History and examination

Look at the Immediate Clinical History

1. Massive Transfusion
    1. Physiological Status
        - Temperature
        - pH
        - Duration of hypotension
        - Extent of resuscitation
    2. Clinical Diagnosis of Coagulopathy
        - Diffuse oozing from surgical sites
        - Bleeding around vascular access sites
    3. Mechanism of Coagulopathy
        - Dilution - Platelets, VIII and V
        - Consumption - Fibrinogen and platelets
2. Cardiopulmonary Bypass
    1. Platelet effects
        - Activation and loss of GPIb - Plasmin, elastase and calpain
    2. Aprotinin
        - Repeat valvular surgery and septic endocarditis
        - 2 mKIU pre incision and 0.5 mKIU/hour during bypass

Take a Personal History

1. Family History
    - The haemophilias follow a pattern of X linked recessive inheritance. However up to 30% of case of haemophilia A are spontaneous mutations with no family history.
    - Von Willebrand's disease is difficult to diagnose because of the variability in inheritance, autosomal dominant and recessive, and the variability among patients in the level of von Willebrand factor present. The level varies according to the ABO blood type, with the lowest levels present in type O and the highest in type AB
2. History of surgical, traumatic events or other triggering events
   Any patient who has had major surgery, a tonsillectomy or dental extractions without unusual bleeding, has had the best evaluation of their coagulation system possible.
3. Frequency of abnormal bleeding
4. Duration of abnormal bleeding
   A bleeding abnormality manifests as moderate bleeding over a prolonged period, not as bleeding at an excessive rate.
5. Location of abnormal bleeding

- Bleeding from skin and mucous membranes tends to occur with platelet disorders.
- Bleeding in joints and muscles tends to occur with the haemophilias

6. Medical Disease
    1. Liver Disease
    2. Renal Disease
    3. Haematological malignancy - leukaemia, myeloproliferative disease
    4. Vitamin K deficiency
    5. Vitamin C deficiency
    6. Solid organ malignancy - Prostate, lung, colon
7. Medication History - aspirin, coumarin, heparin

Exclude surgical causes of bleeding

Obtain help from a haematologist

Whole blood clotting time

1. 5ml of blood is placed in a glass container, kept at body temperature and observed
    1. A clot should occur in 5 to 15 minutes
       Prolonged = Severe deficiency of any of the coagulation proteins
    2. The clot should retract in 30 to 60 minutes
       Weak friable clot = hypofibrinogenaemia
       Early dissolution = enhanced fibrinolysis

Full blood count and examination

1. Red blood cell number
2. Red blood cell morphology abnormalities following intravascular thrombosis or microangiopathy
3. Platelet count and function tests

Platelet Count

Two major techniques are used for automated platelet measurements. They use size thresholds to distinguish between platelets, leucoytes and erythrocytes.

- Light scattering
  This measures the amount of light transmitted as blood elements pass through an aperture
- Electronic aperture-impedance counting:
  This measures the change in electrical resistance/capacitance as blood

elements stream through an aperture connecting a circuit.

Normal number 150 to 400x10^9/L.

The machines are accurate and reliable down to 10-30x10^9/L but are subject to specimen error:

- Poor platelet preservation techniques allow adhesion and clumping, resulting in abnormally low results
- Specimens stored for more than 24 hours allow aggregation of platelets
- Haemolysed red cell fragments and bacterial contamination may be identified as platelets

Genuinely low levels are due to

- **Increased peripheral destruction**
    1. Dilutional - Massive blood transfusion
    2. Sequestration - Look for liver and splenic disease
    3. Destruction
        1. Sepsis
        2. Disseminated intravascular coagulation
        3. Thrombotic thrombocytopaenic purpura / Haemolytic uraemic syndrome
        4. Post cardiopulmonary bypass
        5. Mechanical prosthetic valves
        6. Platelet antibodies
            1. Drug induced - Penicillin
            2. Post transfusion - HLA directed
            3. Collagen vascular disease
            4. Idiopathic thrombocytopaenic purpura = Immune thrombocytopaenic purpura

- **Decreased production**
    1. Hypocellular Bone marrow - Aplastic Anaemia
    2. Hypercellular Bone marrow
        1. Megaloblastic - B_{12} or folate deficiency
        2. Myelodysplastic
    3. Myelophthisic
        1. Leukaemia
        2. Metastatic cancer
        3. Myelofibrosis

Platelet Function

Platelet Aggregation

The addition of an agonist (thrombin, ADP, adrenaline, collagen, ristocetin or arachnidonic acid) to platelet rich plasma normally exhibits a biphasic response of reversible aggregation due to the agonist followed by irreversible aggregation due to the disintegration of the platelets.

Heparin induced platelet aggregation

Used in the diagnosis of heparin-associated thrombocytopaenia.

Hess Test
In vivo assessment of collagen matrix, vascular endothelium and platelet adhesion and aggregation
A syphgomomanometer is inflated to between the systolic and the diastolic pressures for 10 minutes. Normal less than 15 petechiae would occur in a 5cm diameter circle.

International Normalised Ratio <

Quick labeled the test prothrombin time when he devised it in 1935 as he believed it was a simple, accurate, and sensitive measure of prothrombin. He was wrong.

The specimen should be a 3.8% trisodium citrate anticoagulant in a 9:1 ratio with the blood, which is centrifuged to produce platelet poor plasma. A complete thromboplastin (typically from rabbit brain) is then added with calcium. The time to fibrin strand formation is then measured automatically by:

- Photo-optical device.
  This depends on the increase in light scattering associated with the conversion of soluble fibrinogen to soluble fibrin. A photocell detects the decrease in transmitted light as the clot forms and an algorithm analyses the data to produce an endpoint.
- Electromechanical device

Many variables affect the prothrombin time

- The thromboplastin reagent. Poller in 1987 proposed The International Normalised Ratio.
  - All commercial thromboplastins are compared to an International Reference preparation. This determines a "calibration value", called an International Sensitivity Index which must be supplied with every batch of thrompoplastin reagent.
  - The INR = (Patient's prothrombin time / Laboratory's control prothrombin time)^{ISI}
- Specimen collection
  - The first specimen drawn is contaminated by tissue thromboplastin
  - EDTA contamination interferes with the activation process.
  - Underfilling alters the anticoagulant:blood ration of 9:1
  - Polycythaemia alters the anticoagulant:blood ration of 9:1
  - Haemolysis, lipaemia, hyperbilirubinaemia and hyperproteinaemia produce errors in the optical end point analysis.

A Normal INR is between 0.9 and 1.2

Prolonged = Deficiency of factor I, II, V, **VII** or X. The test is most sensitive to decreases in factor VII which is one of the vitamin K dependant factors.

1. Coumarin anticoagulation therapy
2. Vitamin K deficiency
3. Severe Liver disease
4. Massive blood transfusions
5. Disseminated intravascular coagulation
6. High dose heparin therapy

Activated partial thromboplastin time

This test derives its name from the use of a partial thromboplastin, or "cephalin" which is a phospholipid component that is added to a specimen that has been "activated" by exposure to a negatively charged substance (kaolin, celite or ellagic acid).

Normally 25 to 35 seconds

Prolonged = A decrease to less than 30% activity of all the coagulation factors

1. Heparin therapy
2. Haemophilia
3. Massive blood transfusions
4. High dose coumarin anticoagulation

Errors in specimen collection will also affect the result

Factor activity assay

Normal plasma and the patient's plasma are compared in their ability to correct the INR or aPTT of plasma from an individual severely deficient in the factor of interest.

By convention normal plasma is said to have 100% or 1 unit per ml activity. If a 1:10 dilution of a specimen has the correcting power of a 1:100 dilution of normal plasma, the specimen has 10% or 0.1 unit per ml activity.

1. Antithrombin III activity assay
    1. Decreased by consumption
        1. Sepsis
        2. Disseminated intravascular coagulation
        3. Deep vein thrombosis or pulmonary embolism

        2. Decreased due to low levels of the molecule
            1. Decreased synthesis of a normal AT III molecule - Autosomal dominant
            2. Production of a dysfunctional AT III molecule - Autosomal dominant
    2. Factors II, V, VII, VIII, IX, X, XI, XII
    3. von Willebrand factor
    4. Fibrinogen
       The Clauss clottable protein method.
       Thrombin times are performed using a series of serial dilutions. As fibrinogen concentration is the rate-limiting step, a graph of the results is used to extrapolate fibrinogen concentration.
       Specimen collection can affect the result.
    5. Fitzgerald Factor Assay - High Molecular Weight Kininogen deficiency
       A rare disease manifest by a prolonged PTT with no bleeding manifestations and not explained by a lupus anticoagulant, haemophilia, von Willebrand's disease or heparin administration. Some patients are reported to have thromboembolic episodes.
    6. Fletcher Factor Assay - Prekallikrein factor deficiency
       Deficiency is an autosomal recessive pattern with a prolonged PTT and no bleeding tendency. Some patients may have thromboembolic episodes.

Factor Antigen assay (VII, X)

Factor Inhibitor assay (II, V, VII, VIII, IX, X, XI, XII)

The mixing study
The patient's serum is mixed with normal serum and the aPTT of this mixture is measured. A 50:50 mixture will correct a factor deficiency (only 30% activity is needed for a normal aPTT). In the presence of an inhibitor a 50:50 mix will not correct the abnormal coagulation test.

Factor VIII inhibitors

- IgG
- Occur primarily in haemophilia A patients who have received blood component transfusions. They develop a severe coagulopathy that is very difficult to manage
- May occur in a variety of unrelated conditions with a coagulopathy that is variable and usually disappears spontaneously

Lupus Anticoagulant

- Majority of patients do not have systemic lupus erythematosus nor any tendency towards increased bleeding
- IgG directed against the Xa-V-Phospholipid complex
- Markedly prolonges the aPTT

- Clinical tendency towards excessive thrombosis
- Occurs in a variety of conditions
  - Essentially normal patients
  - Lupus 5-10% of patients
  - Infectious diseases
  - Rheumatoid arthritis
  - Lymphoma
  - Prostatic cancer
  - Acquired immunde deficiency syndrome
  - Drug exposure - chlorpromazine, procainamide and antibiotics
- Laboratory tests to isolate the lupus anticoagulant
  - Cardiolipin adsorption
  - Reptilase Test
  - Dilute aPTT
  - Kaolin clotting time
  - Platelet neutralisation procedure.

Thrombin Time

Thrombin is added to plasma and the time taken to form a clot is recorded Normal is less than 15 seconds

Prolonged due to inhibition of thrombin

1. Heparin
2. Fibrin degradation products
3. Lupus anticoagulant

Prolonged due to abnormal fibrinogen

Reptilase Time

Reptilase is added to plasma and the time taken to form a clot is recorded. Normal is less than 14-19 seconds

1. Prolonged due to inhibition of Reptilase
   - Lupus anticoagulant
2. Prolonged due to abnormal fibrinogen

Template bleeding time

A sphygmomanometer on the upper arm is inflated to 40mmHg. A skin incision 5mm long and 1mm deep is made on the extensor surface of the forearm, using a spring loaded template device.. The wound avoids scar tissue and superficial vessels, and must be done within 60 seconds of inflating the sphygmomanometer. Filter paper is used to blot the edges of the wound at 30 second intervals until the bleeding stops. Normal is two to

nine minutes

According to Rodgers & Levin:
[*A critical reappraisal of the bleeding time*. Sem Thromb Haemost 1990: 16: pp1-19]

- The bleeding time is unable to predict aspirin usage
- There is no predictive correlation with the platelet count
  - The only study that claims a correlation is by Harker & Slickter [*The bleeding time as a screening test for evaluation of platelet function.* N Engl J Med 1972; 287: pp155-159]
- There is no correlation with surgical bleeding.

Conventional theory alleges that a prolonged bleeding time is due to

1. von Willebrand factor abnormality or deficiency
2. Platelet deficiency or abnormality - Heparin, Aspirin
3. Anaemia

Activated Coagulation Time

Fresh whole blood is added to a tube containing negatively charged particles and timed for the formation of a clot.

The type of negatively charged particle affects the "normal" length of ACT

Celite = Diatomaceous Earth: normal is 100-170 seconds

1. Used with high circulating levels of heparin - cardiopulmonary bypass
2. Aprotinin prolongs the "normal" ACT
3. Black top glass test tube

Kaolin: normal is 90-150 seconds

1. Used with high circulating levels of heparin - cardiopulmonary bypass
2. ACT not prolonged by aprotinin
3. Gold top glass test tube

Glass particles: normal 110-190 seconds

1. Used with medium circulating levels of heparin - haemodialysis
2. Clear top plastic test tube

None: normal 190-300 seconds

1. Used with low to no circulating levels of heparin - Vascular and general surgery
2. White top glass test tube

Type of machine affects normal and therapeutic values

Hemochron

A warmed test tube is rotated inside the machine. As the blood clots, it

displaces the magnet within the test tube. The clotting time is determined when the magnet has displaced enough to activate a proximity switch

Medtronic HemoTec

A mechanical plunger is dipped in and out of a kaolin activated blood sample. The machine optically senses the time it takes the plunger to move through the specimen. Clotting is defined by the "drop time" threshold for the plunger

The machines do not correlate with one another but in general the times for the Hemochron are 30% greater than the Medtronic HemoTec

Specimen quality affects the values

1. The specimen should never be taken from a line in which heparin is used
2. Sampling from an indwelling line must involve a two syringe technique, with the infusion stopped
    1. Initially withdraw three times the dead space volume to eliminate any dilution from the drip fluid
    2. Obtain the sample with a second syringe
3. Sampling from venipuncture must involve a two syringe technique
    1. Discard the first 2-5ml withdrawn to avoid contamination with tissue factor
    2. Obtain the sample with a second syringe

Daily calibration checks are imperative

1. Three calibration time checks ensure linearity of response
    1. 100 Seconds calibration instrument
    2. 250 Seconds calibration instrument
    3. 500 Seconds calibration instrument
2. Temperature calibration of 37^{o}C is carried out with a magnetised thermometer.

Clinical use of the ACT in assessing adequacy of heparinisation

1. A linear heparin/dose response curve has been well documented
2. Many reports have shown less blood loss with no increase in fibrin formation using ACT guided heparin dosing as opposed to protocol dosing in cardiopulmonary bypass surgery
3. Serial ACT measurements to develop individual heparin/dose response curves should be used.
4. "Target" ACT is very system and unit dependent

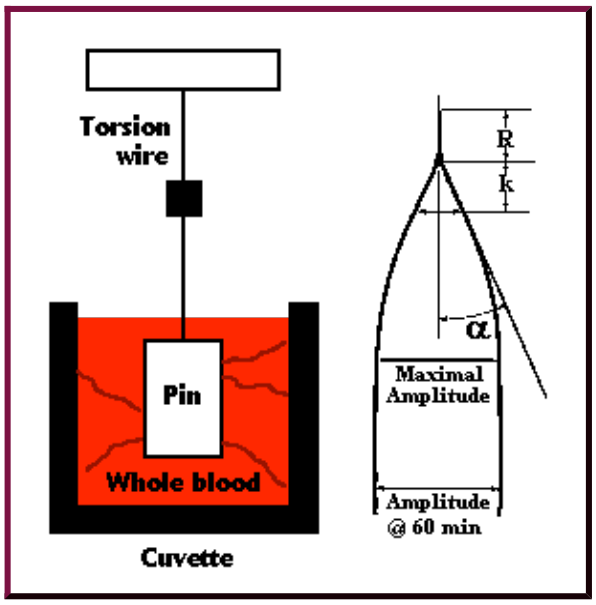
Prolonged times may be due to

1. Heparin effect

2. Hypothermia
3. Platelet dysfunction
4. Haemodilution
5. Cardioplegic solutions
6. Hypofibrinogenaemia
7. Factor deficiencies

The Thromboelastograph

A Sample of celite activated whole blood (0.4ml) is placed into a pre warmed cuvette. A pin suspended from a torsion wire is then lowered into the cuvette. The cuvette is rotated backward and forwards in a small arc. As the fibrin strands interact with the activated platelets on the surface of the pin, the rotational movement of the cuvette is transmitted to the pin. The stronger the clot the more the pin moves. The Haemoscope is connected to a computer and the coagulation profile is then displayed on the screen as an outline of a Thromboelastograph



There are 6 parameters of importance in a TEG tracing

R value = This is the period of time from initiation of the test to the initial fibrin formation and pin movement

k value = This is the measure of time from the beginning of clot formation until the amplitude of the TEG reaches 20mm.

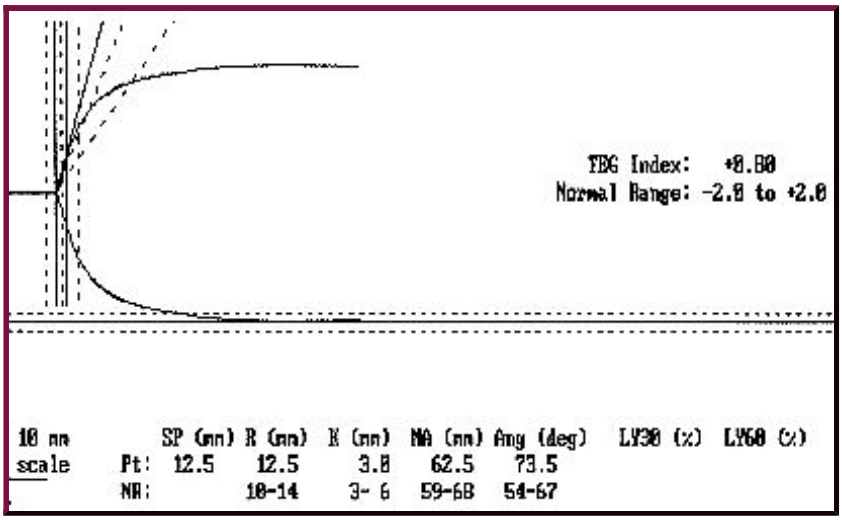
alpha angle = This is the angle between the line in the middle of the TEG tracing and the line tangential to the developing "body" of the TEG

Maximal Amplitude = This is the greatest amplitude of the TEG tracing

Amplitude at 60 minutes = This is the amplitude of the TEG tracing 60 minutes after the Maximal Amplitude is recorded.

Clot Lysis Index = The amplitude at 60 minutes expressed as a percentage of the maximal amplitude.

Normal Thromboelastogram



Alterations of the normal TEG pattern can give information about

The coagulation factor activation - R value

The coagulation factor amplification - k value and alpha angle

The platelet aggregation - Maximal Amplitude

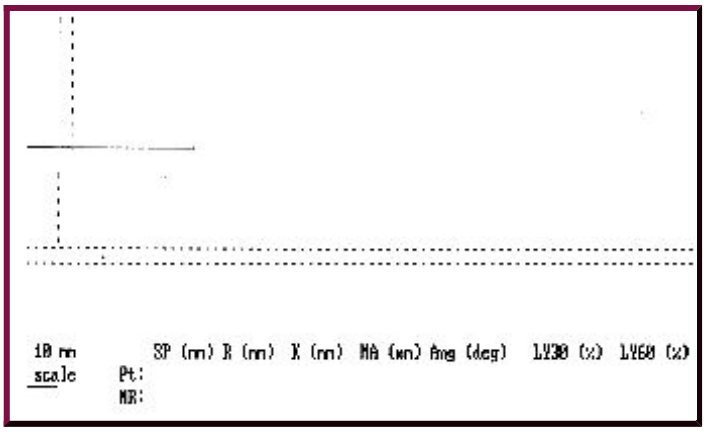
Fibrinolysis - Amplitude 60 minutes after Maximum

Platelet adhesion to the collagen matrix is not assessed

Examples of TEG

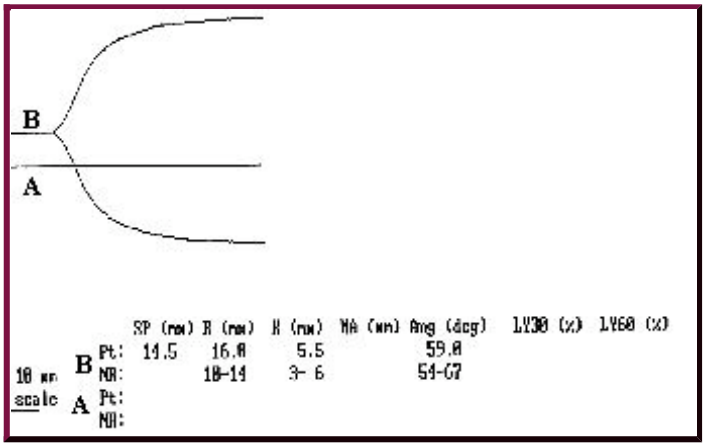
(After Wenker & Wojciechowski)

Example 1



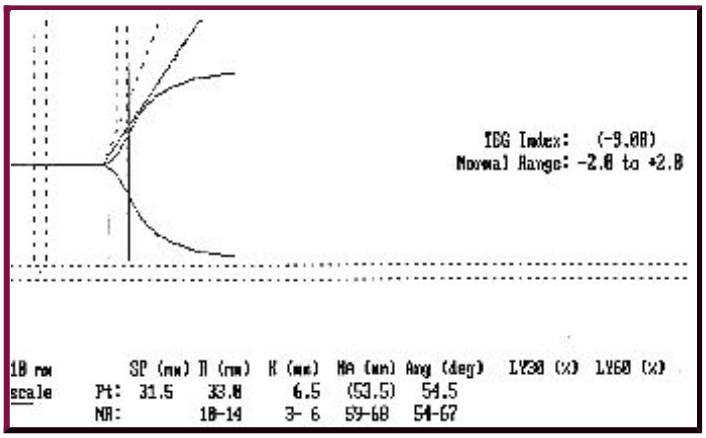
1. No Clot formation
    1. Very low factor levels
    2. Heparin effect

Example 2



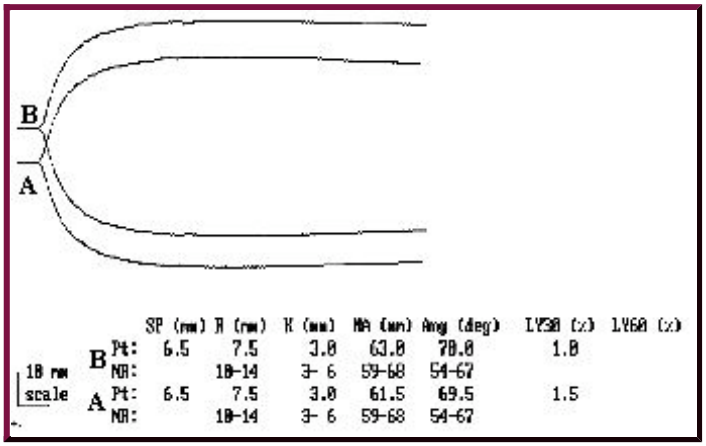
1. A no coagulation at all - Whole blood from a heparinised patient
2. B normal Curve - Whole blood after the addition of heparinase

Example 3



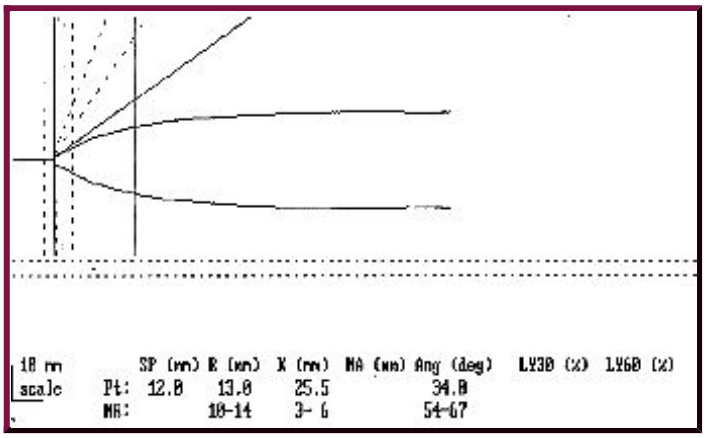
1. Prolonged R value suggesting
    1. Factor deficiency
    2. Minimal heparin effect

Example 4



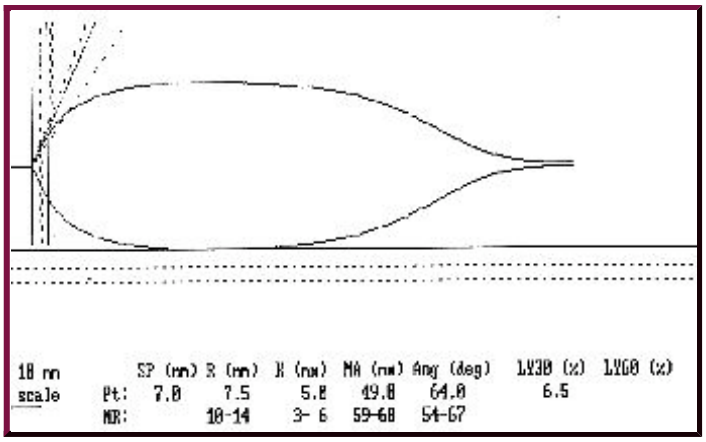
1. Normal coagulation profile with adequate reversal of heparin by protamine, confirmed by the second trace with heparinase added

Example 5



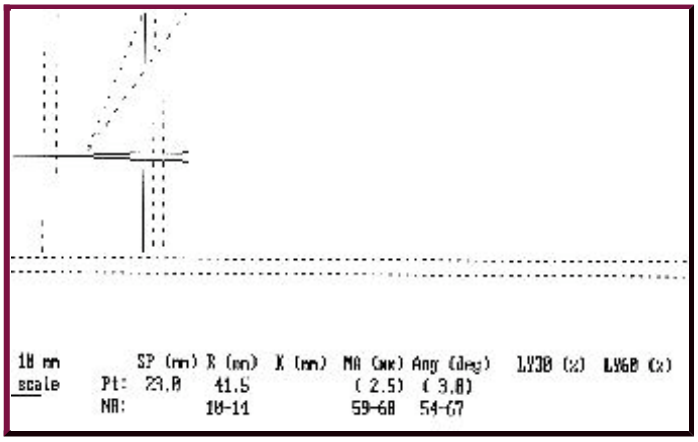
1. Small alpha angle
2. Small maximal amplitude with weak clot formation
    1. Thrombocytopaenia - administration of c7E3 Fab (ReoPro) will eliminate platelet contribution to the maximum amplitude
    2. Thrombocytopathy - administration of c7E3 Fab (ReoPro) will eliminate platelet contribution to the maximum amplitude
    3. Hypofibrinogaemia

Example 6



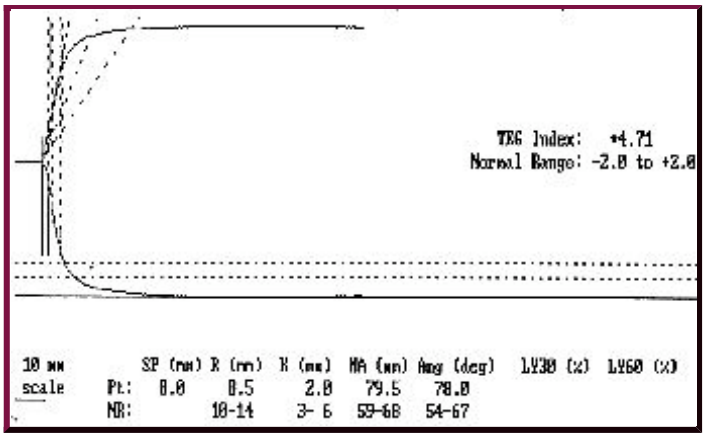
1. Short R value
2. Borderline Maximal Amplitude
3. Significant clot lysis
    1. Poor platelet function
    2. Fibrinolysis - epsilon aminocaproic acid or tranexamic acid can be added to the TEG to see the in vitro effects

Example 7



1. Elongated R value
2. k value not readable
3. Small alpha angle
4. Minuscule maximal amplitude
    1. Technical error in TEG processing
    2. Severe coagulopathy

Example 8



1. Short R value
2. Short k value
3. Large alpha angle
4. Large maximal amplitude
5. No fibrinolysis evident
    1. Secondary to aggressive replacement of all factors
    2. Platelet rich plasma
    3. Chronic hypercoagulable states
        1. Chronic aortic aneurysms
        2. Primary hepatocellular carcinoma
        3. Sclerosing cholangitis
        4. Primary biliary cirrhosis
        5. Budd-Chiari syndrome

Peri-operative & ICU Anticoagulation
Bibliography

Date of First Publication: 1999 **Date of Last Update**: 2006/10/24 **Web page author:** Click here