**tem**®
Redefining Bleeding Control

# ROTEM® Analysis
# Targeted Treatment of
# Acute Haemostatic Disorders

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**ROTEM**®

## Introduction

In this text, the basis of ROTEM® analysis is described together with its use during the management of acute bleeding.

The management of acute bleeding is a complex challenge. Little that is done in this area is fulfilling the hard criteria of evidence based medicine. The recommendations in this compendium are based on the experience of the authors and on the discussion with centres, which use the ROTEM® system in clinical routine. However, these recommendations have not yet been prospectively validated.
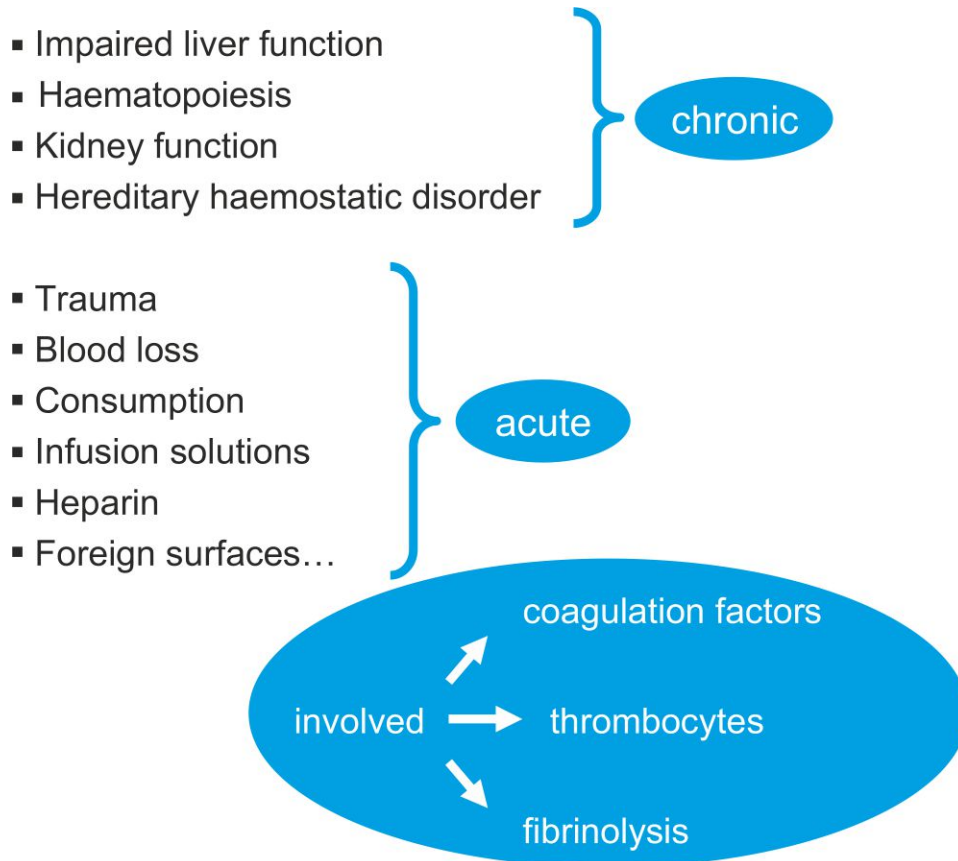
## Causes of Haemostasis Disorders

Haemostasis disorders can have several causes. Rather chronic processes (such as comorbidities of the haemostasis-related organs liver - kidney - bone marrow) or hereditary diseases can be differentiated from more acute alterations due to trauma, haemodilution and the current treatment. The resulting alterations affect the plasmatic coagulation factors, platelets and the fibrinolytic system.
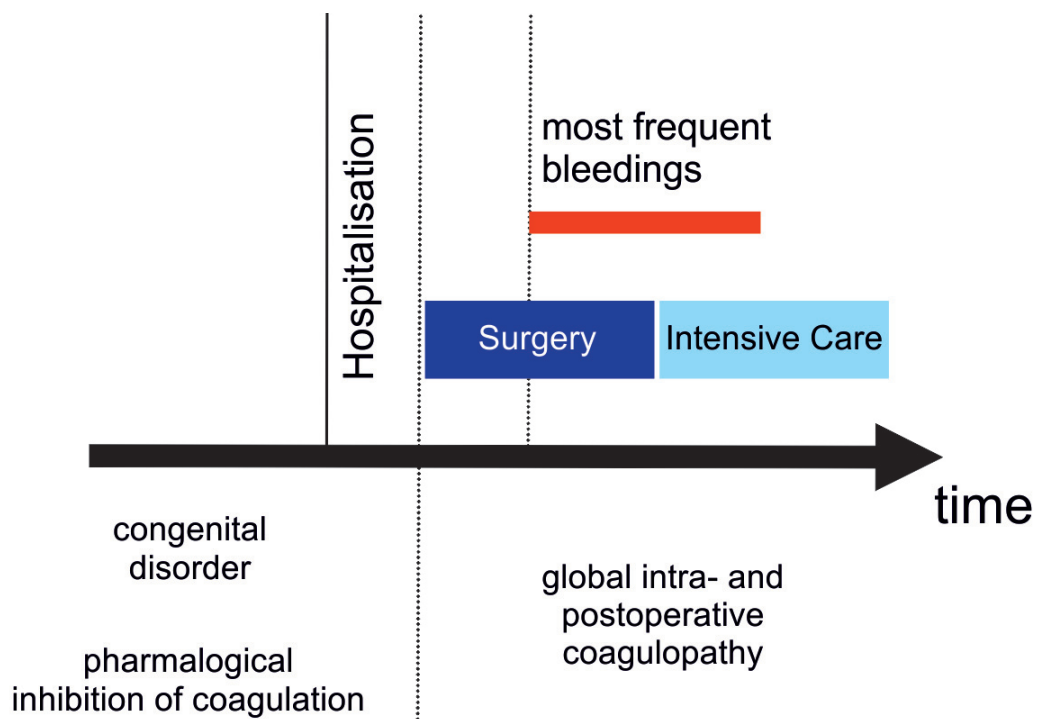
Bleeding most frequently occurs during and after surgical interventions or traumas, i.e. in situations where trauma and secondary alterations (e.g. due to haemodilution) are added to the disposition of the patient. During such complex haemostasis disorders, the clinical significance of the routine parameters PT, aPTT and platelet count is rather weak. This leads to the interest in laboratory methods, which better reflect haemostasis during these complex processes.

A. Calatzis, W. Schramm, M. Spannagl. Management of Bleeding in Surgery and Intensive Care. I. Scharrer / W. Schramm (Ed.), 31 st Hemophilia Symposium Hamburg 2000, Springer Verlag Berlin Heidelberg 2002.

## Alterations of haemostatic causes

- Impaired liver function
- Haematopoiesis
- Kidney function
- Hereditary haemostatic disorder

**chronic**

- Trauma
- Blood loss
- Consumption
- Infusion solutions
- Heparin
- Foreign surfaces…

**acute**

involved → coagulation factors
involved → thrombocytes
involved → fibrinolysis

## Trauma and coagulopathy as a cause of bleeding

Hospitalisation

most frequent bleedings

Surgery | Intensive Care

time

congenital disorder

pharmalogical inhibition of coagulation

global intra- and postoperative coagulopathy

# Thromboelastometry

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## Targeted Treatment of Bleeding Events

During acute bleeding, a multitude of different therapeutic options are at disposition to the physician. The difficulty is to choose the right medication at the right time and to evaluate how much, respectively how often, the respective therapeutic option has to be applied. Typically, only the <u>right</u> therapy will stop the bleeding. It will be of little use to the patient, if he is transfused with FFP while he is bleeding because of thrombocytopenia or hyperfibrinolysis. Although this sounds self-evident, in the clinical everyday routine, a "blind" therapy is often applied. This means that different medication and blood products are administered consecutively until the bleeding stops. If the cause of the bleeding is not the most obvious, unnecessary medication and blood products are administered. Thus, unnecessary costs are created and the patient is exposed to potentially harmful preparations.

## TEG / ROTEM® - History

Thrombelastography was developed during world war II by professor H. Hartert in Heidelberg. Following a quite broad application in the 50's and 60's, the interest in TEG decreased in the 70's. In the 80's it came to a renaissance of TEG, especially in the United States, because of the application in anaesthesia for the management of acute bleeding. The ROTEM® system is an enhancement of thrombelastography and was developed during 1995-1997 in Munich. The instrument includes four measurement channels for simultaneous determinations, an integrated computer for automatic analysis and an electronic pipette for interactive test operation.

*Note:* The term "TEG" was introduced by Hartert in his first publication on thrombelastography in 1948. Surprisingly, in 1993, an American company obtained a trade mark on this term in the USA, after 45 years of its use as a generic medical term. In order to achieve a global uniformity of the name, the manufacturer of the ROTEM® system (Tem Innovations GmbH, Munich) has renamed its instrument from "ROTEG" into "ROTEM" and the tests accordingly from "EXTEG" into "EXTEM", "INTEG" into "INTEM" etc. in 2003. "TEM" thereby stands for "thromboelastometry" (analogous to the term "thromboelastography"), thus the plotting of the clot firmness.

## Bleeding: Therapeutical options

- DDAVP (Minirin®)
- antifibrinolytics
- protamin
  - after heparin exposition
- local / surgical procedure
- blood products
  - thrombocytes
  - FFP
  - fibrinogen
  - PCC
  - FVIII / FIX / FXIII
- recombinant factors
  - rVIIa

**? what , how much**

**? when , how long**

**As a rule, only the appropriate therapy will stop the bleeding**

## ROTEM® Thromboelastometry system

- 4 channels for simultaneous assays
- Automated testing in ROTEM® *sigma*, standardized electronic pipetting for ROTEM® *delta*

ROTEM® *delta*

ROTEM® *sigma*

## ROTEM® thromboelastometry detection method

In the ROTEM® system, the sample is placed into a cuvette and a cylindrical pin is immersed. Between pin and cuvette remains a gap of 1 mm, which is bridged by the blood or the blood clot. The pin is rotated by a spring alternating to the right and the left. As long as the blood is liquid, this movement is unrestricted. As soon as the blood clots, the clot restricts the rotation of the pin increasingly with rising clot firmness. Thus, the rotation of the pin is inverse proportional to the clot firmness. It is detected optically. An integrated computer calculates the ROTEM® curve as well as its numerical parameters.

In contrast, in the TEG according to Hartert, the cuvette is rotated. The pin is suspended freely from a thin wire and does not move until a clot forms. Because of this free suspension of the pin, the TEG according to Hartert is quite susceptible to vibration and mechanical shocks.
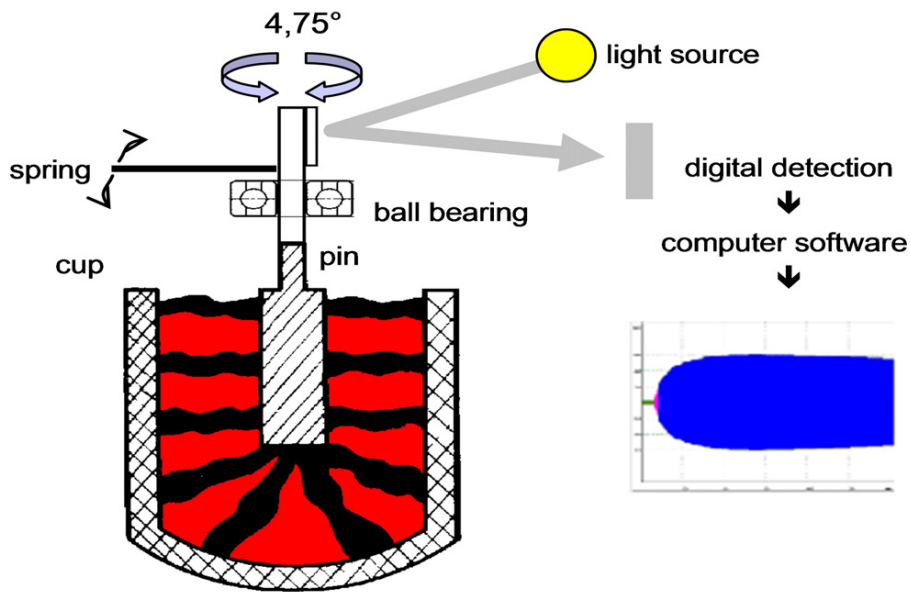
Due to the mechanical measurement principle of ROTEM® analysis, blood or plasma can be analysed likewise. This is advantageous for the point-of-care application, as centrifugation of the sample is omitted there.

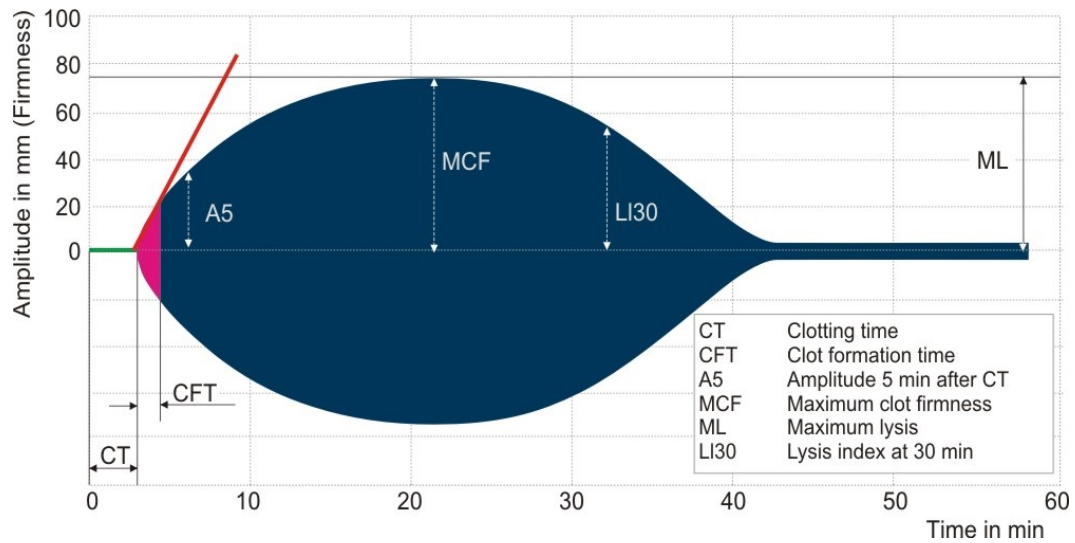## The parameters of ROTEM® thromboelastometry analysis

For historical reasons, the curve is plotted two-sided, expressed in mm.

**CT** (clotting time): time from start of the measurement until initiation of clotting → **initiation of clotting, thrombin formation, start of clot polymerisation**

**CFT** (clot formation time): time from initiation of clotting until a clot firmness of 20 mm is detected → **fibrin polymerisation, stabilisation of the clot with thrombocytes and FXIII**

**MCF** (maximum clot firmness): firmness of the clot → **increasing stabilisation of the clot by the polymerised fibrin, thrombocytes as well as FXIII**

**ML** (maximum lysis): reduction of clot firmness after MCF in relation to MCF → **stability of the clot (ML< 15%) or fibrinolysis (ML > 15% within 1h)**

# ROTEM® thromboelastometry detection method



# ROTEM® thromboelastometry parameters and scaling



| CT | Clotting time |
|------|------------------------|
| CFT | Clot formation time |
| A5 | Amplitude 5 min after CT |
| MCF | Maximum clot firmness |
| ML | Maximum lysis |
| LI30 | Lysis index at 30 min |

# ROTEM® thromboelastometry tests

In the past, "the thrombelastogram" was analysed using freshly drawn blood without the addition of any citrate / calcium and without any activators. The measurements were therefore very time consuming (45 - 60 min.) and quite unspecific.

With the ROTEM®, activated determinations are usually performed. As in the laboratory coagulation analysis, various activators or inhibitors are added to the sample, in order to represent different processes of haemostasis. For the analysis, citrated blood is usually used.

In **EXTEM,** coagulation is activated by a small amount of tissue thromboplastin (tissue factor). This typically leads to the initiation of clot formation within 70 seconds. Thus, clot formation can be assessed within 10 minutes.

In **INTEM,** coagulation is activated via the contact phase (as in the aPTT and ACT). The INTEM is therefore sensitive for factor deficiencies of the intrinsic system (e.g. FVIII) and for the presence of heparin in the sample.

In **FIBTEM,** coagulation is activated as in EXTEM. By the addition of cytochalasin D, the thrombocytes are blocked. The resulting clot is therefore only depending on fibrin formation and fibrin polymerisation.

In **APTEM,** coagulation is also activated as in EXTEM. By the addition of aprotinin or tranexamic acid in the reagent, fibrinolytic processes are inhibited *in vitro*. The comparison of EXTEM and APTEM allows for a rapid detection of fibrinolysis. Furthermore, APTEM enables the estimation if an antifibrinolytic therapy alone normalises the coagulation or if additional measures have to be taken (e.g. administration of fibrinogen).

In **HEPTEM,** coagulation is activated as in INTEM. The addition of heparinase in the reagent degrades heparin present in the sample and therefore allows the ROTEM® analysis in heparinised samples.

| Reagent type | Test name for each reagent type | | | | |
|---|---|---|---|---|---|
| *Single Use* | EXTEM S | FIBTEM S | APTEM S | INTEM S | HEPTEM S |
| *Liquid* | EXTEM (L) | FIBTEM | APTEM | INTEM | HEPTEM |
| *Cartridge* | EXTEM C | FIBTEM C | APTEM C | INTEM C | HEPTEM C |

# ROTEM® *thromboelastometry tests*
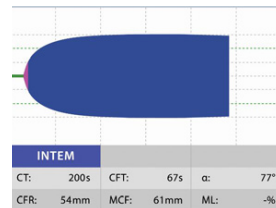
**EXTEM (L, S, C)**: activation of clot formation by thromboplastin (tissue factor).

Assessment of factors VII, X, V, II, I, platelets, fibrinolysis

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 67s | CFT: | 87s | α: | 73° |
| CFR: | 54mm | MCF: | 57mm | ML: | -% |

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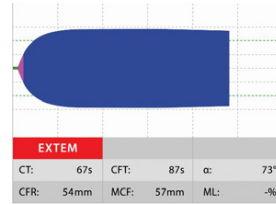
**INTEM (S, C)**: activation of clot formation via the contact phase.

Assessment of factors XII, XI, IX, VIII, X, V, II, I, platelets, fibrinolysis

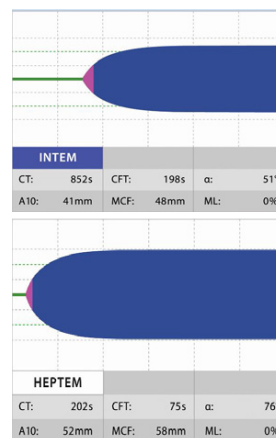| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 200s | CFT: | 67s | α: | 77° |
| CFR: | 54mm | MCF: | 61mm | ML: | -% |

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**FIBTEM (S, C)**: activation as in EXTEM with the addition of cytochalasin D, a platelet blocking substance. In the FIBTEM assay, fibrinogen levels and fibrin polymerisation can be assessed in a functional way.

| FIBTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 66s | CFT: | -s | α: | 57° |
| CFR: | 9mm | MCF: | 10mm | ML: | -% |

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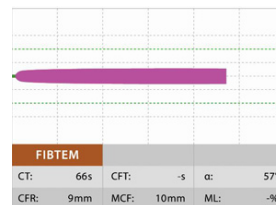
**APTEM (S, C)**: activation as in EXTEM with the addition of aprotinin or tranexamic acid, fibrinolysis inhibitors. In an assay comparing APTEM to EXTEM, fulminant hyperfibrinolysis can be recognised within 10-20 minutes.

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 59s | CFT: | 130s | α: | 65° |
| A10: | 44mm | MCF: | 48mm | ML: | 100% |

| APTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 62s | CFT: | 132s | α: | 64° |
| A10: | 44mm | MCF: | 55mm | ML: | 0% |

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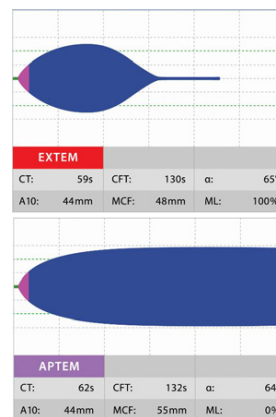
**HEPTEM (S, C)**: activation as in INTEM with the addition of heparinase. Heparinase degrades heparin. When HEPTEM results are compared to INTEM, heparin related coagulation disturbances can be specifically detected.

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 852s | CFT: | 198s | α: | 51° |
| A10: | 41mm | MCF: | 48mm | ML: | 0% |

| HEPTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 202s | CFT: | 75s | α: | 76° |
| A10: | 52mm | MCF: | 58mm | ML: | 0% |

## ROTEM® thromboelastometry expected values

On the opposite page, typical ROTEM® thromboelastometry values are shown, which are found when healthy patients without coagulation disorders are analysed. Depending on the examined population, these values can vary (for example, when healthy younger persons are assessed, lower MCF values are found). It is therefore recommended, at introduction of ROTEM®, to analyse some patients without pathological findings in order to establish respective 'local' reference ranges.

## Interpretation of HEPTEM / APTEM / FIBTEM

In HEPTEM and APTEM, the comparison with INTEM respectively EXTEM is important for the interpretation. A shortening of the clotting time in HEPTEM as compared to INTEM indicates a heparin effect.

The 'spindle' shape of the TEMogram in the EXTEM, INTEM or FIBTEM assays gives an indication of fibrinolysis. The reversal back to a normal TEMogram shape in the APTEM assay confirms the fibrinolysis and allows to judge the patient's clot quality after an optional hyperfibrinolytic treatment.

A reduced MCF in FIBTEM indicates a reduced fibrinogen level and / or a clot polymerisation inhibition. Discrepancies between FIBTEM and the fibrinogen determination in the laboratory are frequently found, as FIBTEM is much more sensitive to clot polymerisation disorders than conventional laboratory assays.

## Classification of the ROTEM® results

The lower right table shows an orientating classification of the ROTEM® results based on our clinical experiences.

Depending on the situation and possible comorbidities of the patient, different target ranges will be aimed for the MCF, respectively CFT. During surgery, we typically aim for a MCF value of at least 40 mm and a CFT of maximal 300 s. In persistent bleeding situations, an almost normalisation of the ROTEM® findings will be aimed for.

Hyperfibrinolysis (lysis of the clot *in vitro*) is always pathological and can be treated with an antifibrinolytic drug. Nevertheless, hyperfibrinolysis can be self-limiting, which can be checked by repeated determinations without any preceding therapy.

# ROTEM® thromboelastometry reference ranges

(Lang et al. 2006 for ROTEM® *delta*, preliminary for ROTEM® *sigma*)

| Test / Parameter | CT (s) | CFT (s) | A10 (mm) | MCF (mm) | LI60 (%) |
|---|---|---|---|---|---|
| EXTEM (S) | 38-79 | 34-159 | 43-65 | 50-72 | ≥ 85* |
| EXTEM C | 50-80 | 46-149 | 43-63 | 55-72 | ≥ 94 |
| INTEM (S) | 100-240 | 30-110 | 44-66 | 50-71 | ≥ 85* |
| INTEM C | 161-204 | 62-130 | 43-62 | 51-69 | ≥ 87 |
| HEPTEM (S, C) | Comparison with INTEM (S,C). A better clot formation in HEPTEM (S,C) as compared to INTEM (S,C) indicates the presence of heparin or heparin-like anticoagulants in the sample. | | | | |
| APTEM (S, C) | Comparison with APTEM (S,C). A better clot formation in APTEM (S,C) as compared to EXTEM (S,C) is a sign of hyperfibrinolysis. | | | | |
| FIBTEM (S) | n.d. | n.d. | 7-23 | 9-25 | n.d. |
| FIBTEM C | n.d. | n.d. | 6-21 | 6-21 | ≥ 89 |

*Historical value

## INTEM (S) / EXTEM (S) results - Clinical interpretation

**MCF**

MCF > 72 mm: enhanced haemostatic reserve

MCF 50-72 mm: normal range

MCF 46-49 mm: usually unimpaired haemostasis with reduced reserve

MCF 40-45 mm: bleeding risk

MCF 30-39 mm: high bleeding risk

MCF < 30 mm: usually no effective haemostasis

**CFT**

CFT   34-159 s: normal range

CFT 160-220 s: usually unimpaired haemostasis with reduced reserve

CFT 221-300 s: bleeding risk

CFT 301-400 s: high bleeding risk

CFT > 400 s: usually no effective haemostasis

**Fibrinolysis**

Lysis of the clot within 20 minutes (fulminant lysis): usually acute bleeding. Lysis of the clot within 20 – 40 minutes: high bleeding risk. Lysis of the clot after more than 40 minutes: frequently clinically insignificant, may however raise to fulminant lysis.

## *Assessment of the ROTEM® thromboelastometry analysis*

The ROTEM® analysis covers the whole process of whole blood coagulation, from the formation of the first fibrin strands over the maximum firmness of the clot until its lysis.

The assessment of the ROTEM® analysis is carried out along the time axis (from left to right): A *disturbed activation of coagulation* is indicated by a prolonged clotting time. As causes, a factor deficiency or a heparin effect have to be considered. The comparison of INTEM and HEPTEM allows for a specific detection of a heparin effect.

An *abnormal clot formation* is indicated by a prolonged clot formation time (CFT) and/or a reduced clot firmness (A10/MCF). The CFT is thereby influenced stronger by a clot polymerisation disorder than the MCF.

A prolonged CFT with at the same time normal A10/MCF indicates therefore a polymerisation disorder, whereas a reduced A10/MCF with a normal CFT rather indicates a deficiency of clottable substrate (fibrinogen and/or platelets).

*Fibrinolysis* is detected by the lysis of the clot (ML > 15%) or by the finding of a better clot formation (shorter CFT, greater MCF) in APTEM (S,C) as compared to EXTEM (S,C). If in APTEM (S,C), with the occurrence of the typical pattern of a hyperfibrinolysis (spindle shaped, total lysis of the clot firmness) in EXTEM (S,C) (as in INTEM (S,C), FIBTEM (S,C), HEPTEM (S,C)), the hyperfibrinolysis is not present, then hyperfibrinolysis is confirmed.

*Limitations*

In the interpretation of ROTEM® analysis it is important to know and consider the limitations of the method. The ROTEM® *delta* and *sigma* tests are not sensitive to the effect of the platelet inhibitors Aspirin®, clopidogrel and Reopro® (only in supra-therapeutic doses). In this situation, ROTEM® *platelet* analysis should be performed. Also, the effect of the von Willebrand factor is not detected. Furthermore, a normal ROTEM® analysis does not exclude the anticoagulants Orgaran®, pentasaccharide, low-molecular-weight heparin as well as oral anticoagulants such as Warfarin®. For analysis of these factors, other diagnostic tests have to be performed.
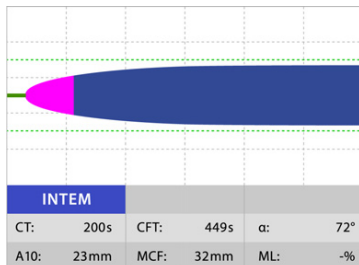
# ROTEM® thromboelastometry: detection and therapy

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 852s | CFT: | 198s | α: | 51° |
| A10: | 41mm | MCF: | 48mm | ML: | 0% |
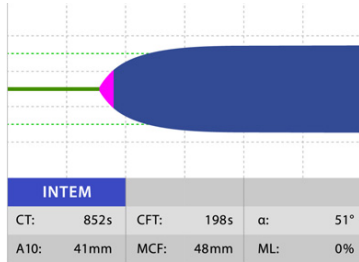
### Activation of coagulation

=> protamin, FFP of PCC
=> differentiation with HEPTEM

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 200s | CFT: | 449s | α: | 72° |
| A10: | 23mm | MCF: | 32mm | ML: | -% |

### Clot formation

=> infusion of platelets and/or fibrinogen/FFP
=> differentiation with FIBTEM

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 200s | CFT: | 88s | α: | 74° |
| A10: | 46mm | MCF: | 48mm | ML: | 100% |
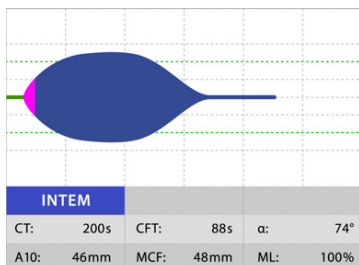
### Fibrinolysis

=> infusion of antifibrinolytics
=> more rapid detection with the combination of APTEM-EXTEM

## Limitations of ROTEM® thromboelastometry

Platelet inhibitors:

- no detection of Aspirin®
- no detection of clopidogrel/Plavix®
- no detection of von Willebrand syndrome
- poor sensitivity to Reopro®

Anticoagulants:

- poor sensitivity to low molecular weight heparin, Orgaran® and pentasaccharide
- poor sensitivity to oral anticoagulants
  (coumarins: Warfarin®, etc.)

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Consequence:

- Combine with other methods (e.g. ROTEM® *platelet aggregation*) where required.
- Consider limitations for interpretation!

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## *Performance of ROTEM® thromboelastometry analysis*

As in all diagnostic tests, correct pre-analytics and correct performance of the assay are essential for meaningful results.

As ROTEM® is run directly with citrated whole blood, a specific sample preparation is not necessary. "Correct sampling" means: Complete filling of the sampling tube (in order to ensure the correct citrate-blood ratio); the assurance, during sampling from catheters, that no contamination with heparin or other anticoagulants occurs; and the avoidance of haemolysis during sampling (prevent excessive stasis, use of a needle with sufficiently wide diameter). We typically aim for an analysis of the sample within 2 hours from the sampling of the blood
(if required up to four hours). The analysis of samples that have been transported by a tube system is usually possible. As a precaution this should be verified (split the sample and analyse with/without transport by the tube system).

The steps to be performed for ROTEM® *delta* analysis are shown on the right. The test operation is generally simple - also for staff without any laboratory experience. Nevertheless, a certain familiarisation period and motivation are necessary.

The ROTEM® *sigma* offers a fully automated, cartridge based system. The familiarisation is reduced to a minimum.

Apart from the correct performance of the analysis – as in every laboratory test – the plausibility control of the analysis is important. Measurements with irregular shapes (steep rise or fall of the clot firmness, noised curves, and start of the clot formation in less than 20 seconds), generally accompanied by error messages, should be repeated.

When using liquid reagents on the ROTEM® system, it has to be controlled optically if the liquid was actually aspirated while pipetting the liquids. A typical source of error is that the pipette tip has not been immersed into the liquid.

Like any other in vitro diagnostic system, the ROTEM® system requires quality control by performing tests with standardised quality control (QC) materials. The ROTEM® standardised system controls ROTROL N and ROTROL P are based upon human plasma and will show reaction curves at two different levels.

## *Performing a ROTEM® delta test*
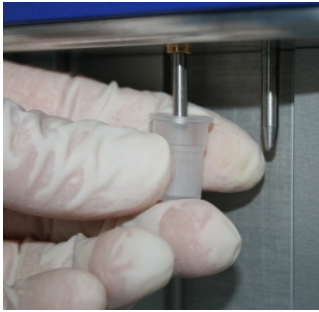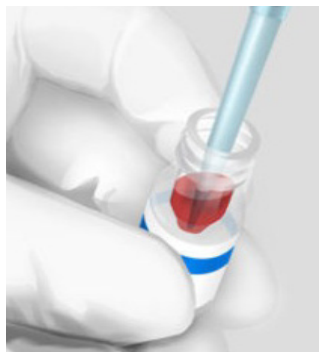


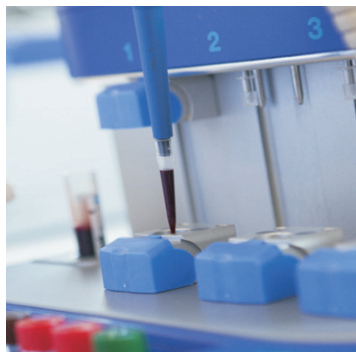1. Properly attach pin



2. Insert cup and bring to position using the MC rod
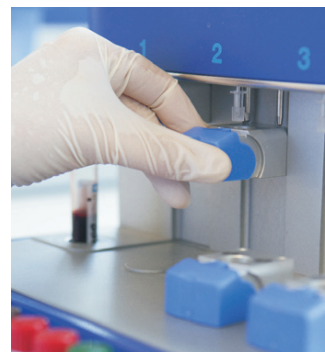


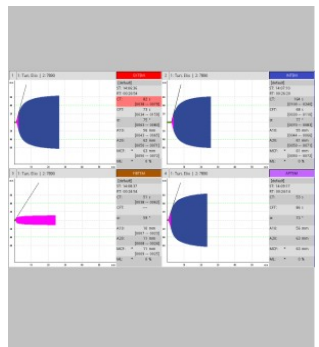3. Select test, enter/ scan patient data



4. Pipetting steps are displayed on the screen



5. Pipetting and mixing of reagents and blood sample



6. Insert cup holder in measurement position



7. On screen display of TEMograms and numeric parameters



8. Discard used cup and pin

# Interpretation of ROTEM® thromboelastometry analysis: examples performed on ROTEM® delta with liquid reagents

On each of the next pages, three typical combinations of ROTEM® tests are shown. The figures are displayed exactly as on the screen of the ROTEM® system. With each measurement you see the respective test name above the parameters. In each case, the figures represent 1-4 measurements of one sample. The measurements are not commented on the right hand page. This shall give the reader the opportunity to reflect the interpretation and therapy on his own.

## Sample 1:

normal coagulation in the ROTEM®. EXTEM and INTEM show a normal coagulation activation (CT normal), normal clot formation (CFT and MCF normal) as well as a stable clot (no lysis of the clot in EXTEM, INTEM or FIBTEM). The FIBTEM shows a normal fibrin clot.

Should the patient bleed clinically, the following causes have to be considered: surgical cause of bleeding, Warfarin® therapy (low sensitivity of EXTEM), Aspirin®, clopidogrel, von Willebrand syndrome (for these drugs respectively pathologies ROTEM® delta and ROTEM® sigma tests show low sensitivity) as well as errors (e.g. sample mix-up).

| EXTEM | | | |
|---|---|---|---|
| CT: 67s | A5: 44mm | A10: 54mm | |
| MCF: 57mm | ML: -% | LI60: -% | |

| INTEM | | | |
|---|---|---|---|
| CT: 200s | A5: 44mm | A10: 54mm | |
| MCF: 61mm | ML: -% | LI60: -% | |

| FIBTEM | | | |
|---|---|---|---|
| CT: 66s | A5: 8mm | A10: 9mm | |
| MCF: 10mm | ML: -% | LI60: -% | |

| APTEM | | | |
|---|---|---|---|
| CT: 74s | A5: 43mm | A10: 53mm | |
| MCF: 61mm | ML: -% | LI60: -% | |
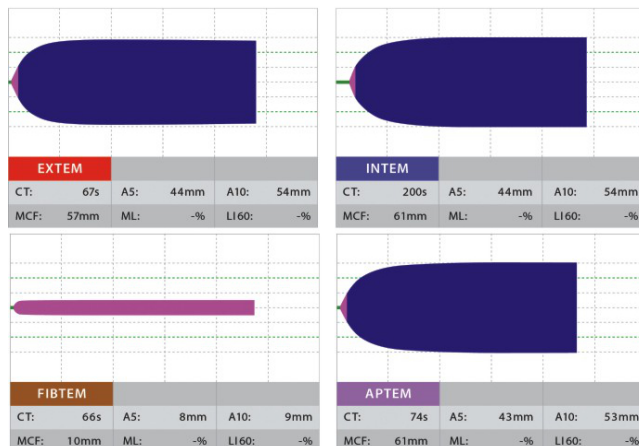
*Sample 2:*

strongly prolonged clot formation time (CFT), strongly reduced clot firmness (MCF) in EXTEM and INTEM show a strongly reduced haemostatic capacity. The zero line in FIBTEM (no clotting) shows a strongly reduced fibrinogen level and/or a disturbed fibrin polymerisation. The first line treatment would be a highly dosed administration of fibrinogen concentrate (2-6 g) or cryoprecipitate or a larger amount of FFP (5-15 units). In cases of massive bleeding it would be considered to concomitantly transfuse platelets.

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 57s | A5: | 15mm | A10: | 23mm |
| MCF: | 35mm | ML: | -% | LI60: | -% |

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 200s | A5: | 15mm | A10: | 23mm |
| MCF: | 32mm | ML: | -% | LI60: | -% |

| FIBTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 3526s | A5: | -mm | A10: | -mm |
| MCF: | -mm | ML: | -% | LI60: | -% |

| APTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 52s | A5: | 14mm | A10: | 25mm |
| MCF: | 35mm | ML: | -% | LI60: | -% |
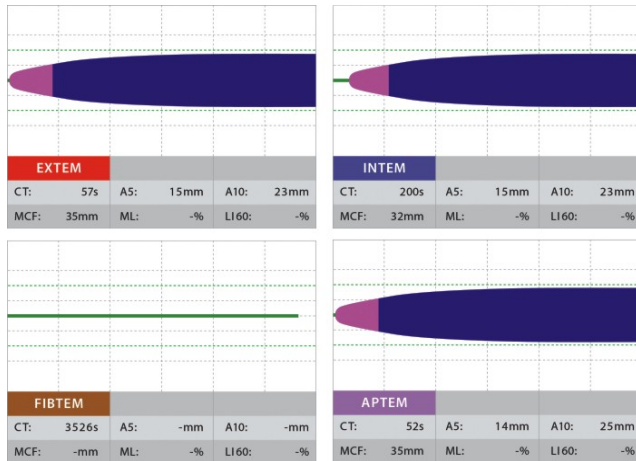
*Sample 3:*

fibrinolysis (lysis of the clot in EXTEM, INTEM and FIBTEM) with an at the same time borderline acceptability of MCF (MCF = 47 mm in APTEM). Good fibrin clot in FIBTEM. Therapy would be an antifibrinolytic drug. In cases of persisting bleeding, administration of platelets would be suggested (for correction of the clot formation).

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 68s | A5: | 37mm | A10: | 43mm |
| MCF: | 45mm | ML: | 94% | LI60: | -% |

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 156s | A5: | 36mm | A10: | 41mm |
| MCF: | 42mm | ML: | 98% | LI60: | -% |

| FIBTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 64s | A5: | 2mm | A10: | 3mm |
| MCF: | 8mm | ML: | 100% | LI60: | -% |

| APTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 75s | A5: | 27mm | A10: | 38mm |
| MCF: | 47mm | ML: | 0% | LI60: | -% |
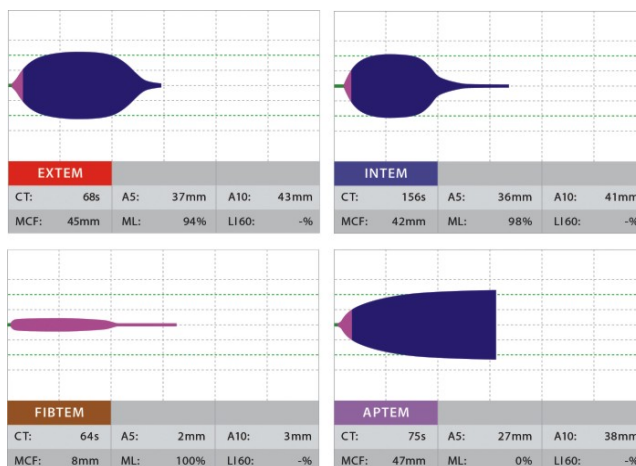
*Sample 4:*

borderline acceptability of clot firmness in INTEM and EXTEM. No evidence of a hyperfibrinolysis. Normal fibrin clot in FIBTEM. Comparable results are sometimes found with or without clinical bleeding. First line therapy for improvement of clot formation would be the administration of platelets. In any case, the patient has typically only a poor haemostatic reserve at further haemodilution. Depending on the situation (further surgical blood loss expected or not), a correction of coagulation can be considered also without the occurrence of acute bleeding.

| EXTEM | | | | |
|---|---|---|---|---|
| CT: | 109s | A5: | 23mm | A10: 31mm |
| MCF: | 38mm | ML: | -% | LI60: -% |

| INTEM | | | | |
|---|---|---|---|---|
| CT: | 236s | A5: | 24mm | A10: 33mm |
| MCF: | 42mm | ML: | -% | LI60: -% |

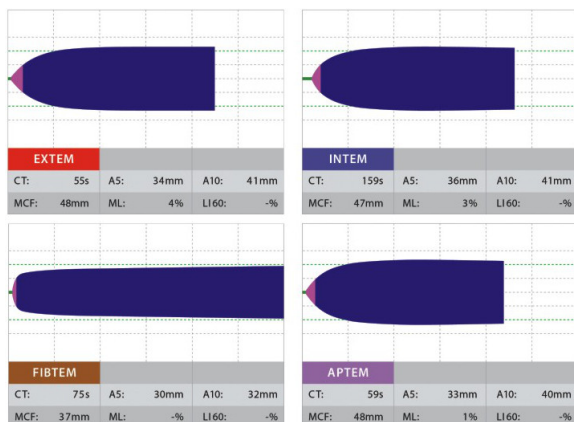| FIBTEM | | | | |
|---|---|---|---|---|
| CT: | 67s | A5: | 14mm | A10: 15mm |
| MCF: | 16mm | ML: | -% | LI60: -% |

| APTEM | | | | |
|---|---|---|---|---|
| CT: | 98s | A5: | 23mm | A10: 31mm |
| MCF: | 40mm | ML: | -% | LI60: -% |
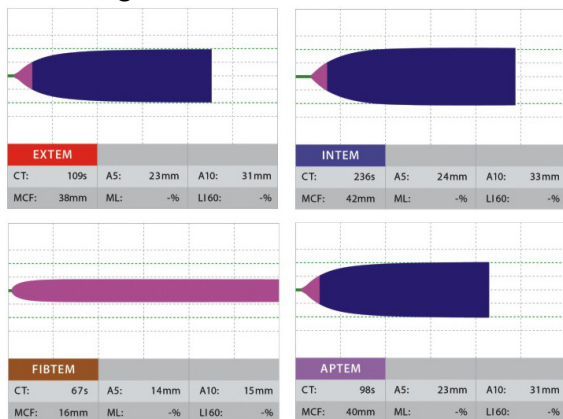
**Sample 5:**

just abnormal / still normal clot formation in EXTEM and INTEM (depending on the investigated reference population). The relatively high clot firmness in FIBTEM (MCF = 37 mm) can lead to a normal whole blood coagulation, also when thrombocytopenia is present. Therefore a blood count should be determined in this situation (in order to assess platelet count directly), and the coagulation in course of further haemodilution should be controlled. Patients with high fibrinogen levels usually tolerate a thrombocytopenia better than patients with normal or reduced fibrinogen levels. Nevertheless, it is reasonable to keep an eye on the blood count in these situations.

| EXTEM | | | | |
|---|---|---|---|---|
| CT: | 55s | A5: | 34mm | A10: 41mm |
| MCF: | 48mm | ML: | 4% | LI60: -% |

| INTEM | | | | |
|---|---|---|---|---|
| CT: | 159s | A5: | 36mm | A10: 41mm |
| MCF: | 47mm | ML: | 3% | LI60: -% |

| FIBTEM | | | | |
|---|---|---|---|---|
| CT: | 75s | A5: | 30mm | A10: 32mm |
| MCF: | 37mm | ML: | -% | LI60: -% |

| APTEM | | | | |
|---|---|---|---|---|
| CT: | 59s | A5: | 33mm | A10: 40mm |
| MCF: | 48mm | ML: | 1% | LI60: -% |

***Sample 6:***

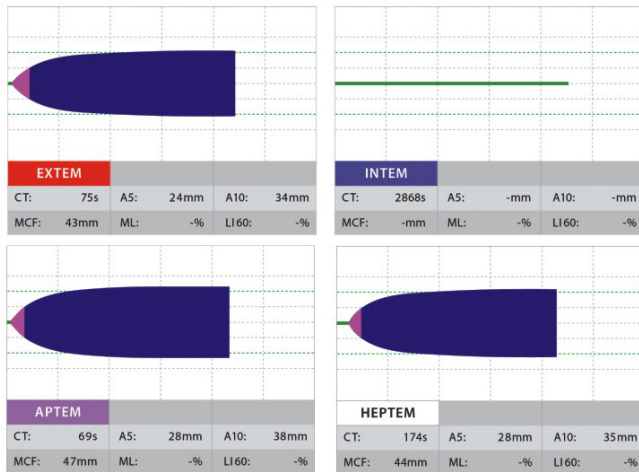combined haemostasis disorder. We see a hyperfibrinolysis (lysis of the clot in EXTEM and INTEM), a prolonged CT in INTEM (heparin effect), a strongly reduced clot firmness in APTEM (indicates a disturbance of clot formation exceeding fibrinolysis) as well as a zero line (no clotting) in FIBTEM (reduced fibrinogen and / or polymerisation disorder). This result is not compatible with clinically normal haemostasis and requires a rapid combined treatment: an antifibrinolytic drug for the treatment of the hyperfibrinolysis, fibrinogen or FFP (large doses) for improvement of the clot formation. In cases of such an insufficient clot formation, a simultaneous platelet administration is also recommended (it would however also be possible to give fibrinogen or FFP first and then check the clot formation).

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 88s | A5: | 19mm | A10: | 23mm |
| MCF: | 26mm | ML: | 100% | LI60: | -% |

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 670s | A5: | 19mm | A10: | 20mm |
| MCF: | 20mm | ML: | 95% | LI60: | -% |

| FIBTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 3721s | A5: | -mm | A10: | -mm |
| MCF: | -mm | ML: | -% | LI60: | -% |

| APTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 99s | A5: | 17mm | A10: | 25mm |
| MCF: | 34mm | ML: | 18% | LI60: | -% |
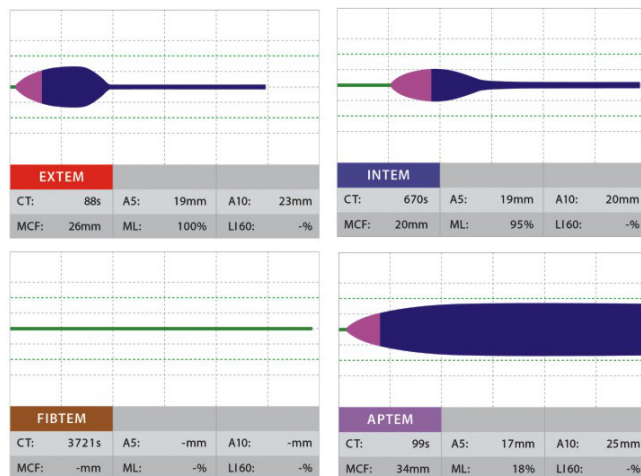
*Sample 7:*

detection of heparin (strongly prolonged CT in INTEM), corrected in HEPTEM. In this situation one can wait (short half-life of heparin) or neutralize the heparin using protamin (during acute bleeding). As seen in HEPTEM, the clot firmness is reduced but still within an acceptable range. Therefore one would usually neutralise the heparin first and see if bleeding stops. If bleeding continues, administration of FFP, fibrinogen or platelets might be necessary.
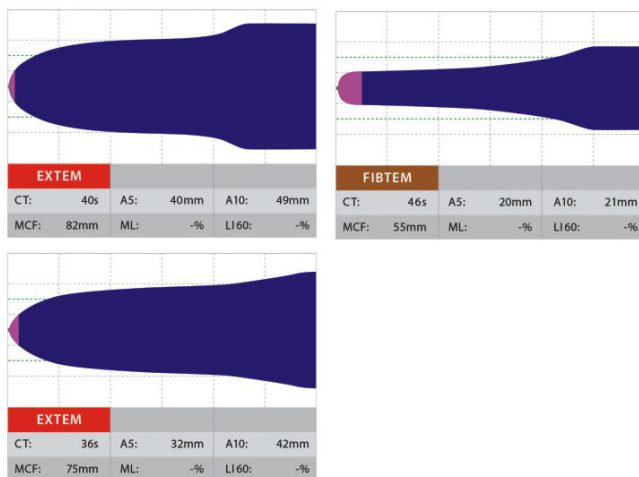
| EXTEM | | | | |
|-------|---|---|---|---|
| CT: | 75s | A5: | 24mm | A10: | 34mm |
| MCF: | 43mm | ML: | -% | LI60: | -% |

| INTEM | | | | |
|-------|---|---|---|---|
| CT: | 2868s | A5: | -mm | A10: | -mm |
| MCF: | -mm | ML: | -% | LI60: | -% |

| APTEM | | | | |
|-------|---|---|---|---|
| CT: | 69s | A5: | 28mm | A10: | 38mm |
| MCF: | 47mm | ML: | -% | LI60: | -% |

| HEPTEM | | | | |
|--------|---|---|---|---|
| CT: | 174s | A5: | 28mm | A10: | 35mm |
| MCF: | 44mm | ML: | -% | LI60: | -% |

*Sample 8:*

erroneous measurement. This error can occur if the pin was not attached completely onto the axis or the cup was not inserted sufficiently into the cup holder. Cup and pin will be in contact with each other when the cup holder is put in place. An error message appears, the measurement should be stopped and started again.

| HEPTEM | | | | |
|--------|---|---|---|---|
| CT: | 172s | A5: | 43mm | A10: | 43mm |
| MCF: | 43mm | ML: | -% | LI60: | -% |
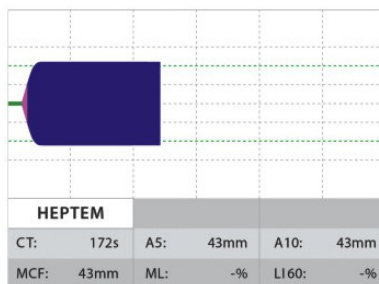
**Sample 9**:

erroneous measurement. After MCF is reached, there is a further increase of the clot firmness after some time. An error message, which is caused by a drying of the sample, appears. A falsely-high MCF is detected. In this case it should be checked whether the cup holder is dirty at its upper surface and the corresponding area on the lower side of the instrument should be cleaned. For this, a moist cloth should be used and no sprays should be applied on the instrument as this could lead to damage of the ball bearing. Should there be no contamination, the cup holder or its plastic clip might be damaged and need replacement.



| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 40s | A5: | 40mm | A10: | 49mm |
| MCF: | 82mm | ML: | -% | LI60: | -% |

| FIBTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 46s | A5: | 20mm | A10: | 21mm |
| MCF: | 55mm | ML: | -% | LI60: | -% |

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 36s | A5: | 32mm | A10: | 42mm |
| MCF: | 75mm | ML: | -% | LI60: | -% |

> **Note:** test results should represent only one aspect of any therapeutic decision. Always the situation (bleeding yes - no), the plausibility of the findings, patient history, comorbidities as well as the expected (surgical) course of the case has to be taken into account. Further tests may be performed if required (PT, antithrombin, d-dimer, platelet function tests, blood count).

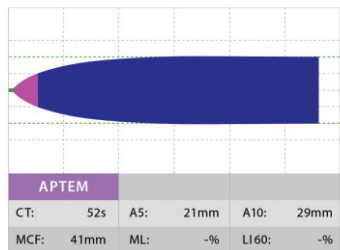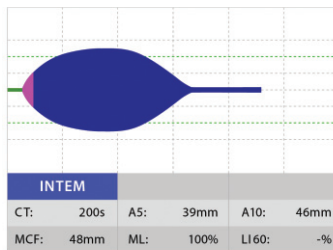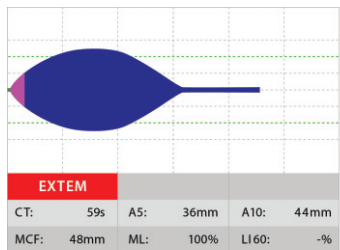**Clinical cases (studied with the ROTEM® liquid reagents)**:

On the following pages, clinical cases with the corresponding ROTEM® analyses are shown.

*Case 1:*

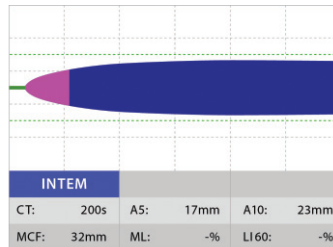On the right page, 3 coagulation conditions during a multiple trauma treatment are shown.

**The first test time point** shows fibrinolysis in EXTEM and INTEM. In APTEM, no lysis appears due to addition of aprotinin in the reagent.
In APTEM, we see an abnormal but still acceptable clot firmness.

The therapeutic consequence was the administration of an antifibrinolytic drug.

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 59s | A5: | 36mm | A10: | 44mm |
| MCF: | 48mm | ML: | 100% | LI60: | -% |

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 200s | A5: | 39mm | A10: | 46mm |
| MCF: | 48mm | ML: | 100% | LI60: | -% |

| APTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 52s | A5: | 21mm | A10: | 29mm |
| MCF: | 41mm | ML: | -% | LI60: | -% |

**9:45: Fibrinolysis: therapeutic consequence: antifibrinolytic drug**

**The second test time point** shows the therapeutic success of the antifibrinolytic drug administration (no lysis detected any more). Nevertheless we see a strongly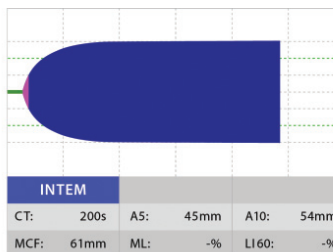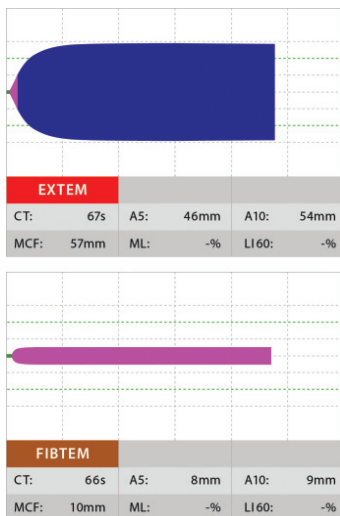 reduced clot firmness (MCF) as well as a strongly prolonged clot formation time (CFT), which was the indication for platelet and FFP administration.

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 57s | A5: | 16mm | A10: | 23mm |
| MCF: | 35mm | ML: | -% | LI60: | -% |

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 200s | A5: | 17mm | A10: | 23mm |
| MCF: | 32mm | ML: | -% | LI60: | -% |

| APTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 52s | A5: | 16mm | A10: | 25mm |
| MCF: | 35mm | ML: | -% | LI60: | -% |
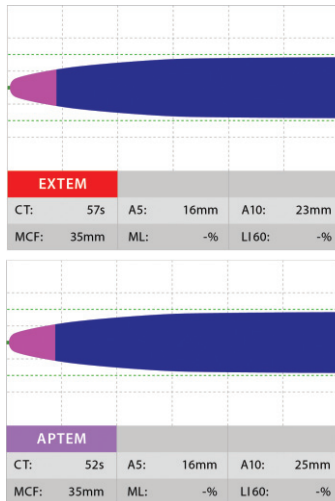
**10:20: reduced clot firmness:
consequence: Platelet and FFP administration**

**The third test time point** represents a normal, whole blood coagulation towards the end of the surgery.

| EXTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 67s | A5: | 46mm | A10: | 54mm |
| MCF: | 57mm | ML: | -% | LI60: | -% |

| INTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 200s | A5: | 45mm | A10: | 54mm |
| MCF: | 61mm | ML: | -% | LI60: | -% |

**12:23: normal whole blood coagulation**

| FIBTEM | | | | | |
|---|---|---|---|---|---|
| CT: | 66s | A5: | 8mm | A10: | 9mm |
| MCF: | 10mm | ML: | -% | LI60: | -% |

**Case 2:**

The second case example shows the therapy control with ROTEM® in a situation in which initially therapy was guided on the basis of the routine laboratory.

We thank Dr. Georg Pfanner, consultant anaesthetist at the Department of Anaesthesia and Critical Care of the Academic Teaching Hospital Feldkirch, Austria (georg.pfanner@lkhf.at), for recording and providing us with this case.

The situation: a patient with a multiple trauma is admitted to the hospital. The patient has been already notably diluted (4 l of infusions).
The initial laboratory findings show a prolonged PT (factor deficiency), a low fibrinogen, low antithrombin and a platelet count of 101.000/µl.

On the basis of these results, fibrinogen, PCC and antithrombin were administered. Because of a strongly increased D-dimer result, the question of an antifibrinolytic therapy aroused.

In the persistent bleeding situation, a control with ROTEM® is carried out. The results show a strongly abnormal clot formation (clot firmness reduced, clot formation time prolonged), in spite of the initial therapy. Despite the initially acceptable platelet count, there is no sufficient whole blood coagulation.
After therapy with fibrinogen, platelets and PCC, clinically a clear improvement of the clinical haemostasis was found together with a normalised whole blood coagulation in ROTEM®.

**Initial situation:**

Polytrauma => GCS 3, suspected thorax-trauma, pelvic fracture

**Severe bleeding from nose, mouth, multiple wounds in the neck**

Infusion therapy: HES 1000 ml, cristalloid 3500 ml

**Laboratory results in hospital (65 min. after arrival):**

PT 40%, aPTT 55.8s, fibrinogen 0.87 g/l, AT 49%, d-dimer 39.7, thrombocytes 101.000/µl

Assessment: reduced fibrinogen level, factor levels low, antithrombin lowered (similar to PT), platelet count still sufficient. Fibrinolysis suspected (very high d-dimer).
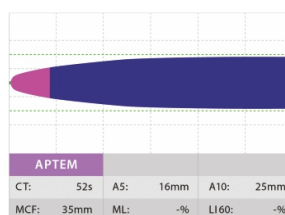
**Initial therapy:** 3 g fibrinogen (Haemocomplettan®), 4000 units PPSB, 3000 units antithrombin

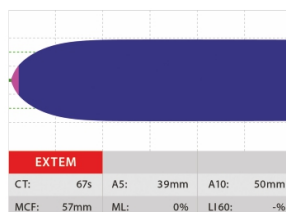**Therapy sufficient? Anti-fibrinolytic therapy required ?**
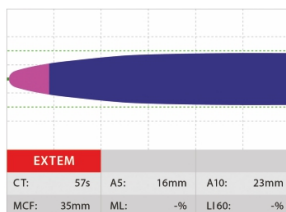
**Therapy control 1:**
Whole blood coagulation is strongly abnormal in spite of the initial therapy. After blocking the platelets (FIBTEM), a weak fibrin clot is observed. Despite strongly elevated d-dimers no sign of hyperfibrinolysis (APTEM=EXTEM).

| EXTEM | | | | |
|---|---|---|---|---|
| CT: | 57s | A5: | 16mm | A10: | 23mm |
| MCF: | 35mm | ML: | -% | LI60: | -% |

| FIBTEM | | | | |
|---|---|---|---|---|
| CT: | 185s | A5: | 2mm | A10: | 3mm |
| MCF: | 3mm | ML: | -% | LI60: | -% |

| APTEM | | | | |
|---|---|---|---|---|
| CT: | 52s | A5: | 16mm | A10: | 25mm |
| MCF: | 35mm | ML: | -% | LI60: | -% |

**3 g fibrinogen, 1 platelet concentrate, 2000 IU PCC**

**Therapy control 2:**
After infusion of fibrinogen and a dose of platelet concentrate coagulation normalises. Further on no sign of hyperfibrinolysis.

| EXTEM | | | | |
|---|---|---|---|---|
| CT: | 67s | A5: | 39mm | A10: | 50mm |
| MCF: | 57mm | ML: | 0% | LI60: | -% |

| FIBTEM | | | | |
|---|---|---|---|---|
| CT: | 71s | A5: | 14mm | A10: | 15mm |
| MCF: | 17mm | ML: | -% | LI60: | -% |

| APTEM | | | | |
|---|---|---|---|---|
| CT: | 62s | A5: | 35mm | A10: | 44mm |
| MCF: | 55mm | ML: | 0% | LI60: | -% |
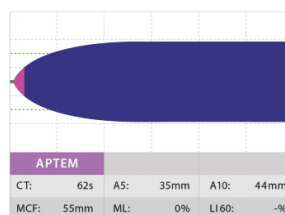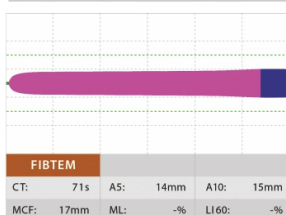
→ OP → minimal bleeding
→ Successful wound treatment and tamponade of the ENT injury

## *Differential diagnosis and therapy: thromboelastometry algorithms*

On the right hand page, the differential diagnostic and therapeutic algorithm used in the Clinic Cologne-Merheim is shown (Reference: Vorweg M, Hartmann B, Knuttgen D, Jahn MC, Doehn M. Management of fulminant fibrinolysis during abdominal aortic surgery. J Cardiothorac Vasc Anesth. 2001 Dec;15(6):764-7).

This algorithm shows how coagulation activation, clot formation and fibrinolysis are assessed starting from EXTEM and INTEM as screening tests. If no coagulopathy is found, other reasons for the bleeding are evaluated: a surgical bleeding or coagulopathy which is not detected by ROTEM® analysis (Aspirin®, von Willebrand factor, warfarin?).

The combination of EXTEM and APTEM allows for a rapid detection of a fulminant fibrinolysis.

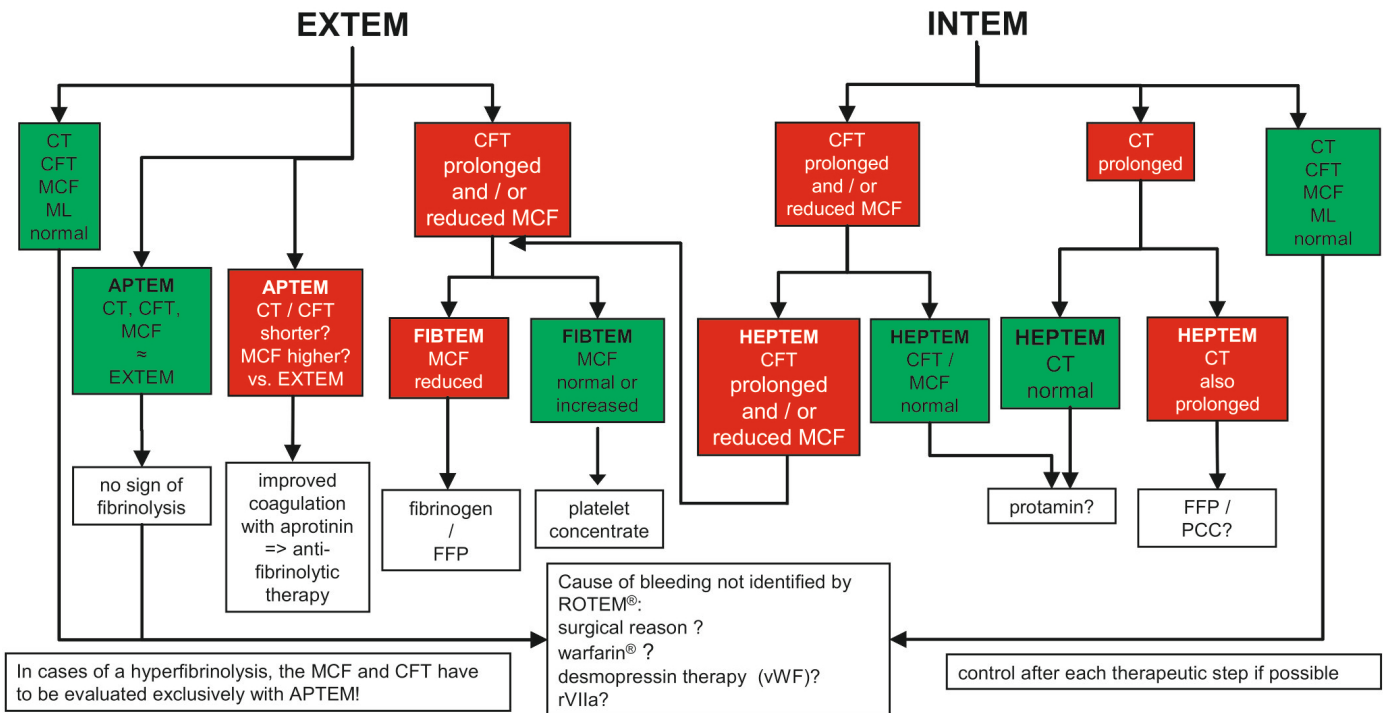The cause for a reduced clot firmness can be differentiated by performing a FIBTEM test.

With the HEPTEM test, a prolonged clotting time in INTEM can be differentiated.

Thus, many causes of acute haemostasis disorders can be recognised rapidly and in consequence be treated appropriately.

**EXTEM**

**INTEM**

CT
CFT
MCF
ML
normal

CFT
prolonged
and / or
reduced MCF

CFT
prolonged
and / or
reduced MCF

CT
prolonged

CT
CFT
MCF
ML
normal

**APTEM**
CT, CFT,
MCF
≈
EXTEM

**APTEM**
CT / CFT
shorter?
MCF higher?
vs. EXTEM

**FIBTEM**
MCF
reduced

**FIBTEM**
MCF
normal or
increased

**HEPTEM**
CFT
prolonged
and / or
reduced MCF

**HEPTEM**
CFT /
MCF
normal

**HEPTEM**
CT
normal

**HEPTEM**
CT
also
prolonged

no sign of
fibrinolysis

improved
coagulation
=> anti-
fibrinolytic
therapy

fibrinogen
/
FFP

platelet
concentrate

protamin?

FFP /
PCC?

Cause of bleeding not identified by
ROTEM®:
surgical reason ?
warfarin® ?
desmopressin therapy (vWF)?
rVIIa?

In cases of a hyperfibrinolysis, the MCF and CFT have
to be evaluated exclusively with APTEM!

control after each therapeutic step if possible

# Aggregometry

Dr. Klaus Görlinger, An Ruland

Platelets are a key blood component in haemostasis. In response to a vascular injury, they are able to adhere to the damaged vessel wall and trigger an event that leads among others to aggregation of additional platelets and therefore, together with other blood components, to the formation of a stable clot.

The ROTEM® *platelet* module measures platelet aggregation respectively via electrical impedance based on impedance aggregrometry by Cardinal and Flower (1980).
The ROTEM® *platelet* module is an impedance aggregometer intended for the assessment of platelet function in anticoagulated whole blood samples. It provides quantitative and qualitative information about the platelet aggregation by assessing the electrical impedance changes after platelet activation with different reagents.

The ROTEM® *platelet* module is intended to be used in patients treated with antiplatelet drugs or other drugs which may have an impact on platelet function, as well as in patients with a suspected platelet dysfunction due to extracorporeal circulation, trauma, sepsis or other reasons. It is for use in clinical laboratories, hospitals or other clinical care sites by health care professionals. The ROTEM® *platelet* module is used in conjunction with the ROTEM® *delta* system, but does not necessarily have to be complemented by viscoelastic testing.

Acute bleeding during or after surgery requires rapid differentiation between surgical induced bleeding and haemostasis disorders. The combination of the ROTEM® *delta* with the ROTEM® *platelet* and additional diagnostic methods, considering the given limitations, facilitates further differential treatment strategies.

# ROTEM® *platelet system*



- 2 channels for simultaneous assays
- Can be used while thromboelastometry measurements are running
- Used in combination with ROTEM® *delta*
- Electronic pipetting facilitates the use outside of established laboratories
- Ready to use single use reagents

## *Detection method: impedance aggregometry with ROTEM<sup>®</sup> platelet*

Whole blood is pipetted into a cuvette containing a stirring bar and special electrodes, energized with a certain voltage. Before inducing platelet aggregation, an impedance baseline is determined. After adding aggregating agents, the platelets are activated and start to aggregate. The increase of the electrical impedance is measured over
the time of aggregation. It is directly proportional to the extent of platelets involved in coating the electrodes by aggregation. The results of the measurement are processed with a specific software.

## *The parameters of ROTEM<sup>®</sup> platelet analysis*

**AUC**  (Area under the curve):

> The AUC represents the area under the aggregation curve from the start of the measurement until 6 minutes of runtime.

> AUC reflects the overall platelet aggregation.


**MS**   (Maximum Slope):

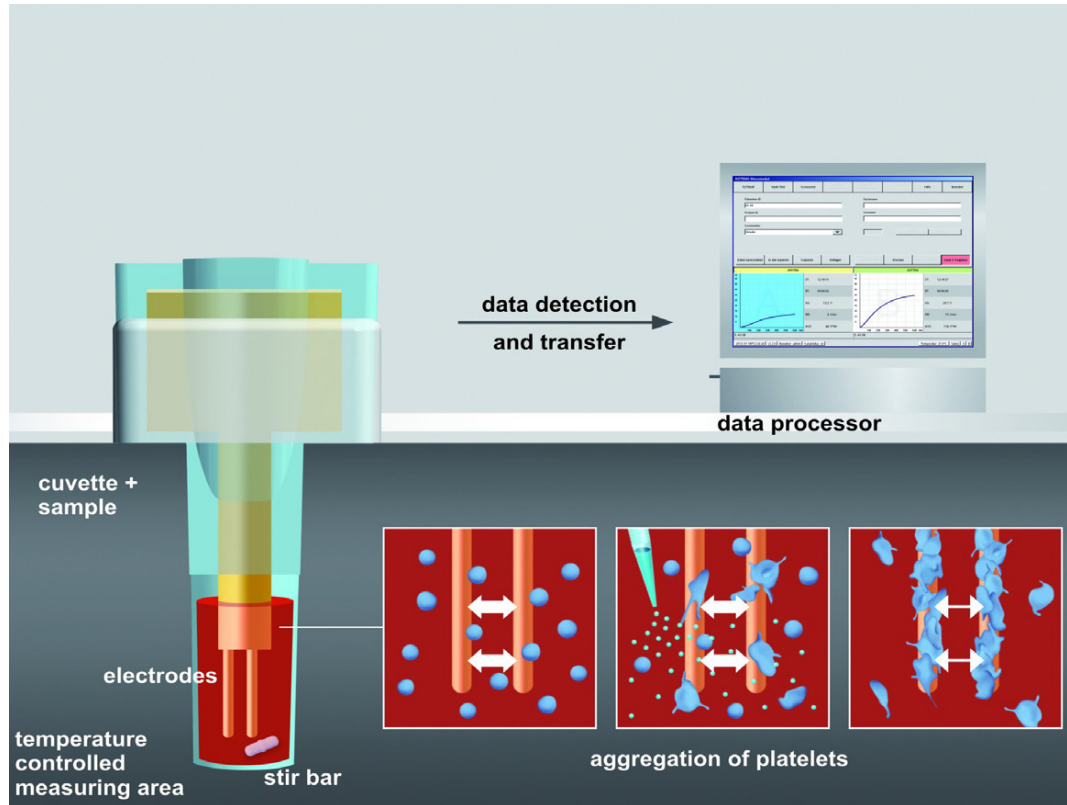> The MS is the maximum slope to the aggregation graph.

> MS is a measure for the rate of aggregation.


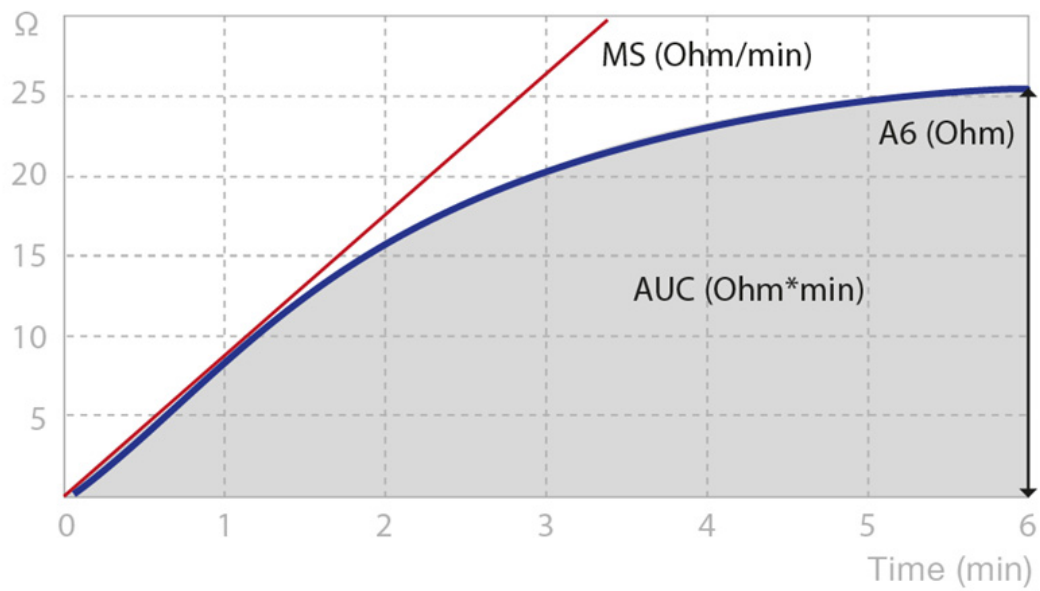**A6**   (Amplitude at 6 minutes):

> The A6 reflects the measured impedance, 6 minutes after starting the test.

> A6 is a measure for the extent of platelet aggregation.

## ROTEM® platelet detection method



## ROTEM® platelet parameters and scaling

## ROTEM® *platelet tests*

The ROTEM® *platelet* analysis extends the resulting diagnostic power by a number of additional tests and parameters, which
• allow differentiation between different platelet drug effects on platelet aggregation.
• allow to detect platelet dysfunction due to e.g. extracorporeal assist devices, surgery...[1]

In **ARATEM**, the platelets are activated with arachidonic acid. Platelet function is assessed for example in patients treated with cyclooxygenase inhibitors (e.g. acetylsalicylic acid).

In **ADPTEM**, the platelets are activated with adenosine diphosphate. Platelet function is assessed for example in patients treated with ADP receptor antagonists (e.g. clopidogrel).

In **TRAPTEM**, the platelets are activated with thrombin receptor activating peptide. Platelet function is assessed for example in patients treated with PAR-1 receptor antagonists (e.g. vorapaxar) or GP IIb/IIIa receptor antagonists (e.g. abciximab).

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1.Petricevic M.et al.; Bleeding risk assessment in patients undergoing elective cardiac surgery using ROTEM® *platelet* and Multiplate® impedance aggregometry. Anaesthesia 2016 Jun; 71(6):636-47

# ROTEM® platelet tests

**ARATEM**:

platelet activation

with arachidonic acid



| ARATEM | |
|---|---|
| ST: | 16:55:41 |
| RT: | 00:06:00 |
| A6: | 22.7 Ω |
| MS: | 8 Ω/min |
| AUC: | 92 Ω*min |

**ADPTEM**:

platelet activation

with ADP
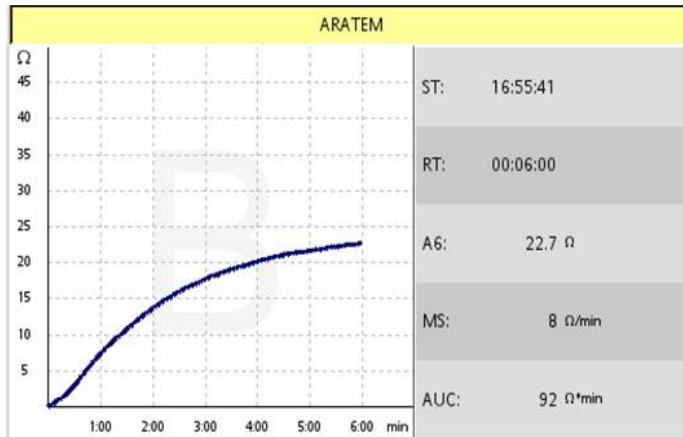


| ADPTEM | |
|---|---|
| ST: | 11:46:24 |
| RT: | 00:06:00 |
| A6: | 25.1 Ω |
| MS: | 8 Ω/min |
| AUC: | 98 Ω*min |
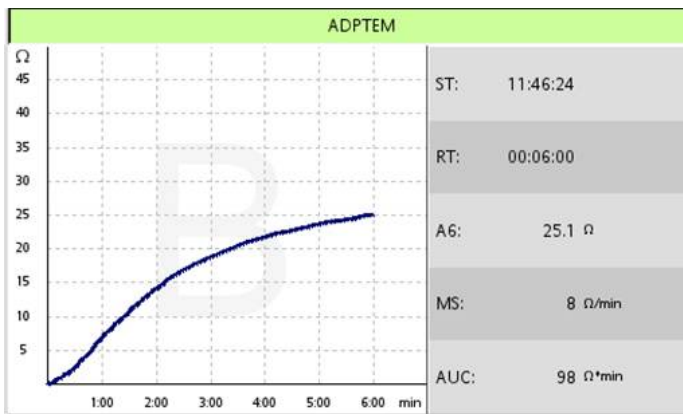
**TRAPTEM**:

platelet activation

with TRAP



| TRAPTEM | |
|---|---|
| ST: | 10:53:47 |
| RT: | 00:06:00 |
| A6: | 27.0 Ω |
| MS: | 10 Ω/min |
| AUC: | 112 Ω*min |
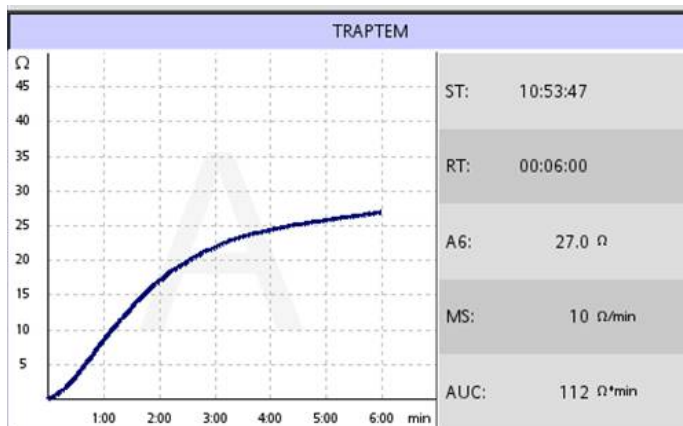
## ROTEM® *platelet expected values*

On the opposite page, typical ROTEM® aggregometry values are shown, which are found when healthy patients without aggregation disorders who are not taking antiplatelet drugs are analysed. Depending on the examined population, these values can vary. It is therefore recommended, at implementation of ROTEM® *platelet*, to analyse some patients without pathological findings in order to establish respective 'local' reference ranges.

The reference values for the different tests depend on the sample type used (citrate, heparin or hirudin sample tubes).

## *Interpretation of ARATEM, ADPTEM, TRAPTEM*

In case of impaired platelet function, several parameters (AUC, A6 and MS) are reduced. The cause of platelet impairment may be anti-platelet or other influencing drug intake or non-drug induced (e.g. due to cardiopulmonary bypass, extracorporeal assist devises, trauma, surgery, infection or sepsis or in cases of thrombocytopenia).

Non-drug induced platelet dysfunction may be detected on all tests (ARATEM, ADPTEM and TRAPTEM). However, in sepsis[1] for example, the effect may be more pronounced on the ADPTEM test and in trauma[2] on the TRAPTEM test. Drug induced platelet dysfunction may show different test patterns depending on the drug (see below, page 37).

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1.Adamzik M. et al.; Whole blood impedance aggregometry as a biomarker for the diagnosis and prognosis of severe sepsis. Crit. Care. 2012 Oct 22; 16(5):R204
2.Chapman MP et al.; Early TRAP pathway platelet inhibition predicts coagulopathic hemorrhage in trauma. Shock.2015; 43 (6 Suppl1):33

# ROTEM® platelet preliminary reference ranges

For citrated samples

| Test / Parameter | AUC (Ohm*min) | A6 (Ohm) | MS (Ohm/min) |
|---|---|---|---|
| ADPTEM (n=20) | 56-139 | 16-38 | 4-11 |
| TRAPTEM (n=175) | 61-156 | 15-36 | 5-14 |
| ARATEM (n=20) | 70-153 | 19-41 | 6-13 |

For heparinized samples

| Test / Parameter | AUC (Ohm*min) | A6 (Ohm) | MS (Ohm/min) |
|---|---|---|---|
| ADPTEM (n=20) | 57-133 | 16-34 | 4-12 |
| TRAPTEM (n=60) | 66-169 | 15-38 | 6-18 |
| ARATEM (n=20) | 69-144 | 17-37 | 6-14 |

For hirudinized samples

| Test / Parameter | AUC (Ohm*min) | A6 (Ohm) | MS (Ohm/min) |
|---|---|---|---|
| ADPTEM (n=20) | 86-201 | 23-52 | 7-17 |
| TRAPTEM (n=60) | 67-155 | 17-37 | 6-15 |
| ARATEM (n=20) | 84-193 | 21-52 | 7-16 |

### *Assessment of the ROTEM® platelet analysis*

Drug induced or non-drug induced platelet dysfunction is detected by decreased AUC, A6 and MS test results.

A. In patients treated with cyclooxygenase inhibitors (e.g. acetylsalicylic acid) platelet aggregation may be impaired. This will be detected in the ARATEM test.

B. In patients treated with ADP receptor antagonists (e.g. clopidogrel) platelet aggregation may be impaired. This will be detected in the ADPTEM test.

C. In patients treated with dual antiplatelet therapy (e.g. acetylsalicylic acid and clopidogrel) platelet aggregation may be impaired. This will be detected in ADPTEM and ARATEM.

D. In patients treated with PAR-1 receptor antagonists (e.g. vorapaxar) platelet aggregation may be impaired. This will be detected in TRAPTEM.

E. In patients treated with GP IIb/IIIa inhibitors (e.g. abciximab) platelet aggregation may be impaired. This will be detected in all tests: ADPTEM, TRAPTEM and ARATEM.

Non-drug induced platelet dysfunction may also show impaired platelet aggregation (e.g. due to cardiopulmonary bypass, extracorporeal assist devises, trauma, surgery, infection or sepsis or in cases of thrombocytopenia). This may be detected in all tests: ADPTEM, TRAPTEM and ARATEM. However, in sepsis for example, the effect may be more pronounced on the ADPTEM test and in trauma on the TRAPTEM test.
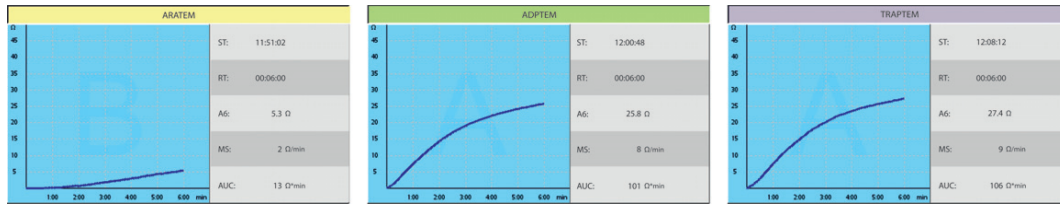
### *Limitations*

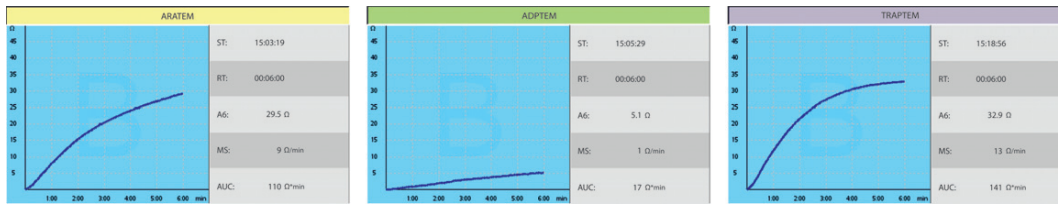Low platelet count may show abnormal aggregation.

## *Assessment of the ROTEM® platelet analysis*

Examples of impaired platelet aggregation after drug intake.

### A. Patient treated with acetylsalicylic acid:



| ARATEM | | ADPTEM | | TRAPTEM | |
|---|---|---|---|---|---|
| ST: | 11:51:02 | ST: | 12:00:48 | ST: | 12:08:12 |
| RT: | 00:06:00 | RT: | 00:06:00 | RT: | 00:06:00 |
| A6: | 5.3 Ω | A6: | 25.8 Ω | A6: | 27.4 Ω |
| MS: | 2 Ω/min | MS: | 8 Ω/min | MS: | 9 Ω/min |
| AUC: | 13 Ω*min | AUC: | 101 Ω*min | AUC: | 106 Ω*min |

### B. Patient treated with clopidogrel:



| ARATEM | | ADPTEM | | TRAPTEM | |
|---|---|---|---|---|---|
| ST: | 15:03:19 | ST: | 15:05:29 | ST: | 15:18:56 |
| RT: | 00:06:00 | RT: | 00:06:00 | RT: | 00:06:00 |
| A6: | 29.5 Ω | A6: | 5.1 Ω | A6: | 32.9 Ω |
| MS: | 9 Ω/min | MS: | 1 Ω/min | MS: | 13 Ω/min |
| AUC: | 110 Ω*min | AUC: | 17 Ω*min | AUC: | 141 Ω*min |

### C. Patient treated with clopidogrel and acetylsalicylic acid:



| ARATEM | | ADPTEM | | TRAPTEM | |
|---|---|---|---|---|---|
| ST: | 11:51:02 | ST: | 12:00:48 | ST: | 12:08:12 |
| RT: | 00:06:00 | RT: | 00:06:00 | RT: | 00:06:00 |
| A6: | 4.0 Ω | A6: | 6.8 Ω | A6: | 27.4 Ω |
| MS: | 1 Ω/min | MS: | 2 Ω/min | MS: | 9 Ω/min |
| AUC: | 12 Ω*min | AUC: | 24 Ω*min | AUC: | 106 Ω*min |

### D. Patient treated with vorapaxar:



| ARATEM | | ADPTEM | | TRAPTEM | |
|---|---|---|---|---|---|
| ST: | 10:40:02 | ST: | 10:55:48 | ST: | 11:08:16 |
| RT: | 00:06:00 | RT: | 00:06:00 | RT: | 00:06:00 |
| A6: | 24.7 Ω | A6: | 22.8 Ω | A6: | 6.8 Ω |
| MS: | 9 Ω/min | MS: | 10 Ω/min | MS: | 2 Ω/min |
| AUC: | 102 Ω*min | AUC: | 98 Ω*min | AUC: | 21 Ω*min |
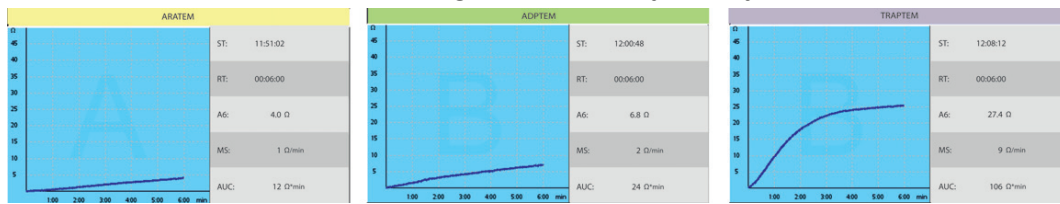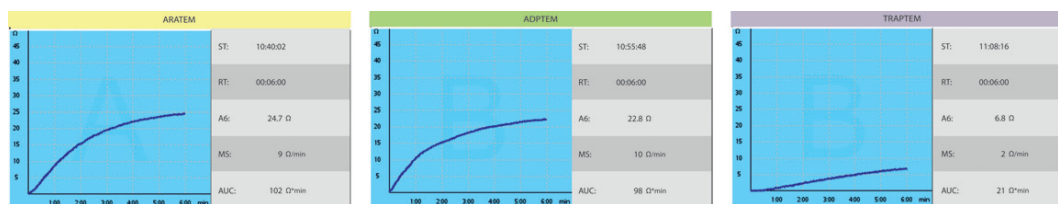
### E. Patient treated with abciximab:



| ARATEM | | ADPTEM | | TRAPTEM | |
|---|---|---|---|---|---|
| ST: | 17:19:43 | ST: | 17:18:56 | ST: | 17:26:56 |
| RT: | 00:06:00 | RT: | 00:06:00 | RT: | 00:06:00 |
| A6: | 9.9 Ω | A6: | 9.9 Ω | A6: | 9.8 Ω |
| MS: | 3 Ω/min | MS: | 3 Ω/min | MS: | 3 Ω/min |
| AUC: | 34 Ω*min | AUC: | 34 Ω*min | AUC: | 38 Ω*min |
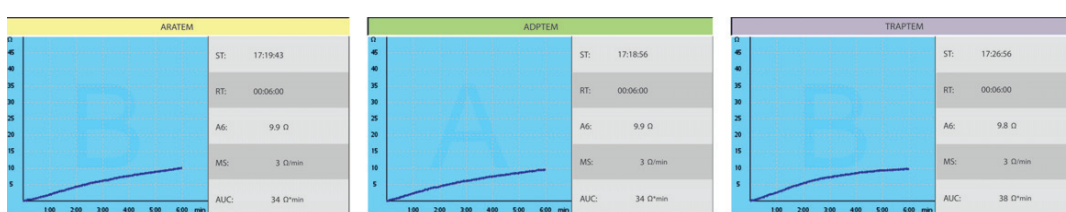
### *Assessment of the ROTEM® platelet analysis*

As in all diagnostic tests, correct pre-analytics and correct performance of the assay are essential for meaningful results.

"Correct sampling" means: Complete filling of the sampling tube (in order to ensure the correct anticoagulant-blood ratio); avoidance of haemolysis during sampling (prevent excessive stasis, use of a needle with sufficiently wide diameter).

Three sample tube types may be used: heparin, citrate and hirudin. Normal values have been established for each sample type in combination with all available tests. Citrated samples are not recommended in situations where the patient's blood may contain heparin. According to the chosen anticoagulant in the sample tube, the corresponding sample resting time (between 2-30 min.) needs to be observed (refer to the reagents' instructions of use).

A pneumatic tube transportation system may influence the sample's platelets. As a precaution, this should be verified (split the sample and analyse with/without transport by the tube system).

The samples should be stored at room temperature until analysis.

ROTEM® *platelet* analysis should be performed within two hours after blood sampling.

The steps to be performed for ROTEM® *platelet* analysis are shown on the right. The test operation is generally simple - also for staff without any laboratory experience. Nevertheless, a certain familiarisation period and motivation are necessary.

Apart from the correct performance of the analysis – as in every laboratory test – the plausibility control of the analysis is important. Measurements with irregular shapes (e.g. noised curves), generally accompanied by error messages, should be repeated.

In case of unexpected results, a normal donor sample with known aggregation level should be tested to verify system integrity. The normal donor should not have ingested acetylsalicylic acid or clopidogrel or acetylsalicylic acid- or clopidogrel-containing compounds in the preceding 10 days.

## *Performing a ROTEM® platelet test*
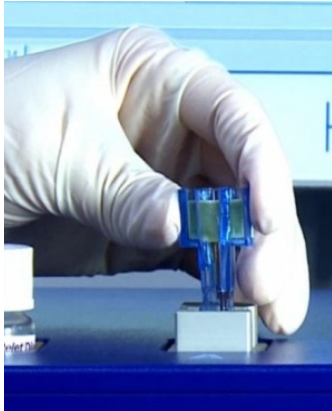


1. Insert the cuvette
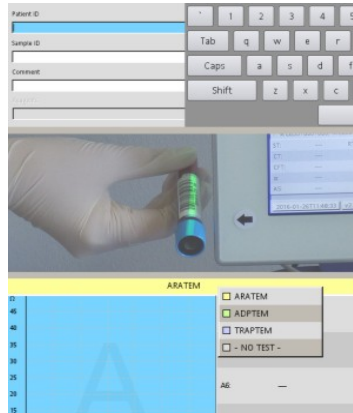


2. Select test, enter/ scan patient data



3. Pipetting steps are displayed on the screen



4. Pipetting of diluent, blood and reagent
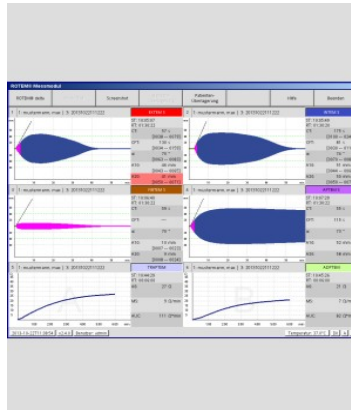


5. On screen display of graphs and numeric parameters
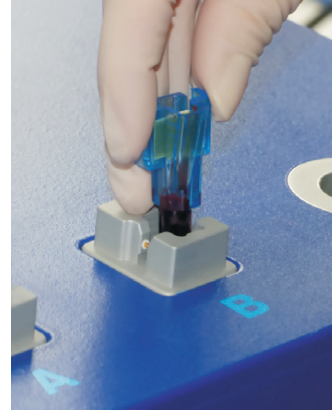


6. Discard used cuvette

## Differential diagnosis and therapy: algorithms

Acute bleeding during or after surgery requires rapid differentiation between surgical induced bleeding and haemostasis disorders. The combination of the ROTEM® *delta* with the ROTEM® *platelet* and additional diagnostic methods, considering the given limitations, facilitates further differential treatment strategies.

```
                    ┌─────────────────────────┐
                    │   Patient drug history   │
                    └─────────────────────────┘
                                 │
                    ┌─────────────────────────┐
                    │    Bleeding patient      │
                    └─────────────────────────┘
```

| ROTEM® *delta* analysis | | ROTEM® *platelet* analysis | |
|---|---|---|---|
| Abnormal | Normal | Normal | Abnormal |
| Haemostasis disorder: Coagulopathy (or thrombocytopenia) | Consider surgical bleeding | | Haemostasis disorder: Platelet dysfunction (or thrombocytopenia) |

### ROTEM® *platelet* analysis

| ara-tem® | adp-tem® | trap-tem® |
|---|---|---|
| Influencing drugs e.g. ASA, GP IIb/IIIa blockers etc. | Influencing drugs e.g. ADP receptor blockers, GP IIb/IIIa blockers etc. | Influencing drugs e.g. PAR-1 receptor blockers, GP IIb/IIIa blockers etc. |

### Platelet enhancement therapy
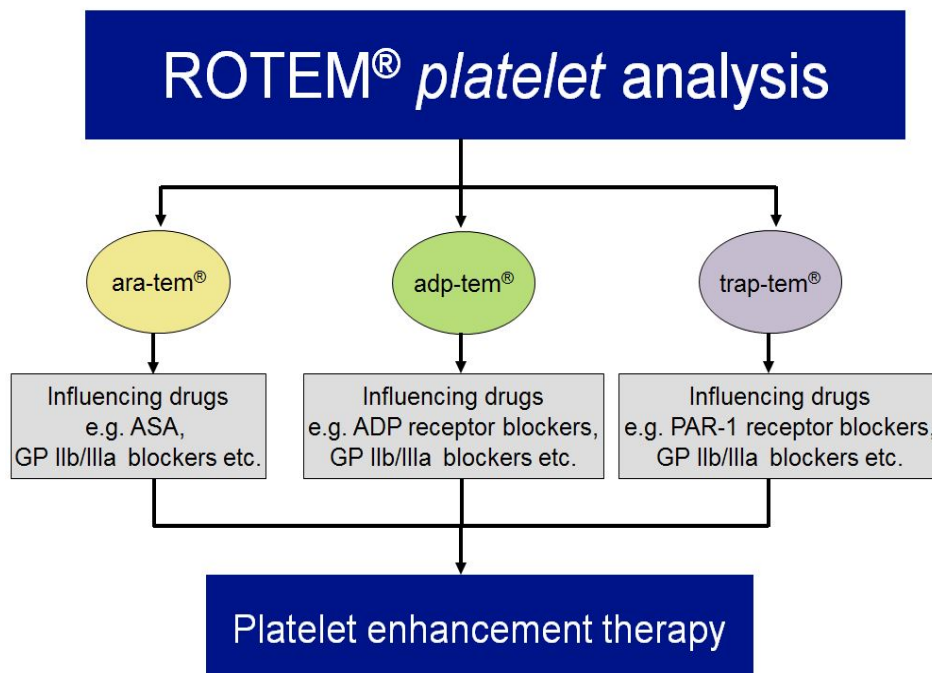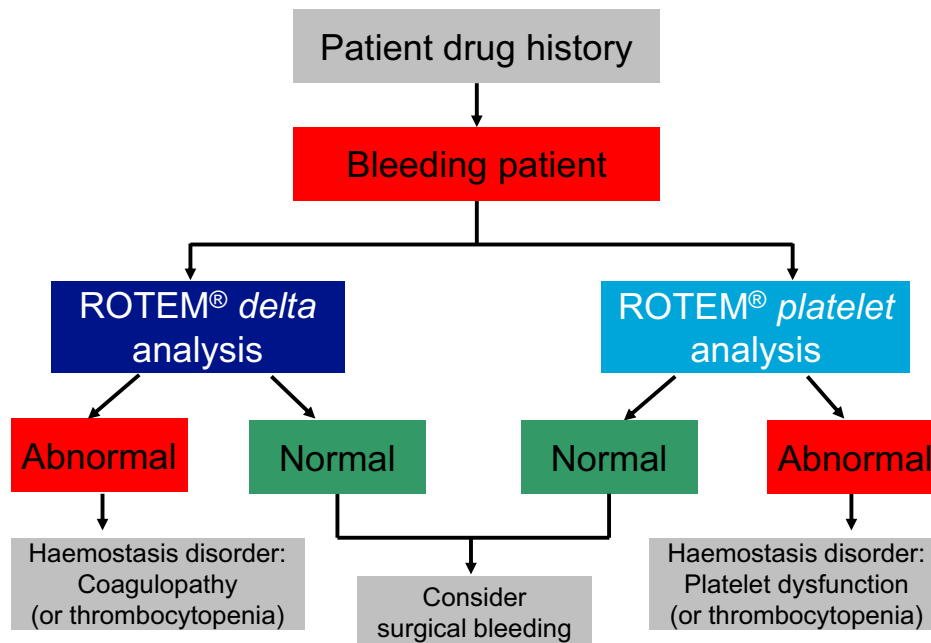
## Differential diagnosis and therapy: algorithm example

**Severe Bleeding Algorithm**
Diffuse bleeding and blood transfusion considered

— CHECK → Hemorrhagic shock  or
BE < -6 mmol/L  or
Hb < 10 g/dL  or
ISS ≥ 25  or
TASH-Score ≥ 15

**YES** ↓   NO

**A5$_{EX}$ < 35 mm**  or
**CT$_{FIB}$ > 600 s**  or
**ML ≥ 5%** (within 60 min)

— YES → Tranexamic acid
25 mg/kg as a single bolus
(if not already given prophylactically)

YES (from Hemorrhagic shock box) ↓

DONE

**NO** ↓

A5$_{EX}$ < 35 mm
__and__
**A5$_{FIB}$ < 8 mm (12 mm)**

— YES → Fibrinogen concentrate
or Cryoprecipitate
(dose cal.)
**Target: A5$_{FIB}$ ≥ 12 mm
(16 mm)**

**NO** ↓

**A5$_{EX}$ < 35 mm** __and__
A5$_{FIB}$ ≥ 8 mm (12 mm)
__or__ platelet dysfunction

— YES → Platelet concentrate
1-2 pooled or
apheresis[1]

**NO** ↓

**CT$_{EX}$ > 80 s**

— YES → PCC   15-25 IU / kg bw
or
FFP   10-15 mL / kg bw

**NO** ↓

**CT$_{IN}$ > 240 s**

— YES → CT$_{HEP}$ > 240 s

— YES → Consider FFP
10-15 mL / kg bw

— NO → Consider Protamine
25-50 mg (2.5-5 mL)

**NO** ↓

Ongoing bleeding

— YES → Re-check after 10-15 min
using a new blood sample

**[1] Platelet concentrate (PC) transfusion:**
Check platelet function with ROTEM® *platelet* (**ADPTEM** and **TRAPTEM**)
Consider tranexamic acid (25 mg/kg) and/or desmopressin (DDAVP; 0.3μg/kg)
in patients with dual antiplatelet therapy and/or **ADPTEM** < 30 Ω·min
Expected increase per pooled/apheresis PC per 80 kg: 8-10 mm in A5$_{EX}$ →

A5$_{EX}$ < 35 mm (or **ADPTEM** < 30 Ω·min): 1 pooled or apheresis PC
A5$_{EX}$ < 25 mm (or **ADPTEM** < 30 Ω·min and **TRAPTEM** < 50 Ω·min): 2 pooled or apheresis PC
A5$_{EX}$ < 15 mm: 2 platelet concentrates + fibrinogen substitution (≥ 4 g)

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*The ROTEM® system is an improvement of thromboelastography as described by Professor Helmut Hartert. Andreas Calatzis developed the ROTEM® system in collaboration with the physicist Pablo Fritzsche. Michael Spannagl is a consultant for internal medicine and angiology. He has been working for many years on the diagnosis and management of acute and chronic disturbances of the haemostatic system. Matthias Vorweg, University Hospital Bonn, has introduced ROTEM® analysis in the anaesthesiology department of the Cologne-Merheim hospital more than 10 years ago. The Cologne-Merheim hospital was one of the first centres to introduce the concept of the ROTEM® based differential diagnosis and targeted therapy in the clinical routine. Klaus Görlinger was the ROTEM® pioneer in the Department of Anaesthesiology of the University Hospital Essen. One of his major fields of expertise is the development and implementation of Point of Care (POC) guided algorithms for goal directed coagulopathy management. Dr. Görlinger is now the medical director of TEM international in Munich, Germany.*

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