Hemophilia

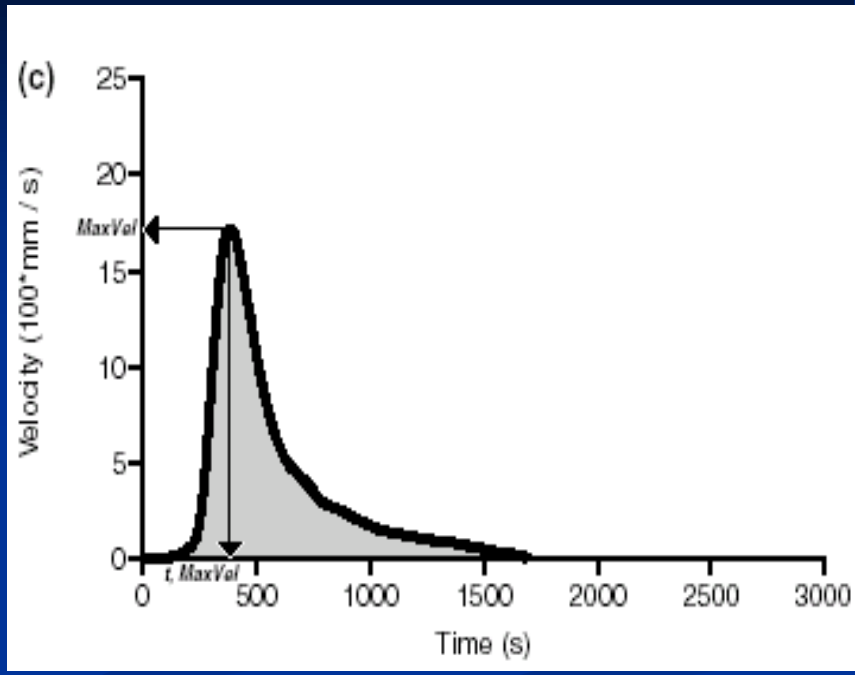
- Very low concentration of TF necessary to detect abnormal clotting profile in hemophilia patients (1:17,000)
- Use of very low concentration of TF introduces 3 issues:
  - Parameters of TEG different between whole blood and citrated blood
  - Minimum rest time of 30 minutes required
  - Very large inter-individual variation of results

Sorensen et al. J Thromb Haemos 2004

- Traces obtained in severe hemophilia patients poorly modified:
  - initiation phase (CT) increased
  - no significant change in clot firmness (MCF)
- Wide variation of clotting profiles observed making results difficult to interpret

Sorensen et al. J Thromb Haemos 2004

- Sorensen proposed new system for data calculation and graphical display
- Velocity profile : first derivative of ROTEG course
  - Maximum velocity of whole blood clot formation
  - Time to maximum velocity
  - Area Under Curve =maximum clot formation



- Courses of the whole blood clot formation very similar to thrombin generation curves reported in plasma

Sorensen et al. J Thromb Haemos 2003

Monitoring replacement therapy

- No laboratory testing is available to monitor bypassing agents
- Thromboelastography evaluated to monitor rFVIIa treatment in hemophilia patients with inhibitors
- Sorensen has shown that decreased velocity profile observed in severe hemophilia patients partially normalized by addition of rFVIIa
- Very large interindividual variation observed in 11 severe hemophilia patients treated by rFVIIa

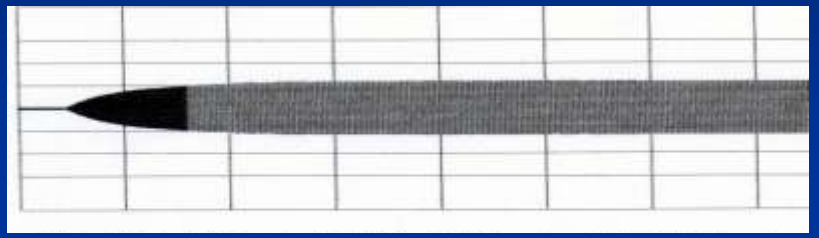
Sorensen et al. J Thromb Haemos 2003/ 2004

- Dose-response multicenter trial in hemophiliacs with inhibitors (n = 16) :
  - Only 1 patient : clear concentration-response relation
  - Other samples: very large intersubject variation in baseline profiles
  - No dose-response after addition of escalating rFVIIa doses

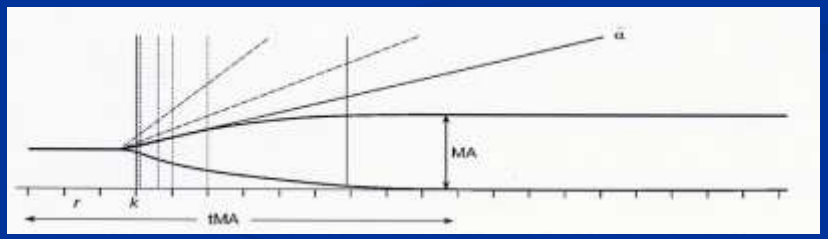
Young et al. Blood Coag Fibrinolysis 2008

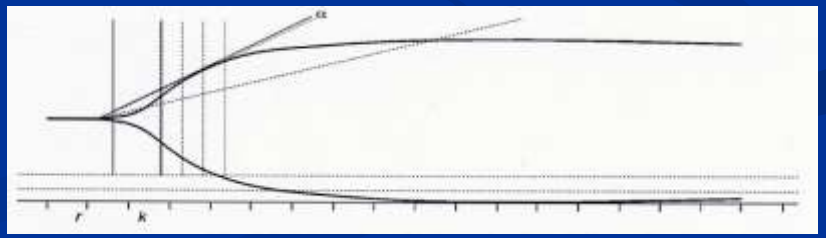
Assessment of platelet function disorders: Glanzmann thrombasthenia patients

- Clot formation time increased (CT and CFT)
- Clot firmness decreased (MCF)
- Abnormal TEG® parameters normalized after platelet infusion.



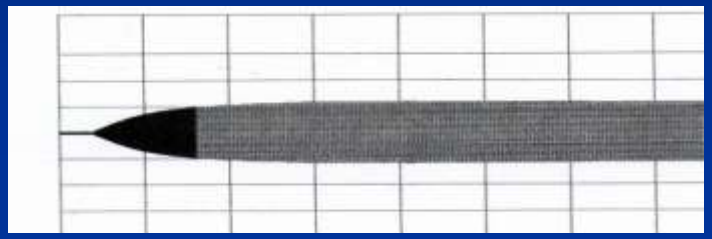
ex-TEM



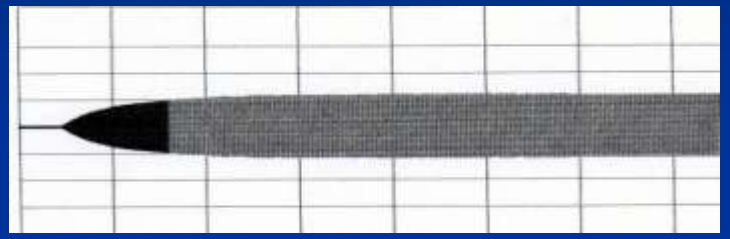


Monte et al. Br J Anaes 2002

- No change in ROTEM® parameters observed 15 min after rFVIIa



ex-TEM at T0



ex-TEM at T15 ’

- Lak reported from a large cohort of Glanzmann patients (n=28) that effect of added rFVIIa
  - Only on clotting time (decreased CT)
  - Clot firmness remained unchanged (MCF)

Lak et al. Haemophilia 2008

Conclusion

- TEG = whole blood method which assesses several processes of clot formation
- Using standardized reagents, results available within 15 minutes
- Correlation between TEG parameters and laboratory coagulation tests

Conclusion

- Advantages of TEG:
  - To detect earlier hyperfibrinolysis state and to guide antifibrinolytic therapy
  - To detect heparin effect versus coagulation abnormalities
  - To help to guide blood component therapy
  - May be useful in management of patients with severe FXIII deficiency receiving prophylactic regimen

Conclusion

- Diluted TF reagent for detection of bleeding disorders results in very large variation in baseline profiles
- Usefulness not clearly demonstrated for monitoring rFVIIa treatment in hemophiliac or Glanzmann patients

Acknowledgements

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