Point of care testing (POCT) in major haemorrhage

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Nov 2012

Outline

- What coagulation tests are needed in major haemorrhage
- What POCT tests are available
- How do you go about setting up a new test

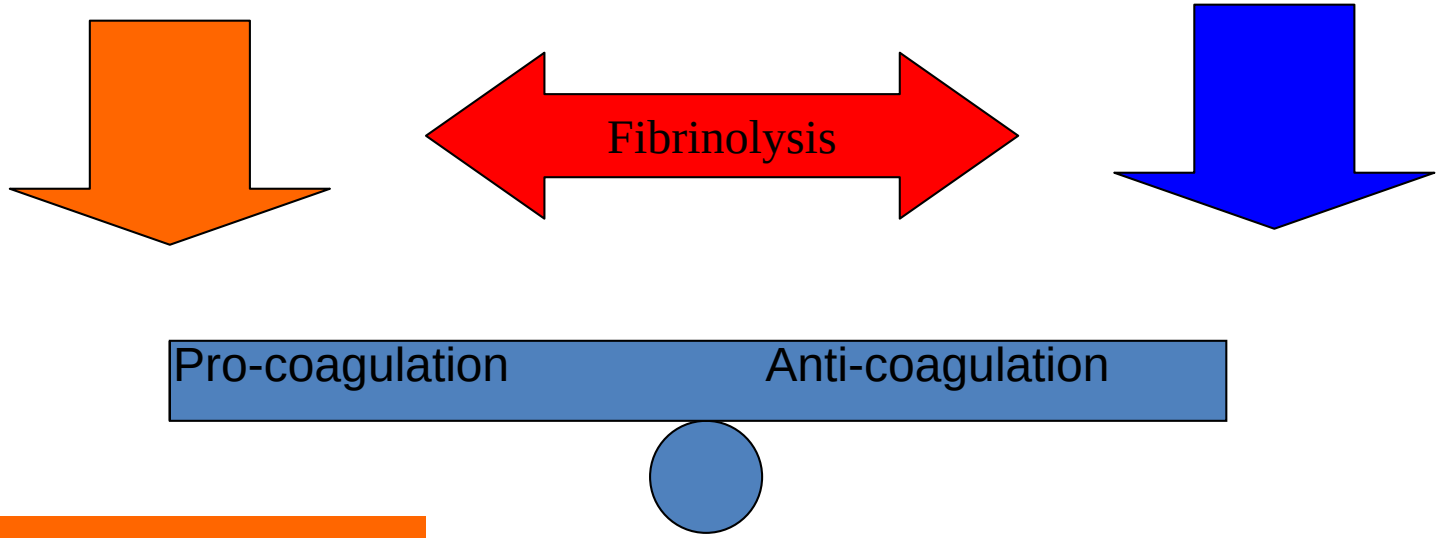
POCT: any analytical test performed for a patient by a healthcare worker outside the laboratory setting

Bleeding and Clotting

Endothelial surface
Platelets
Von Willebrand Factor
Coagulation Factors

Natural Anticoagulants

(Drugs)



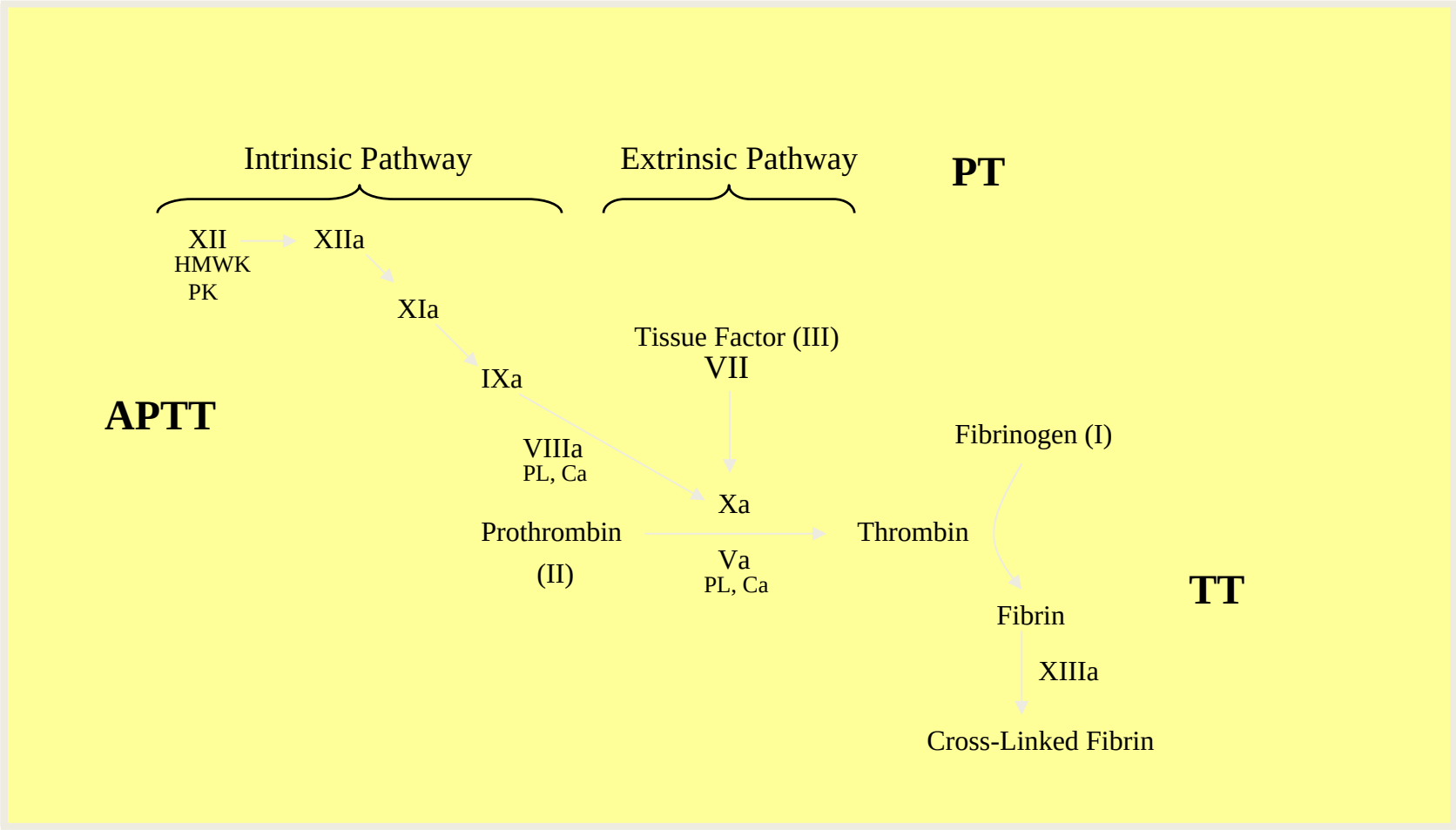
Inherited or acquired bleeding disorders

Inherited clotting tendency
Risk factors

What information from tests would be helpful

- Identification of coagulation abnormalities and results that guide treatment
- Ability to monitor individual's response to replacement therapy ?is clot forming
- Predict bleeding risk ? How strong is the clot
- ? Is the clot stable
- Predict thrombotic risk 'hypercoaguability'

Coagulation Cascade



APTT: Activated partial thromboplastin time
PT: Prothrombin Time
TT: Thrombin Time

Limitations of Routine coagulation laboratory tests tests

- Existing tests only look at a small part of the process
- They use plasma rather than whole blood
- They are tested in a static process
- They are not tested at patient's temperature
- They are not generally done at the bedside and analysis takes time

Tests available

- Routine : PT, APTT, Fibrinogen, TT, D-dimers
- FBC, platelets
- Global assays endogenous thrombin generation

POCT: FBC / Haemoglobin concentration
PT/ APTT – require sample centrifugation platelet poor plasma and sample/ reagent pipetting; ACT

POCT: Coaguchek INR

Viscoelastic haemostatic assays (VHA): TEG, ROTEM

CoaguChek®

- Establish INR in patients on warfarin
- Interface with laboratory result system
- Potential value in patients who require urgent surgery and may need warfarin reversal eg fracture NOF
- Patients bleeding known to be on warfarin BUT also need to check APTT, fibrinogen and FBC

NB All bleeding in a patient on warfarin should be taken seriously. Bleeding may occur when the INR is therapeutic. If the INR is sub-therapeutic e.g. <1.5, bleeding may be due to factors other than warfarin and reversal may not be appropriate. Always check FBC and coagulation screen to identify other causes. If in doubt discuss with haematologist.

NRHG GUIDE TO WARFARIN REVERSAL

BLEEDING

Life / Limb /Sight Threatening

CONTACT HAEMATOLOGIST

•Intracranial (CT or MRI)

Patients with rapid onset neurological signs while on warfarin do URGENT INR and CT scan (within 1 hour). If INR>1.5, consider urgent reversal with Beriplex (see below), without waiting for CT scan. NB ensure CT scan is reported and acted on immediately

•Retroperitoneal (CT or MRI)
•Intra-ocular (NOT conjunctival)
•Spontaneous muscle bleed with compartment syndrome
•Pericardial
•Active bleeding from any orifice plus either BP ≤ 90 mmHg systolic, oliguria or 2 g fall in haemoglobin

Vitamin K 5 mg IV[2] and Prothrombin complex concentrate IV (Beriplex)[3] 30 units/kg

Check INR Immediately

Adequate correction

Repeat INR & APTT in 4-6 hours

Inadequate correction

Consider other factors contributing to prolonged coagulation tests eg DIC, Congenital coagulation fact deficiency, Liver disease. **A further dose of 20 units/kg Beriplex may be indicated- seek**

Significant bleeding[4] without haemodynamic compromise

Vitamin K 2 mg IV[2]

Check INR at 4-6 hours or sooner if clinical deterioration

Minor

Vitamin K 2mg PO[1]

Oral vitamin K is safe and adequate treatment for the majority of patients. There may be some clinical circumstances when 1-2 mg IV vitamin K should be considered e.g. gross over-anticoagulation or unsteady patients

Check INR at 24 hours or sooner if clinical deterioration

[1]Oral vitamin K - there are marked differences between formulations of vitamin K. The most effective preparation is IV Konakion (Roche) given orally. The vial contains 10 mg/ml dilute appropriate dose in small amount of juice/water after drawing up in 1 ml insulin syringe. Alternatively the Konakion MM paediatric formulation may be used.

[2]Vitamin K IV may rarely cause anaphylaxis. Give by slow IV bolus

[3]Prothrombin complex concentrate (PCC) may induce a prothrombotic state. Use with caut in patients with DIC or decompensated liver disease

[4]In serious but non-life-threatening bleeding (e.g. GI bleeding or epistaxis without haemodynamic compromise) prompt reversal with IV vitamin K is indicated.

NRHG GUIDE TO WARFARIN REVERSAL

NEED FOR SURGERY

Assess urgency of surgery and degree of reversal required

EMERGENCY SURGERY (IMMEDIATE):

Vitamin K 5mg IV[2] and Prothrombin complex concentrate IV (Beriplex)[3] 30 units/kg

URGENT (WITHIN 24 HOURS):

If surgery can be delayed for 6-12 hours, give Vitamin K 2mg IV[2]. If it can delayed for 24 hours, give Vitamin K 1-2mg po[1]

[1]Oral vitamin K - there are marked differences between formulations of vitamin K. The most effective preparation is IV Konakion (Roche) given orally. The vial contains 10 mg/ml -dilute appropriate dose in small amount of juice/water after drawing up in 1 ml insulin
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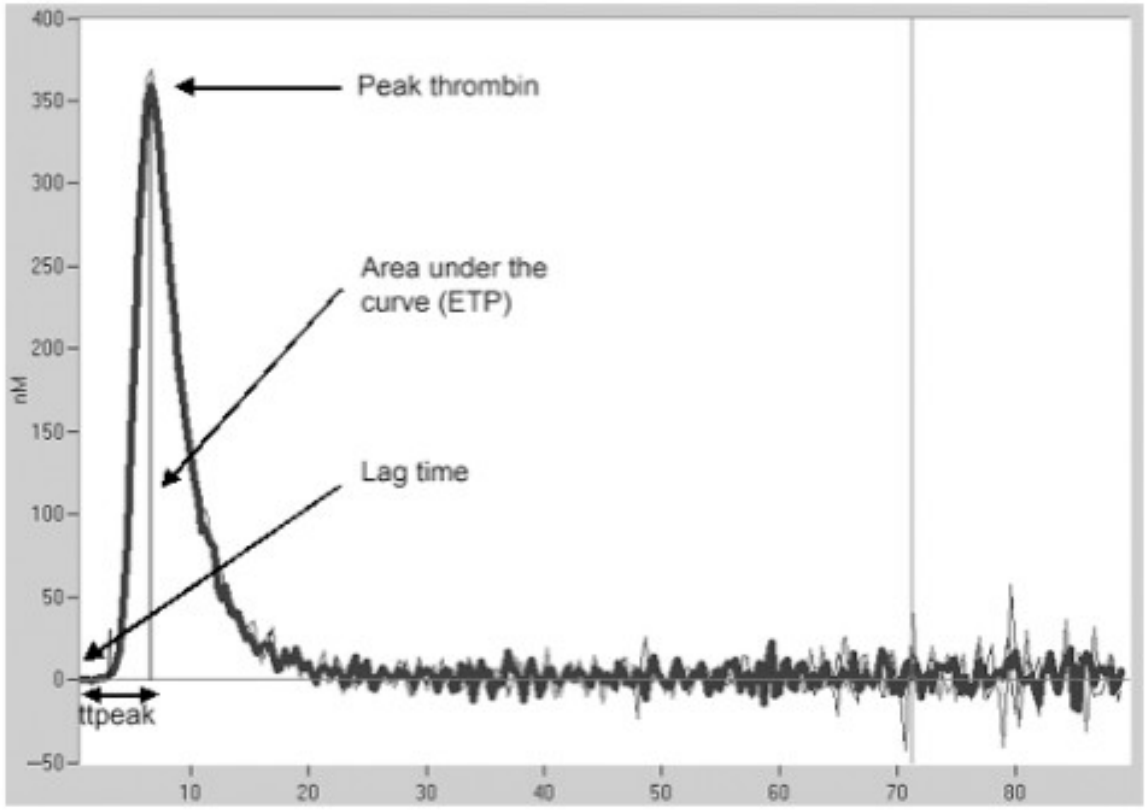
Thrombin generation curve



- Lag time
- Time to peak
- Peak thrombin
- Endogenous thrombin potential

Thromboelastography (TE) and rotational elastometry (ROTEM)

- Thromboelastography [TE] was first described by Hartert in 1948.
- Thromboelastography® (TEG®) and Thromboelastometry (ROTEM®) provide global information on the dynamics of clot development, stabilisation and dissolution that reflect *in vivo haemostasis*.
- *Although TE has not been subjected to the same evaluation processes as conventional haemostatic tests, its use as a POCT monitor in complex major surgery has been shown to significantly reduce the use of blood component therapy and overall blood loss.*

Thromboelastography (TEG)

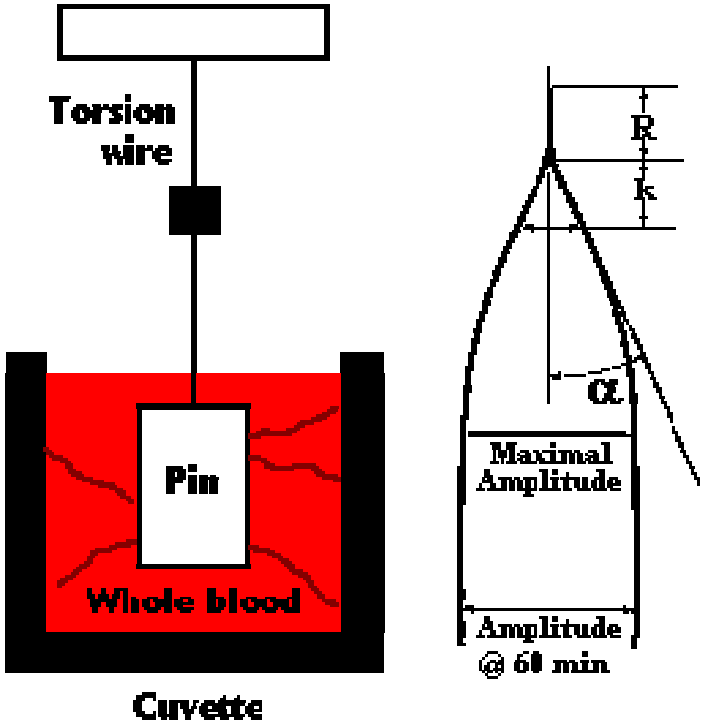
"Measures the viscoelastic properties of whole blood as it is induced to clot in a low shear environment resembling venous blood flow"

- Clot formation
- Clot kinetics
- Clot strength/stability
- Clot resolution

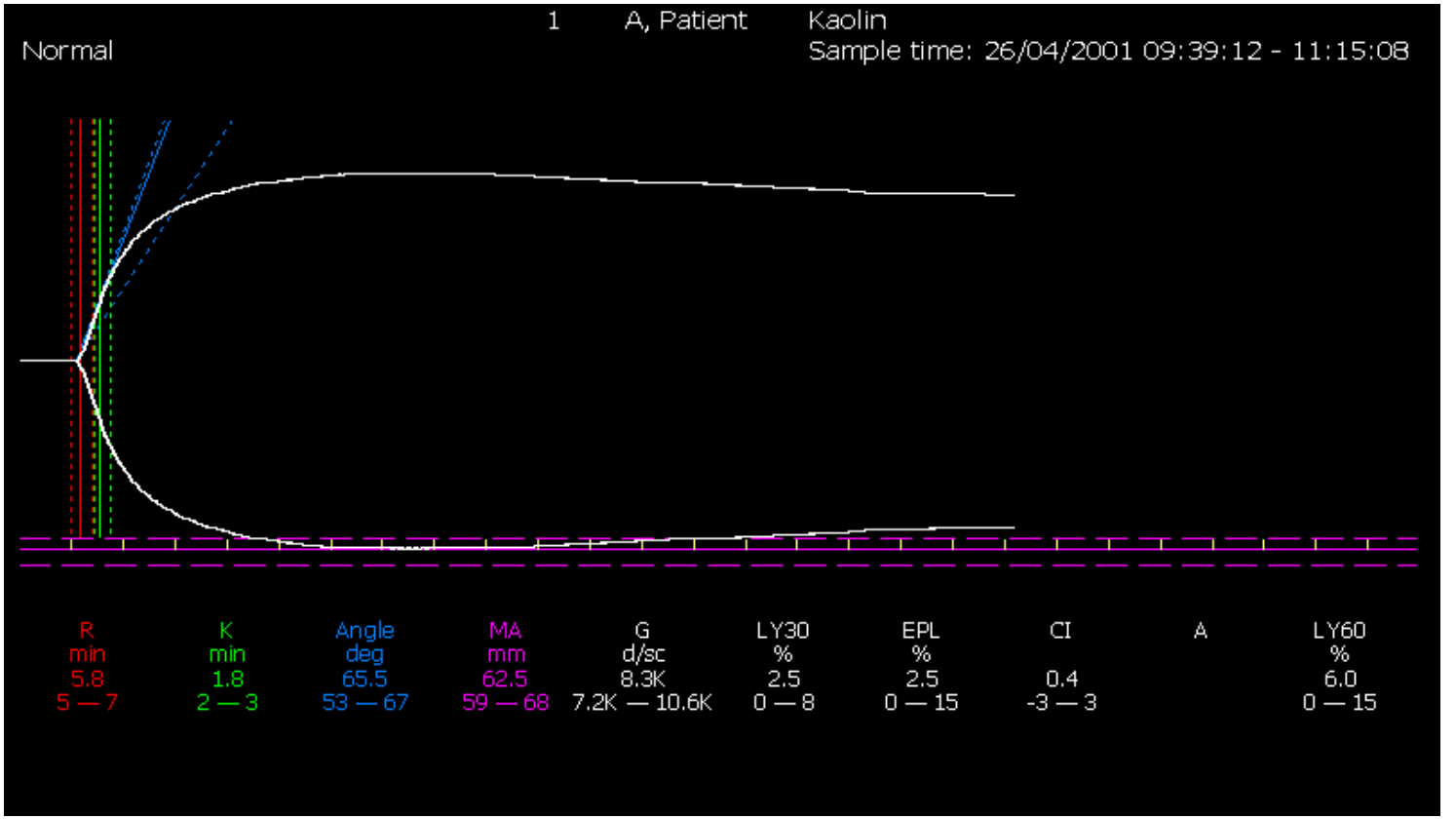
Thromboelastography- Basic principles

- Heated (37^{0}C) oscillating cup
- Pin suspended from torsion wire into blood
- Development of fibrin strands “couple” motion of cup to pin
- Increased tension in wire detected by EM transducer and transmitted to create TEG trace
- Deflection of trace increases as clot strength increases and decreases as

  clot strength decreases



A normal TEG trace



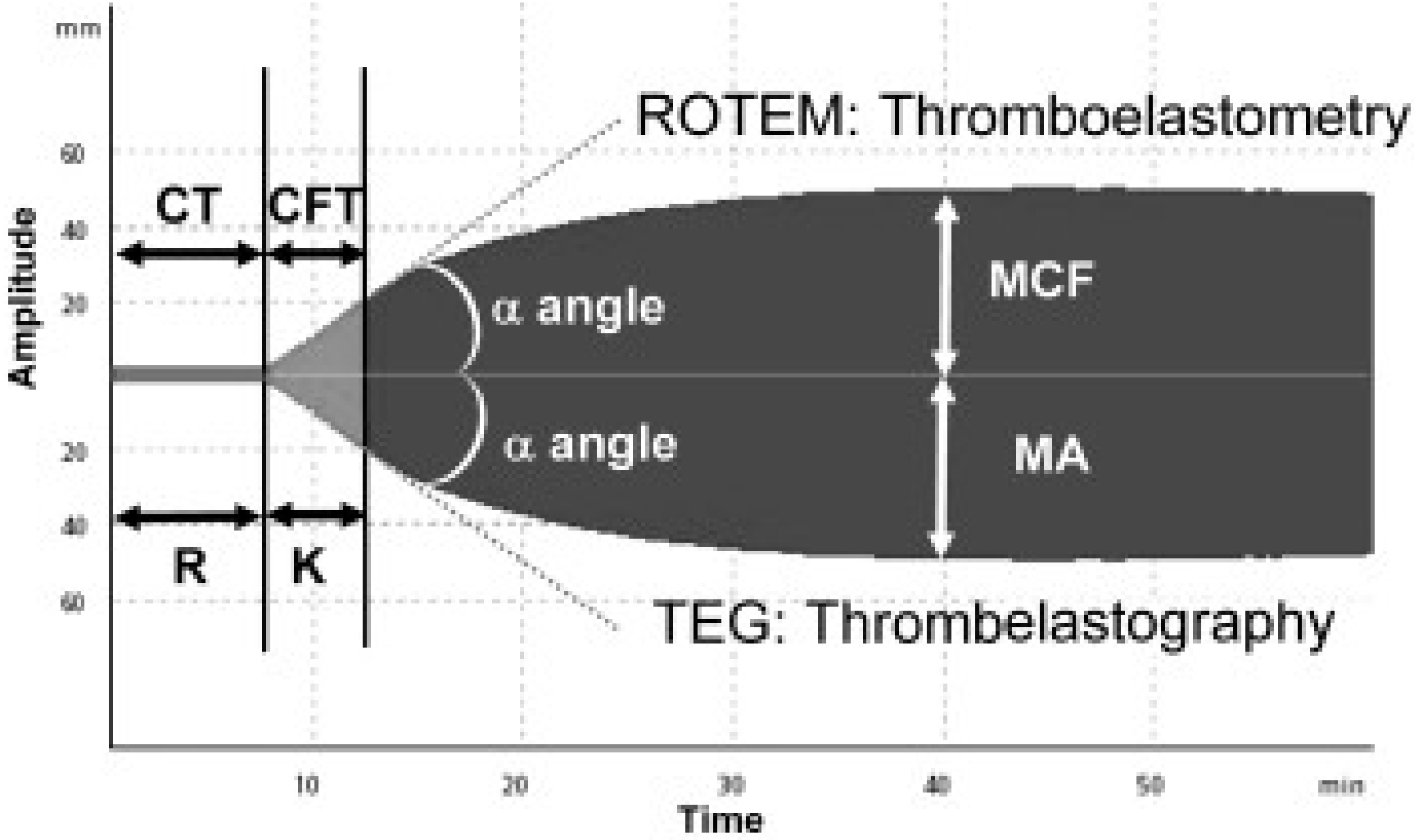
R (Reaction) time = Time taken for blood to clot, i.e. clotting factors

K (Kinetic) time/ α angle = Measure of clot kinetics, i.e. speed of fibrin build-up

MA (Maximum amplitude) = Measure of clot strength, i.e. interaction between activated platelets and fibrin

LY (Lysis) 30 = Measure of clot stability, i.e. fibrinolysis

ROTEM


mm
60
40
20
20
40
60
Amplitude
CT
CFT
R
K
α angle
α angle
MCF
MA
ROTEM: Thromboelastometry
TEG: Thrombelastography
10
20
30
40
50
min
Time

Variable	TEG®	ROTEM®
Measurement period	-	Reaction Time [RT]
Time from start to when the waveform reaches 2mm above baseline	R	Clotting Time [CT]
The time from 2mm above baseline to 20mm above baseline	K	Clot Formation Time [CFT]
Alpha angle [°]	α [slope between R and K]	α [angle of tangent at 2mm amplitude]
Maximum angle	-	CRF
Maximum strength	Maximal Amplitude [MA]	Maximal Clot Firmness [MCF]
Time to Maximum strength	-	MCF-t
Amplitude at a specific time	A30, A60	A5, A10...
Clot elasticity	G	MCE
Maximum lysis	-	CLF
Clot Lysis[CL] at a specific time [minutes]	CL30, CL60	LY30, LY45, LY60
Time to lysis	2mm from MA	CLT [10% difference from MCF]

Fibrinolysis	The degree of fibrinolysis can be established from either a native sample with no activator, from the Tissue Factor activator or the combined Tissue Factor/kaolin activated TEG. Hyperfibrinolysis is increasingly recognised as a cause of perioperative microvascular bleeding and is readily detected by analysing the clot lysis index on the TEG or ROTEM . The ability to detect and determine the severity of fibrinolysis avoids empirical or inappropriate anti-fibrinolytic therapy. Mathematical derivations of changes in elastic modulus derived from the amplitude have been used to quantify the extent of fibrinolysis in clinical and laboratory settings, as well as to guide antifibrinolytic therapy
Hypercoagulability	The TEG may be helpful in screening for hypercoagulable states. TEG analysis of patients with a history of thromboembolic complications showed shorter R values and accelerated clot propagation compared to healthy reference subjects
Fibrinogen and platelet function	The MA is primarily a reflection of clot strength and is affected by changes in fibrinogen, platelet count and function. The MA is established either from a native sample with no activator or from the combined Tissue Factor/kaolin activated TEG. There is a strong linear correlation between the log platelet count and MA. Abciximab is a potent platelet GpIIb/IIIa inhibitor and an abciximab-modified TEG can help to discriminate between hypofibrinogenemia and platelet dysfunction as a cause of decreased MA.

Modification	Interpretation
Tissue Factor	The use of an activator when undertaking thromboelastography is generally recommended to standardise the initiation of the clotting process. Tissue Factor activation of the TEG enables the maximal amplitude (MA) to be established within 10 minutes but will result in significant shortening of the reaction time (R value) and as a result much of this latter information is lost.
R Time and Heparinase	The R value in a native TEG is sensitive to trace amounts of heparin and endogenously released heparan sulphate. The use of a heparinase-coated reaction cuvette for the TEG will demonstrate any heparin present in the sample or in the patient and enables assessment of haemostasis in patients who are fully anticoagulated with heparin e.g. on CPB.
Tissue factor/kaolin activated TEG and the ACT	By incorporating both tissue factor and kaolin into the TEG cuvette, the TEG approximates to the Activated Clotting Time [ACT.]

- Rotational Thromboelastometry (ROTEM®)The ROTEM analyser provides a trace similar to that of the TEG with related parameters including clotting time (CT) and maximum clot firmness (MCF). Additional tests include:**Test Interpretation**

- INTEM Contains phospholipid and ellagic acid as activators and provides information similar to that of the APTT (Intrinsic system)
- EXTEM Contains Tissue Factor as an activator and provides information similar to that of the PT (extrinsic system)
- HEPTEM Contains lyophilised heparinase for neutralising heparin
- APTEM Contains aprotinin for inhibiting fibrinolysis
- FIBTEM Utilises cytochalasin D, a platelet inhibitor which blocks the platelet contribution to clot formation, allowing qualitative analysis of the functional fibrinogen component.
- ECATEM Contains Ecarin and so is similar to the Ecarin Clotting Time. This makes it very sensitive to presence of direct thrombin inhibitors.

Use of TEG in cardiac surgery with bypass - Monitoring protocol

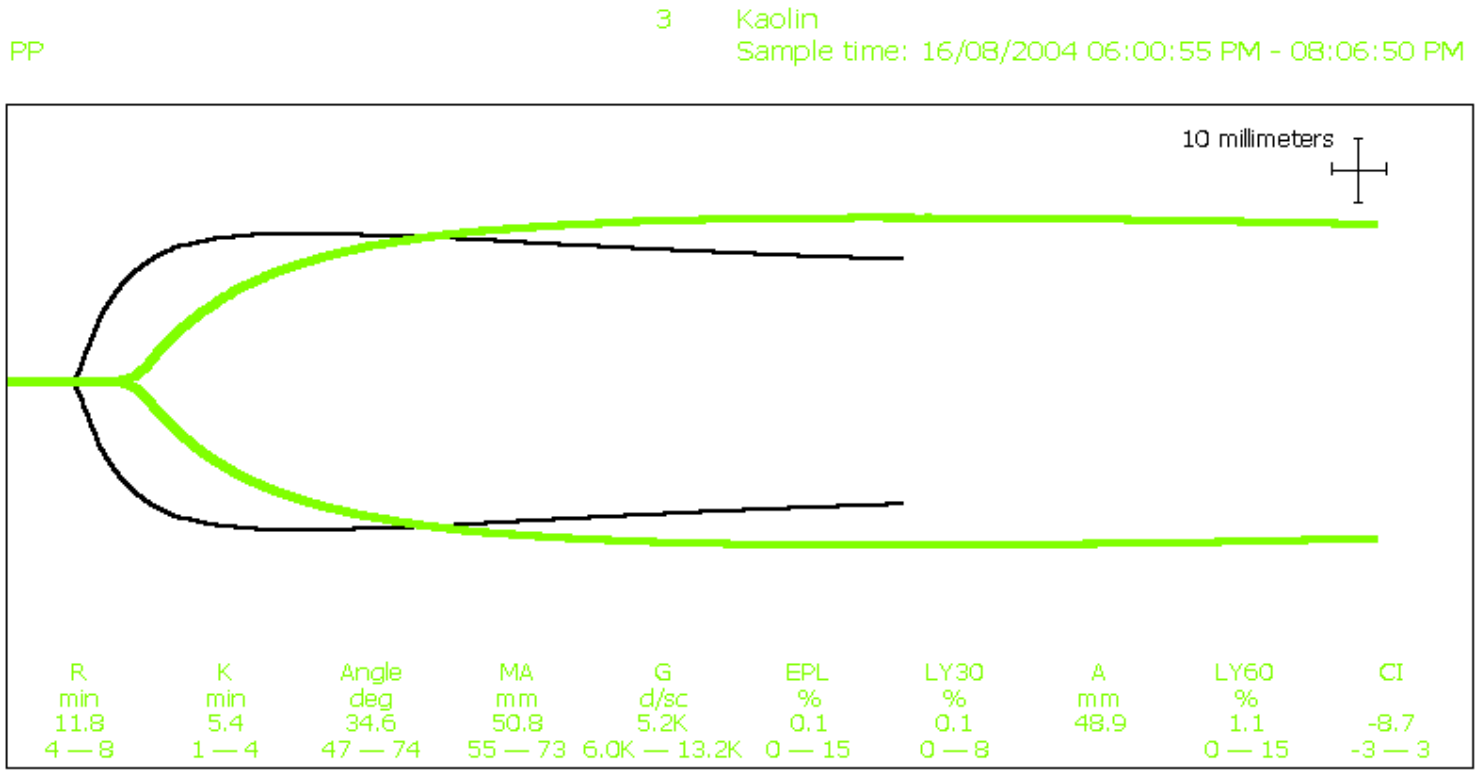
When ?	Cup type	Why?
On induction	Plain	Baseline haemostatic profile
At re-warming/ end of CPB	Plain Heparinase	Early identification of coagulopathy
10 mins post protamine	Plain Heparinase	1. Check heparin reversal 2. Identify cause of bleeding
Post-op	Plain Heparinase	If bleeding

Use of TEG in cardiac surgery with bypass - Treatment protocol

TEG values	Clinical cause	Suggested treatment
R 11-14 mins	↓clotting factors	X 2 FFP
R > 14 mins	↓↓clotting factors	X 4 FFP
MA 42-47 mm	↓platelet function	1 platelet pool
MA < 42 mins	↓↓platelet function	2 platelet pools
LY30 >7.5%	Fibrinolysis	Antifibrinolytic
R < 3 mins, MA > 75 mm	Prothrombotic state	Anticoagulant

TEG in cardiac surgery

Post-CABG, bleeding coming off bypass

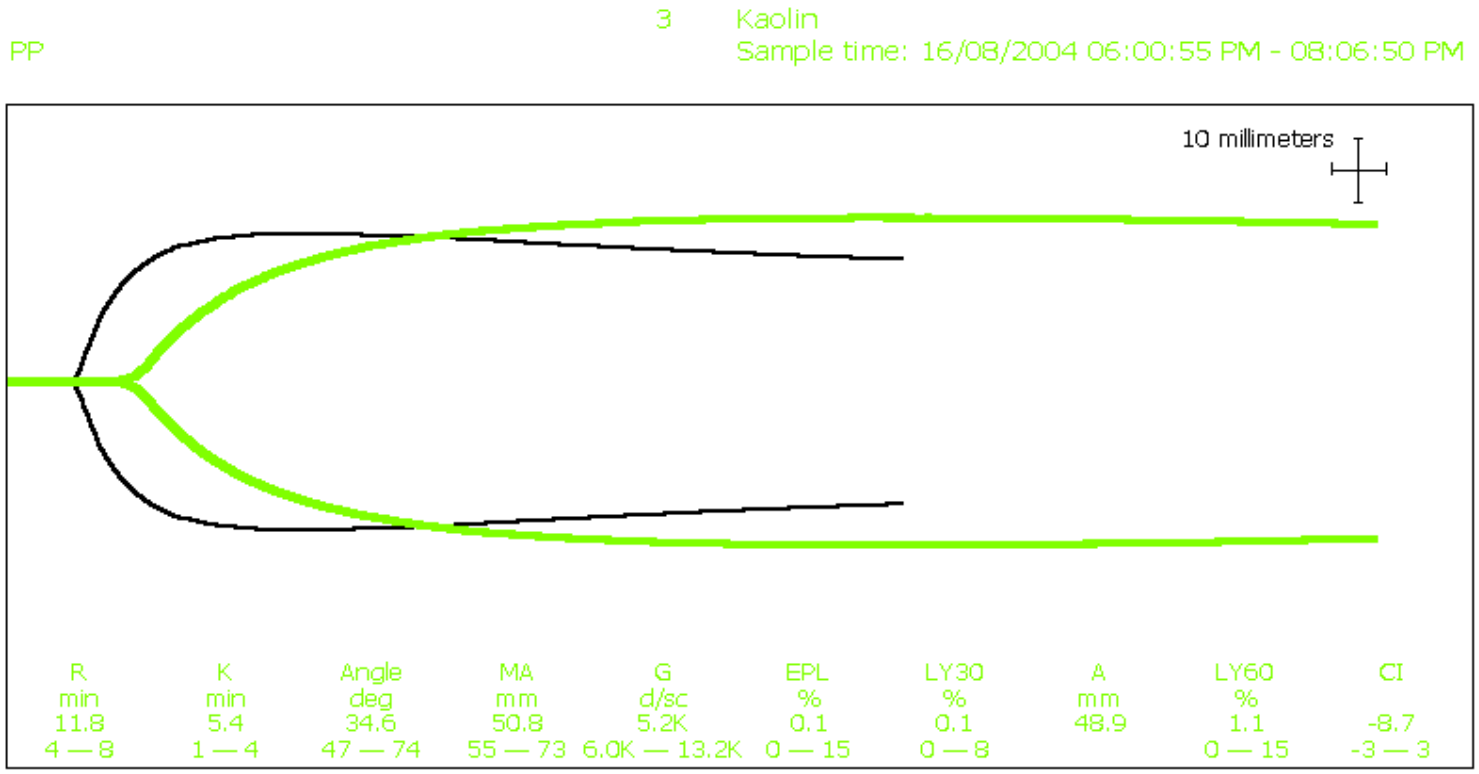


Kaolin

Heparinase

TEG in cardiac surgery - residual heparin

Give more protamine

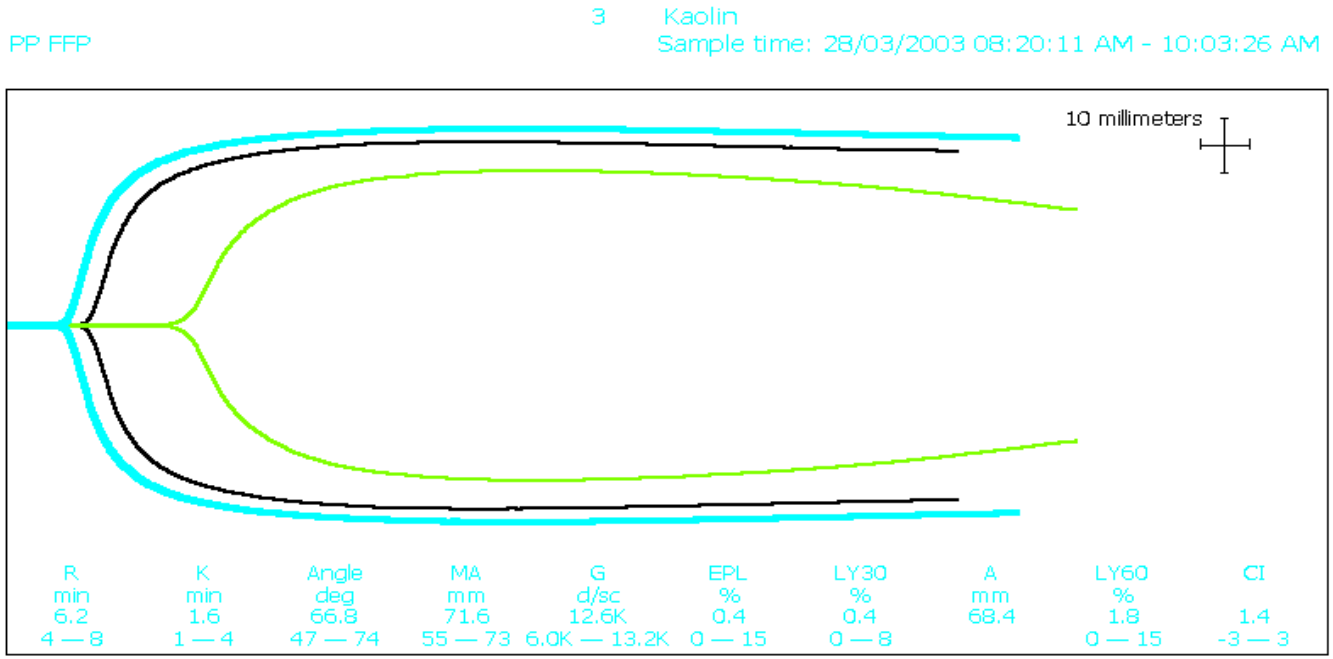


Kaolin

Heparinase

TEG in cardiac surgery

During cardiac surgery, patient bleeding +++

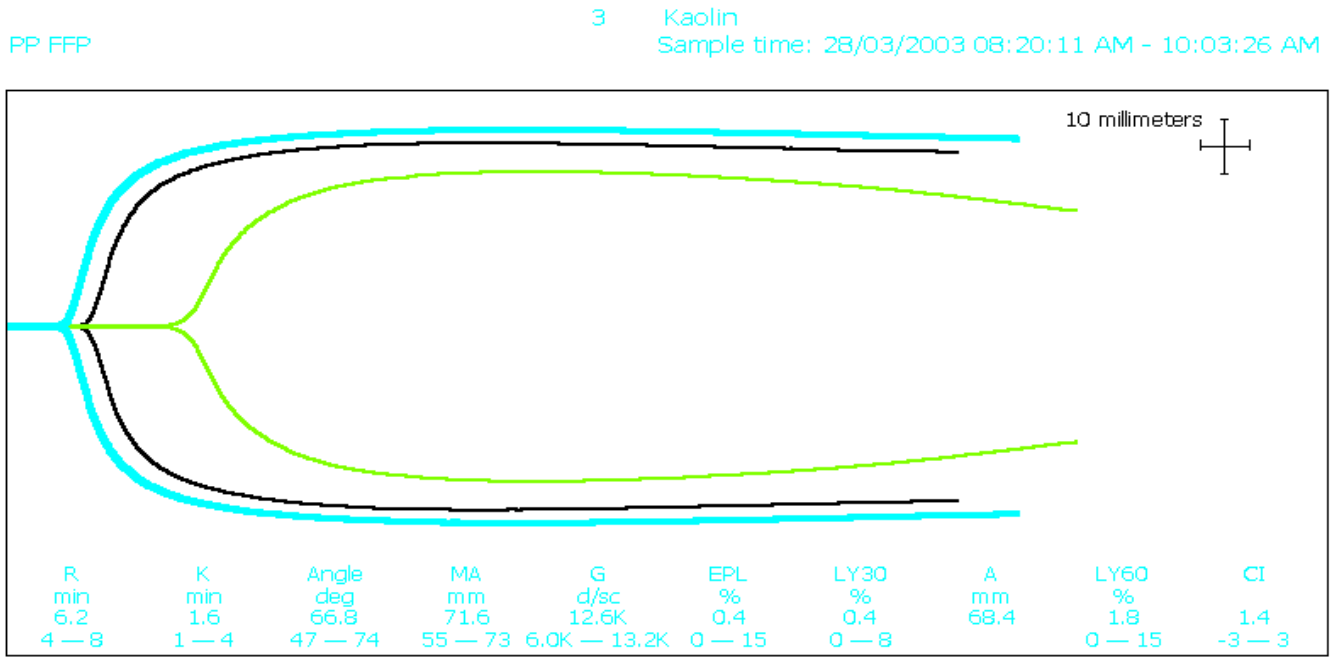


Normal trace

Patient (heparinase)

TEG in cardiac surgery
- Long R time, clotting factor deficiency

Administer FFP

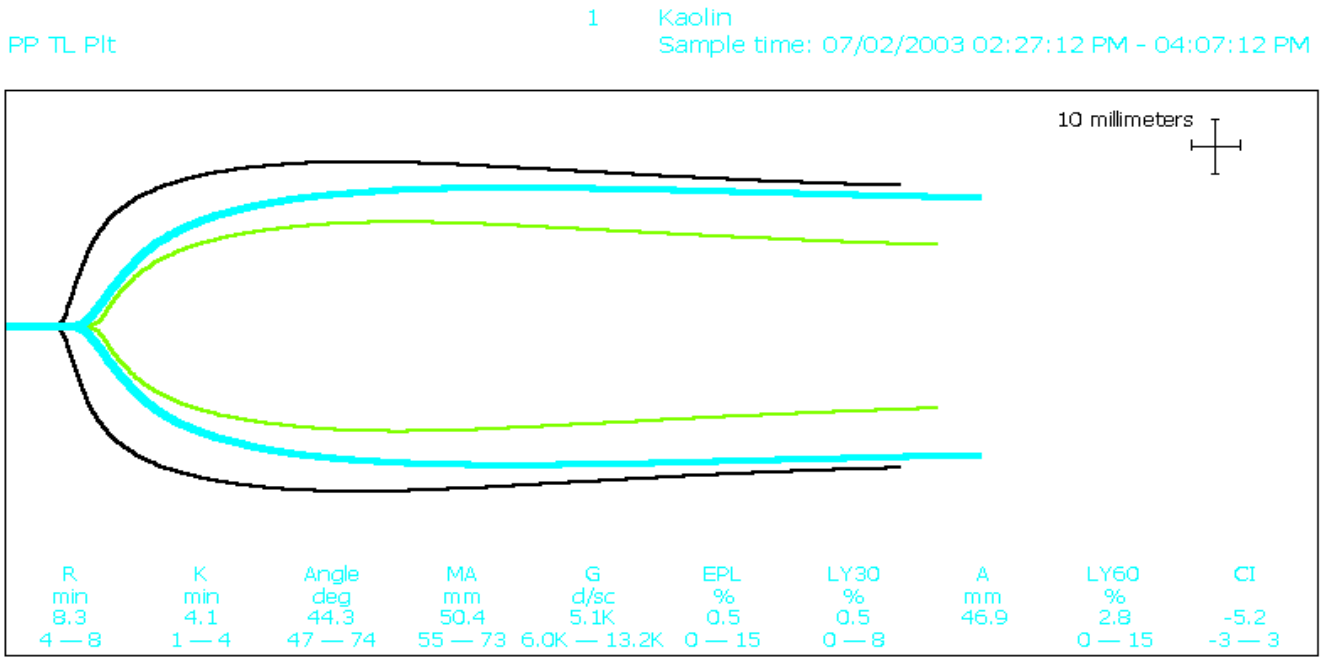


Normal trace

Patient (heparinase)

TEG in cardiac surgery

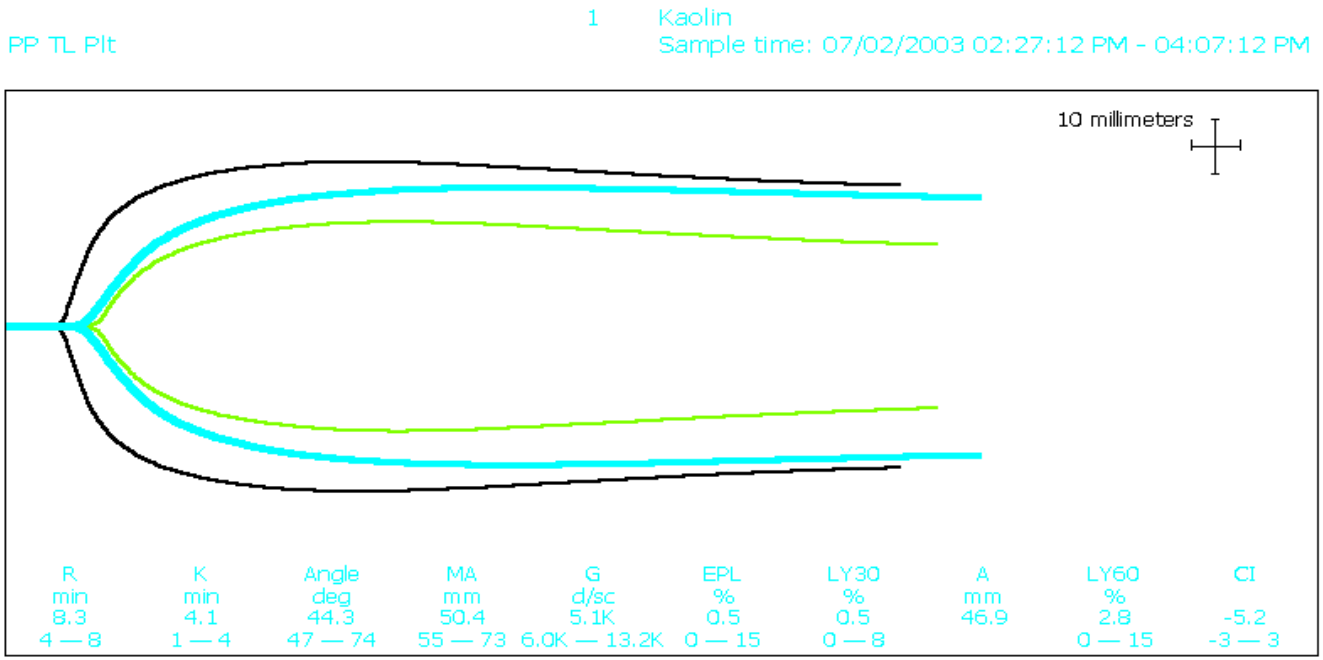
During cardiac surgery, patient bleeding +++



Patient (heparinase)

TEG in cardiac surgery
- Low MA, platelet dysfunction

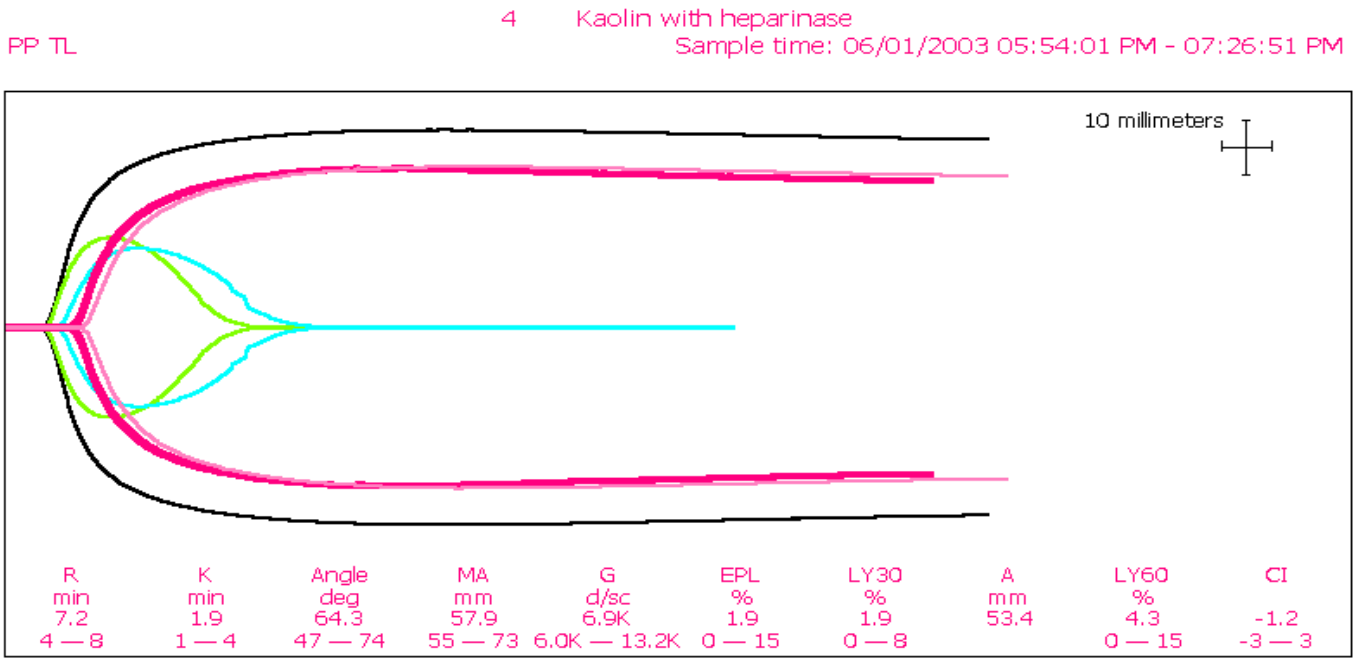
Administer platelet concentrate



Patient
(heparinase)

TEG in cardiac surgery

During cardiac surgery, patient continuing to bleed despite protamine, FFP and platelet transfusion

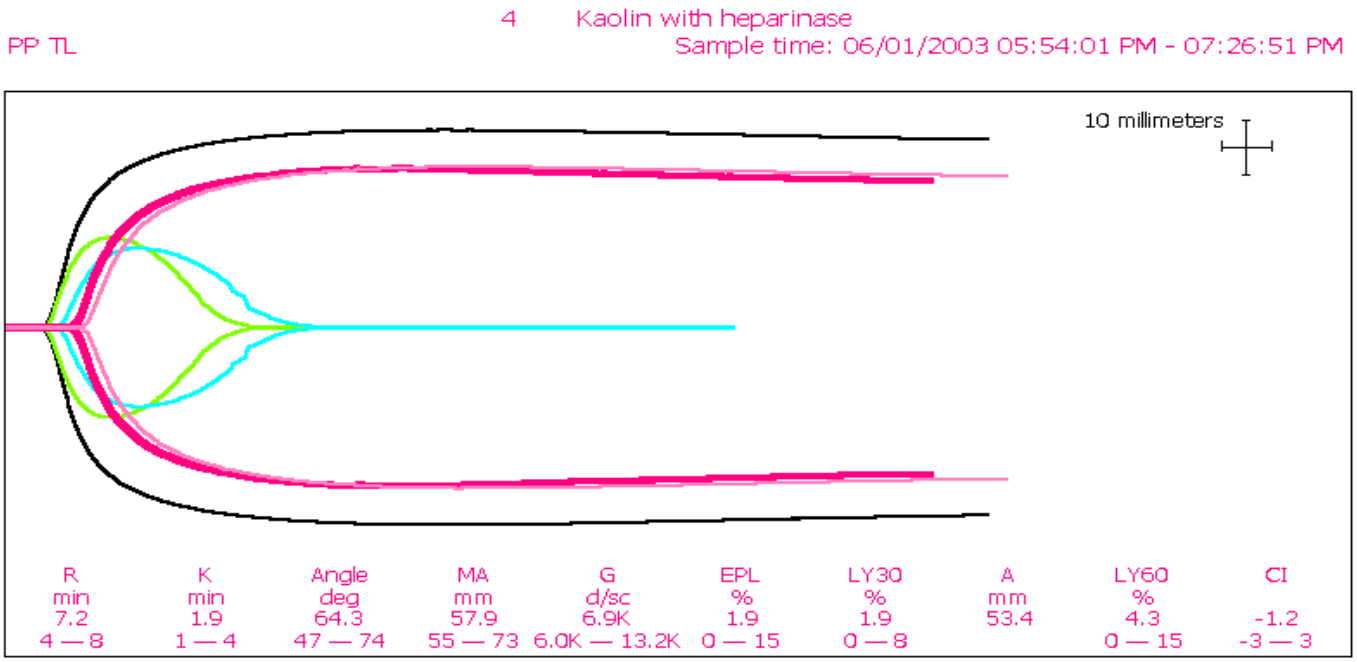


Normal

Patient

TEG in cardiac surgery - Fibrinolysis

Administer antifibrinolytic agent

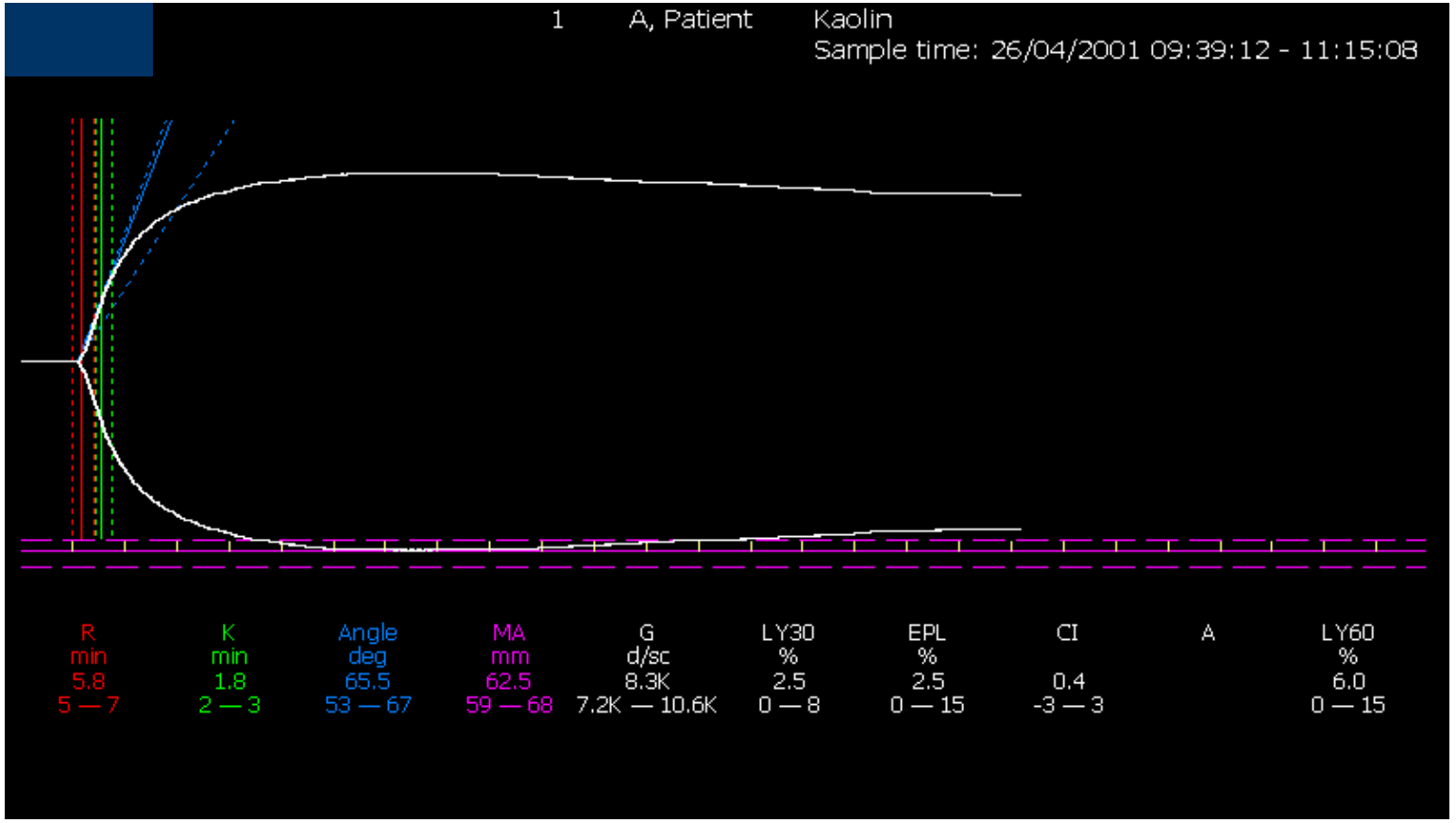


Normal

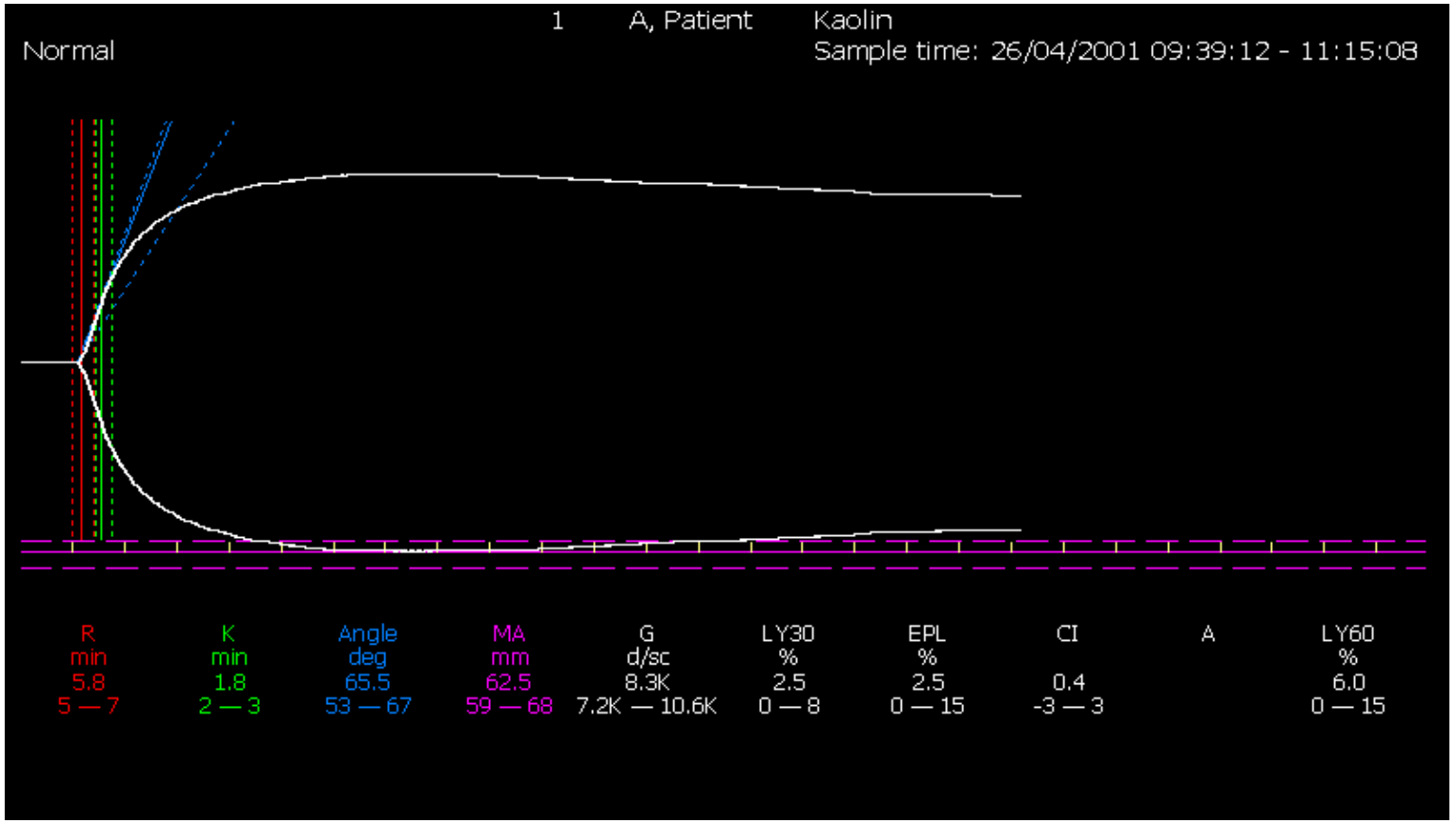
Patient

TEG in cardiac surgery

Post-operative bleeding ++ from one mediastinal drain,
not on anticoagulant therapy



TEG in cardiac surgery
- Surgical bleeding



TEG- Cardiac surgery

Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery

Shore-Lesserson et al. *Anesth Analg* 1999;88:312-9

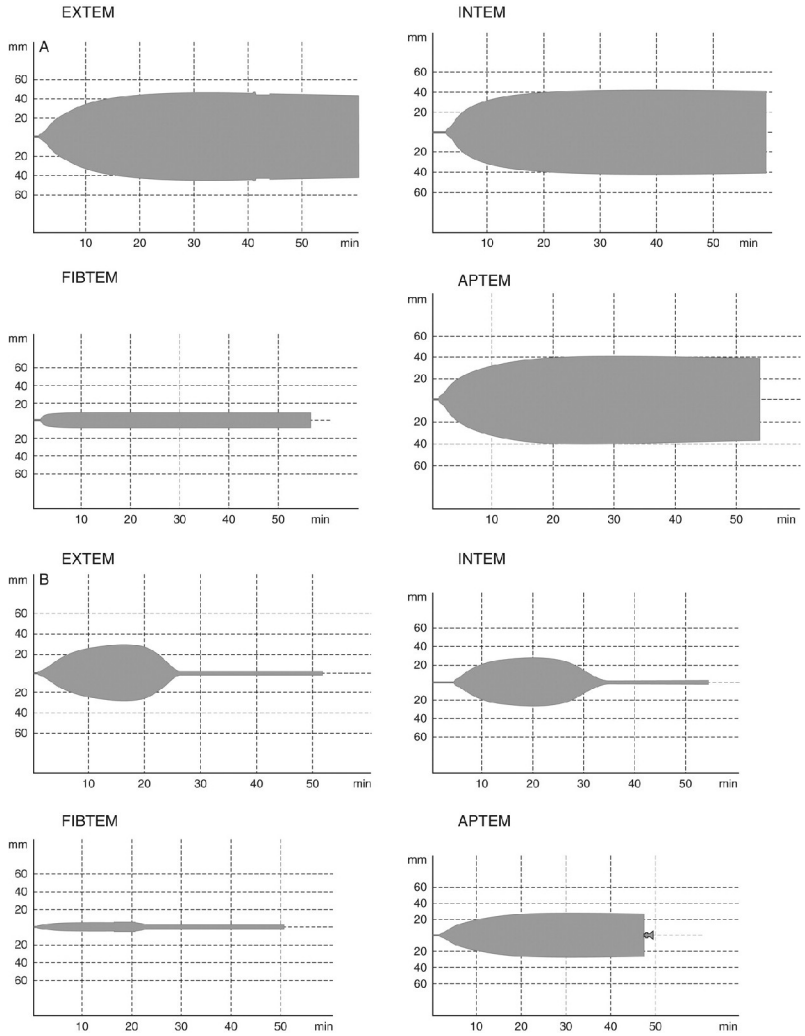
Reduced hemostatic factor transfusion using heparinase modified TEG during cardiopulmonary bypass

Von Kier et al. *Br J Anaesthesia* 2001;86:575-8

- Both used TEG algorithm-directed therapy vs. clinician-guided therapy
- Both reported reduced blood product usage in TEG group and one reported lower volumes of blood in mediastinal drains

  - Early recognition and prompt correction of haemostatic abnormalities during surgery
  - More rapid recognition of surgical bleeding
  - Identification of the need for further protamine infusion

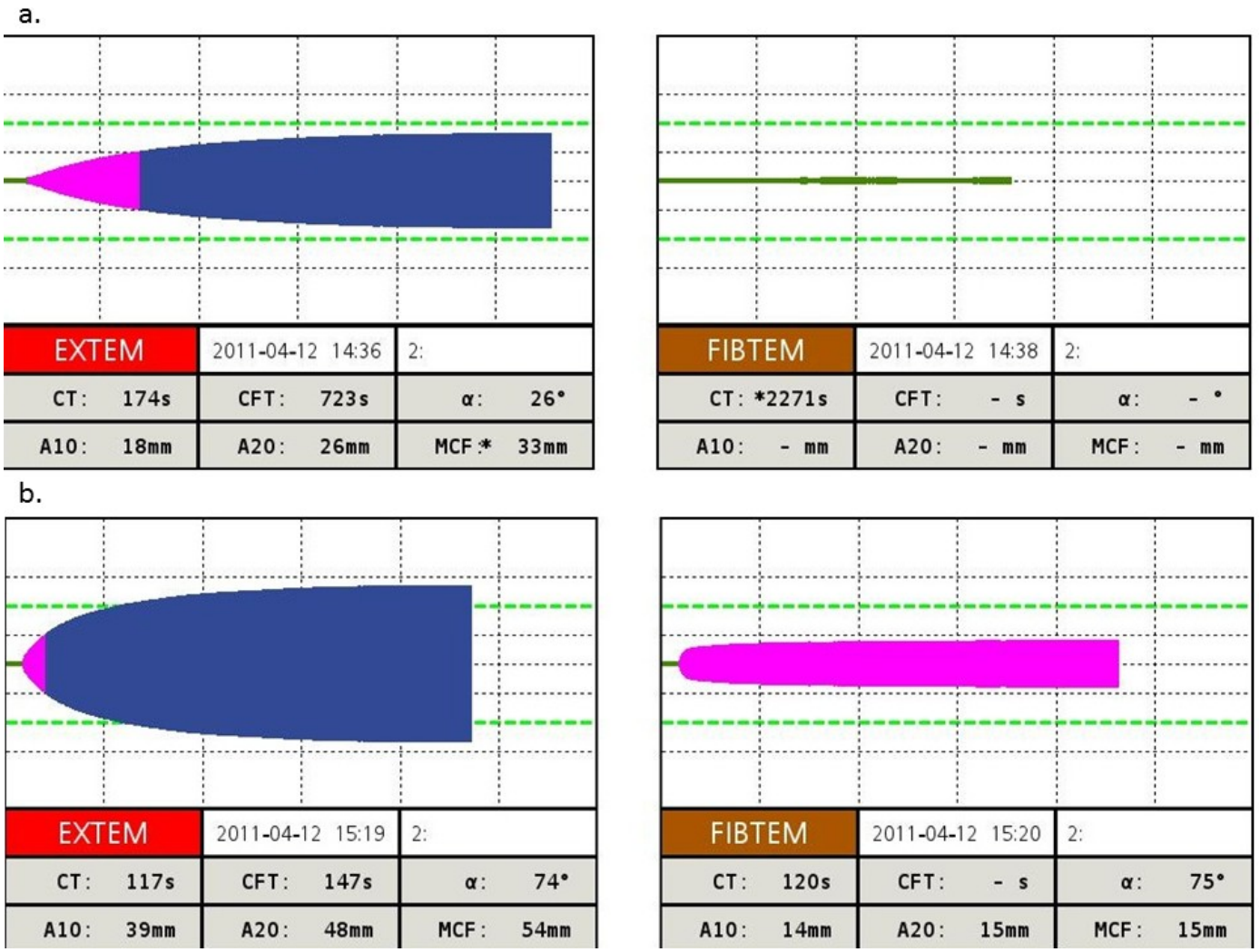
(a) Normal ROTEM® tracing.



Roullet S et al. Br. J. Anaesth. 2010;bja.aeq022

 (a) Normal ROTEM® tracing. (b) ROTEM® tracing depicting severe coagulation abnormalities with hyperfibrinolysis corrected by the addition of aprotinin (APTEM).

BJA British Journal of Anaesthesia



**ROTEM traces from a trauma patient treated according to the AUVA Trauma Hospital algorithm: a. upon admission to the ER (EXTEM coagulation time and clot formation time are prolonged; maximum clot firmness is reduced; no clot formation in the FIBTEM test). b. 40 minutes after treatment with 2 g tranexamic acid, 10 g fibrinogen concentrate, 1800 U prothrombin complex concentrate and 1250 U factor XIII (normal coagulation).Schöchl *et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2012 20:15 doi:10.1186/1757-7241-20-15* *Download authors' original image*

TEG- Trauma

- Guiding transfusion of blood products
- Potential to reduce blood product use by earlier detection of coagulopathy
- Can look at fibrinogen activity and hyperfibrinolysis
- Use of point-of-care RapidTEG (20 mins vs. 30 mins for Kaolin-activated TEG)
- Ability to use as basis for goal directed treatment decisions and to monitor response to treatment
- An adjunct to other tests
- Larger studies needed

Limitations of VHA: TEG/ROTEM

- In vitro tests done in low shear conditions
- Absence of vascular endothelium
- Unmodified VHA cannot be used to assess platelet function with anti-platelet drugs
- LMWH and warfarin effect
- Different reagents and activators give different results important when establishing algorithms

- Wide range of normality – important to monitor change within an individual relative to baseline

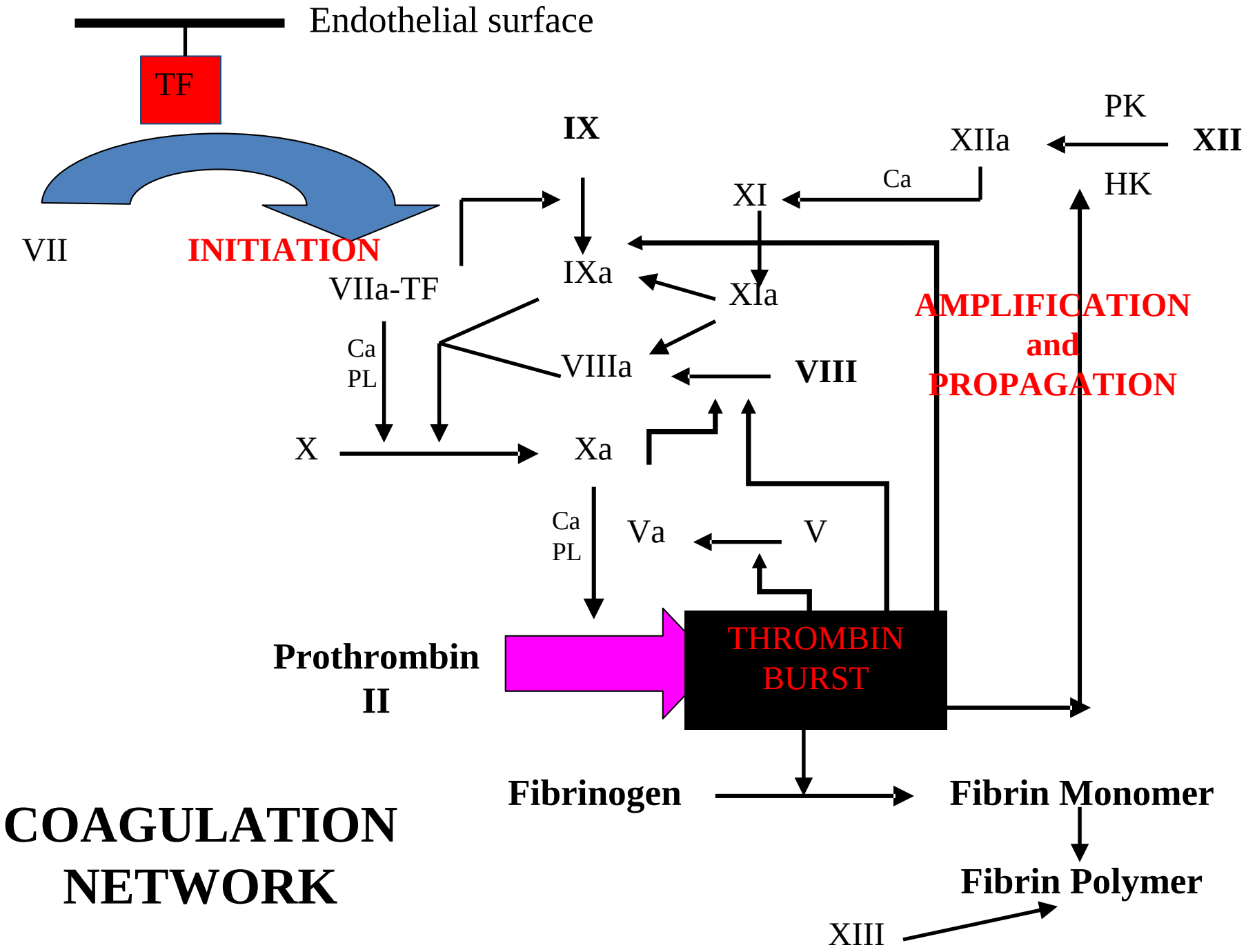
- Moderate complexity of tests – operators require training and SOP, IQA and EQA

- How to go about setting up POCT
- Guidelines on POCT
  British Journal of Haematology, 2008 142, 904–915
- Contact your hospital / trust POCT lead for help

- The purpose, nature and potential benefits of POCT at a particular site should be defined before initiating the service
- POCT devices should deliver results comparable to the local lab; need IQA an EQA
- Cost benefit analysis
- Need clear clinical procedural protocols and clear clinical guidelines
- Oversight of POCT committee for procurement, user training, writing SOP, monitoring and reviewing service
- Audit on patient care, quality and training

Conclusion

- There is not ‘a one fit for all’ POCT solution for all departments
- Any new POCT needs evaluation, planning and then ongoing monitoring to ensure reliability of results; laboratory POCT committee and engagement of clinical users
- Models of VHA use in cardiac and liver surgery and military experience support further assessment in trauma, but further evaluation needed


Endothelial surface
TF
VII
INITIATION
VIIa-TF
IX
IXa
XI
XIa
XIIa
PK
XII
HK
Ca
Ca
PL
VIIIa
VIII
AMPLIFICATION
and
PROPAGATION
X
Xa
Ca
PL
Va
V
Prothrombin
II
THROMBIN
BURST
Fibrinogen
Fibrin Monomer
Fibrin Polymer
XIII
COAGULATION
NETWORK

TEG Pattern Recognition