

# Coagulation management during liver transplantation

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## Keywords

Liver transplantation, LTX, point-of-care coagulation management, thrombelastometry, hyperfibrinolysis

## Summary

In the course of liver transplantation many patients develop coagulation and bleeding disorders. On the other hand, some patients suffer thromboembolic events in the perioperative period with sometimes fatal outcome. For this reason, in 1999 we changed our coagulation management for liver transplantation and abolished the routine prophylaxis with antifibrinolytic drugs. In this context we implemented the ROTEM® system (Pentapharm GmbH, Munich) in our perioperative point-of-care coagulation management.

From 2000 to 2005, we analysed more than 18.000 ROTEM® measurements in the context of 642 liver transplantations. Prophylactic administration of antifibrinolytic drugs was only done in patients with fulminant liver failure or if MCF in ExTEM  $\leq 35$  mm at the beginning of surgery. In the other patients hyperfibrinolysis could be detected in 60% during the operation. However, therapy with an antifibrinolytic drug was only necessary in 40% of the patients. Our experience with ROTEM® analysis was summarised in an algorithm for ROTEM® based perioperative coagulation management for liver transplantation.

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**D**uring liver transplantation most of the patients show multifactorial disorders in their haemostatic balance (74) (Fig. 1). The biosynthesis of coagulation factors and inhibitors is reduced secondary to liver cirrhosis. Therefore pro- and anticoagulants are in an unstable balance at a low level. These patients are at risk for two types of complications:

- thrombosis (e. g. in the portal vein or cava inferior) and
- severe bleeding (e. g. from oesophageal varices).

As a result of reduced biosynthesis of fibrinolysis inhibitors and diminished clearance

by the reticuloendothelial system of the liver an increased activity of the fibrinolysis system often can be detected. This leads to an enhanced risk of hyperfibrinolysis – especially in the anhepatic phase of liver transplantation (Fig. 5). Portal hypertension and drainage of blood flow through the spleen result in platelet sequestration and thrombocytopenia. Disorders of platelet function can often be found in patients with liver cirrhosis – especially in context with renal insufficiency.

In addition to these preexisting disorders of the haemostasis system, massive blood loss and subsequent volume replacement during liver transplantation result in an impairment of haemostasis in terms of dilutional coagulopathy. Hyperfibrinolysis during anhepatic phase may lead to a complete lapse of haemostasis with consequent afibrinogenemia. Furthermore during reperfusion of the liver graft release of heparinoids has to be taken into account (27, 40).

Beside these factors, which increase the bleeding tendency, there is a risk of thrombosis (pelvic and deep leg veins and vena cava inferior) during vena cava clamping, a risk of vascular occlusion in the region of the anastomosis (portal vein and hepatic artery) and a risk of microthrombosis of the pulmonary circulation by platelet aggregates activated in the liver graft during reperfusion (25, 72). These complications often occur in patients with preexisting risks of thrombosis (e. g. Budd-Chiari-syndrome, portal vein thrombosis, pelvic and deep leg vein thrombosis, Factor V-Leiden (APC resistance), protein C deficiency), with chronic inflammation at the biliary system (e. g. primary biliary cirrhosis, primary sclerosing cholangitis) and malignant liver tumors (64, 75).

The aim of perioperative coagulation management in liver transplantation is to stabilize the coagulation system in order to

prevent severe coagulopathic bleeding and yet to avoid thromboembolic complications and closure of the vessels of the liver transplant. In this context the maximum clot firmness (MCF) in thrombelastography (TEG) seems to be an important prognostic factor (53).

## Cell based model of haemostasis

Our conception of haemostasis system has been altered dramatically within the past few years. The classical model of the clotting cascade with an extrinsic and an intrinsic system has been replaced by a cell based model of coagulation. This model, with its three consecutive phases of

- initiation,
- amplification and
- propagation

reflects much better the close interactions between cellular and plasmatic factors in haemostasis than the classical model (33, 69).

## Complexity of perioperative coagulation disorders during LTX

Perioperative coagulopathies – especially in case of liver transplantations – frequently have a multifactorial background (Fig. 1). These include congenital and acquired coagulation disorders, dilution, loss and consumption of coagulation factors, the occurrence of hyperfibrinolysis, release of endogenous and exogenous heparinoids, and accumulation of citrate. Moreover, inadequate

synthesis of coagulation factors in case of liver cirrhosis, renal insufficiency or damage to the bone marrow may also be relevant. Basic conditions (e. g. hypothermia, acidosis, hypocalcaemia and anaemia) may also have an important influence on haemostasis. In the course of determination of preexisting coagulation problems – including those induced by medications – a standardized questionnaire is of particular importance (41).

## Problems with classical coagulation tests

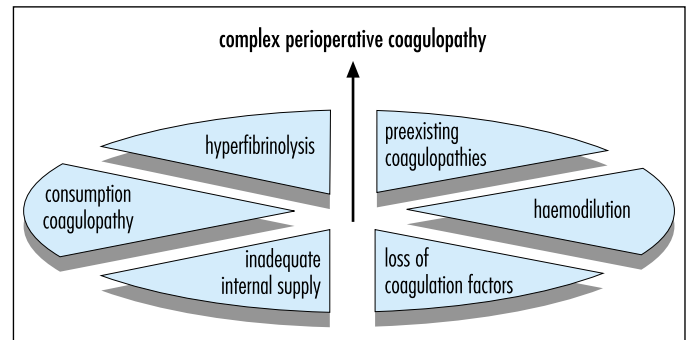
The problems of classical coagulation tests (Fig. 2) for diagnosis and therapy of perioperative coagulation disorders can be summarised as follows:

- no reliable detection of hyperfibrinolysis,
- false high fibrinogen measurement in the presence of colloids (like HES or gelatine), fibrin(ogen) split products and heparin,
- false long PT and aPTT in case of hypofibrinogenaemia and afibrinogenaemia,
- platelet count for its own has a low force of expression,
- clotting times (e. g. PT, aPTT and TT) only determine the speed of thrombin generation, but not the mechanical stability of the clot
- results of coagulation tests performed in a central laboratory are usually available not until 30 to 60 minutes in the operating theatre.

## Intentions of point-of-care coagulation testing

Point-of-care (POC) diagnostic has the aim to use rapid and simple coagulation tests to enable fast and specific therapeutical interventions. Therefore it is of prime importance that the correct test method has been used for the respective question and that the results are interpreted correctly in close connection with the clinical situation. The ROTEM<sup>®</sup>-analyser is established as a POC tool in our hospital for six years.

**Fig. 1**  
Complexity of perioperative coagulopathy



From January 2000 to December 2005 we performed 642 liver transplantations with a ROTEM<sup>®</sup>-guided perioperative coagulation management. In this context we analysed more than 18 000 ROTEM<sup>®</sup> measurements.

## Principles of measurement and potency of the ROTEM system

ROTEM<sup>®</sup> system allows evaluation of the coagulation system as an holistic dynamic process and enables predictions far beyond informations from classical coagulation tests. It provides us not only with informations about the time needed to start coagulation, but also about the mechanical and temporary stability of the clot.

Thus ROTEM<sup>®</sup> system allows reliable detection of hyperfibrinolysis and fibrinogen deficiency, differentiation between platelet and plasma coagulation disorders and detection of effects of endogenous and

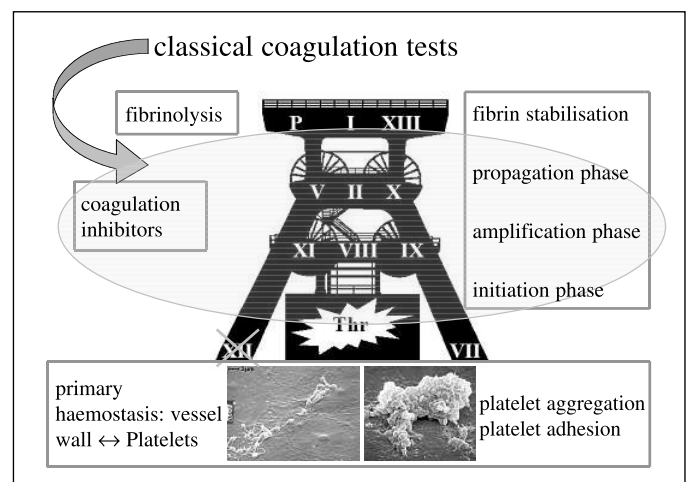
exogenous heparinoids (8, 27, 40, 44, 78) (Fig. 3). The addition of heparinase enables monitoring of haemostasis even in completely heparinised patients (58). As the ROTEM<sup>®</sup> system enables measurements at patient temperature (30–40°C), the effect of hypothermia and hyperthermia on the coagulation system can be verified. Finally, diagnostic or therapeutic additives (e. g. aprotinin, heparinase, ecarin, recombinant factor VIIa, Factor VIII, Factor XIII) can be used for in vitro tests, e. g. before starting a risky or expensive in vivo therapy.

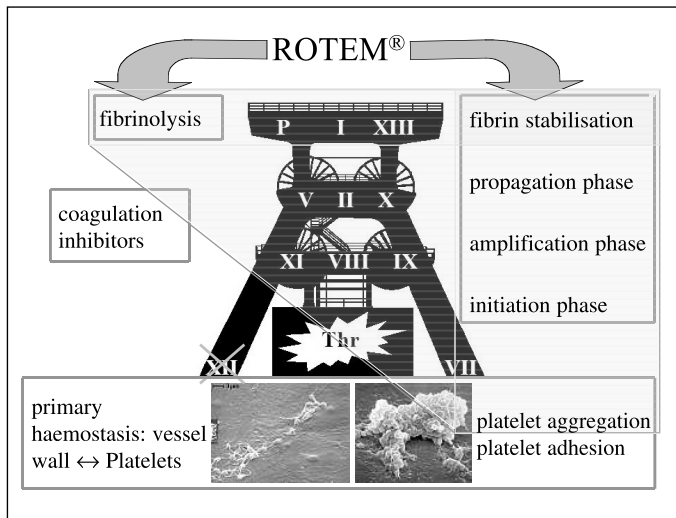
## Measurement time points, tests and parameters

ROTEM<sup>®</sup> analyses are performed at defined time points during liver transplantation:

- at beginning of surgery (baseline),
- every 60 minutes during the preanhepatic phase,
- at beginning of the anhepatic phase,

**Fig. 2**  
Diagnostic potential of classical coagulation tests





**Fig. 3**  
Diagnostic potential of rotational thrombelastography (ROTEM®)

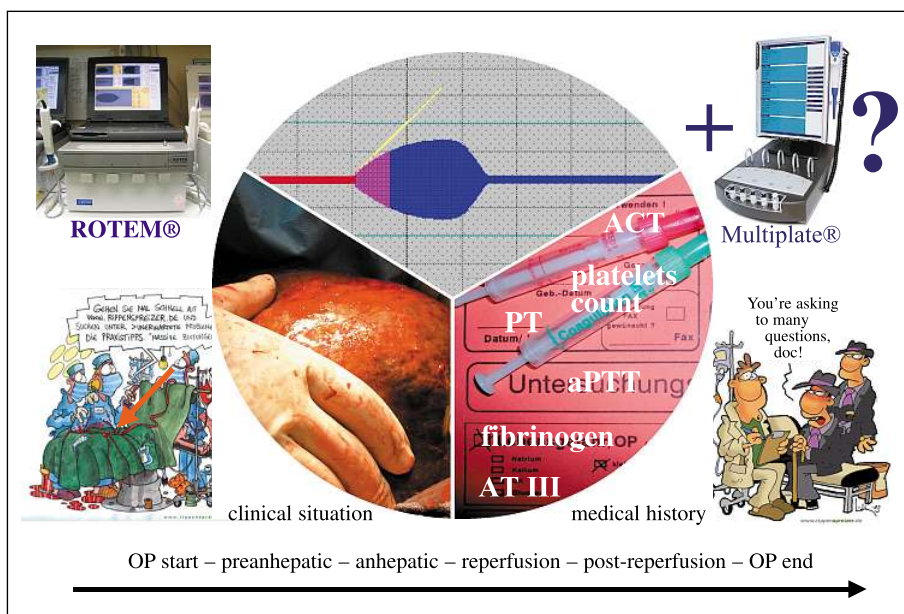
- MCF (maximum clot firmness),
- A10, A15, A20, ... (amplitude (of clot firmness) after 10, 15, 20, ... min.),
- ML (maximal lysis),
- CLI (clot lysis index),
- LOT (lysis onset time).

Many other parameters are available, but these are of scientific interest only.

### Limitations of ROTEM system

The following issues are very important to avoid incorrect interpretations of ROTEM® results:

- There is a minor correlation between the CT in EXTEM and the PT, i.e. determination of the PT in addition to the ROTEM® test is helpful for calculation of the therapeutic dosis of prothrombin complex concentrate (PCC).
- ROTEM® does not detect the activity of coagulation inhibitors (e. g. AT, protein C, protein S), i. e. additional determination of AT-activity is worthwhile for calculation of dosage for antithrombin therapy.
- ROTEM® does not detect the effect of „weak“ antiplatelet substances (e. g. acetylsalicylic acid, ticlopidine, clopidogrel, ginkgo, ginseng), i. e. ROTEM® is not a substitute for an adequate medical history! Additional platelet function tests, e. g. using impedance aggregometry (Multiplate®, Dynabyte medical, Munich), may also be helpful (Fig. 4).



**Fig. 4** Value of classical coagulation tests, ROTEM® and Multiplate® analysis in perioperative coagulation management

- every 30 minutes during the anhepatic phase,
- 15 minutes after detection of fulminant hyperfibrinolysis in the late anhepatic phase or after reperfusion,
- 5–10 and 30 minutes after reperfusion,
- 10 minutes after therapy with coagulation factors or platelet concentrates,
- about 30 minutes before the end of surgery (abdominal wall closure).
- standard tests: EXTEM, INTEM, FIBTEM, APTEM,
- in intensive care patients or patients with a  $CT_{IN} > 240$  sec: additional HEPTEM,
- in special situations: recombinant factor VIIa, VIII or XIII as an additive into standard ROTEM® tests (EXTEM or INTEM).

The most important parameters of ROTEM tests are:

- CT (coagulation time),
- CFT (clot formation time) or alpha-angle,

During liver transplantation we carried out the following ROTEM® tests:

### ROTEM-guided coagulation management in liver transplantation

#### Use of antifibrinolytic drugs

As hyperfibrinolysis occurs frequently – predominantly in the anhepatic phase of liver transplantation or during reperfusion of the liver graft – antifibrinolytics are prophylactically used in many transplant centres (63). The most frequently used drugs are aprotinin and tranexamic acid (6, 18, 46, 67). The risk of prophylactical application of

antifibrinolytics is, that in some cases this is associated with perioperative vascular occlusion of the graft, thromboembolic events and renal dysfunction (4, 19, 68).

This association could not be confirmed in controlled studies of liver transplantations (59). However, recent studies of fibrinolysis inhibitors in cardiopulmonary bypass surgery have shown a significantly increased incidence of renal, myocardial and cerebral complications (38, 49). Therefore, the benefit of prophylactic administration of antifibrinolytics in liver transplantation has been assessed differently by different transplant centres (45, 87).

In our opinion only in patients with an elevated risk of hyperfibrinolysis prophylaxis with antifibrinolytic drugs should be done. Other patients should only be treated if hyperfibrinolysis occurs. This treatment assumes perioperative haemostasis monitoring by using thromboelastography so that hyperfibrinolysis can be detected early. Rotation thromboelastometry (ROTEM®) is well established for this purpose. In our patients, the incidence of hyperfibrinolysis in liver transplantation was 60% defined as  $CLI_{60} < 85\%$  (23) (Fig. 5, Fig. 8). One third of these cases were self-limiting after reperfusion of the liver graft. Therefore, only manifest diffuse bleeding needs to be treated in these patients. The other two thirds show a non-self-limiting hyperfibrinolysis and require therapy with antifibrinolytic drugs.

Below the Essen algorithm for perioperative coagulation management in liver transplantation is described (24) (Fig. 6).

### Prophylactic administration of antifibrinolytic drugs

In fulminant liver failure, as well as in patients with significantly reduced clot firmness with an  $MCF_{EX} \leq 35$  mm at the beginning of liver transplantation, more than 90% of patients develop hyperfibrinolysis in the anhepatic phase (80). Prophylactic administration of antifibrinolytics seems justifiable in these cases.

In Essen, patients receive either 2 million KIU aprotinin (25 000 KIU per kg body weight) or 2 g tranexamic acid (25 mg per kg body weight). Continuous administration of

antifibrinolytics to these patients can be avoided because of close matched controls with ROTEM®. A recurrence of hyperfibrinolysis after successful therapy with an antifibrinolytic is extremely uncommon.

**Contraindications:** As mentioned previously, antifibrinolytics should not be given prophylactic to patients with a medical history of thrombotic events, chronic inflammatory biliary tract diseases, or malignant liver tumours because they have a particularly high rate of perioperative thromboembolic complications (64, 75). This applies also to patients with hypercoagulability in form of disseminated intravascular coagulation (DIC stage I) or an  $MCF_{EX} > 60$  mm at the beginning of surgery.

Patients who have already been treated with aprotinin (e. g. in case of heart surgery with cardiopulmonary bypass) have a significantly increased incidence of allergic reactions. These patients should therefore better be treated with tranexamic acid than with aprotinin (Fig. 6).

### Therapeutic administration of antifibrinolytic drugs

The challenge in ROTEM®-guided coagulation management in liver transplantation is not only the reliable detection of hyperfibrinolysis, but in deciding whether hyperfibrinolysis requires treatment or not. Therefore it is important to differentiate between an early lysis (lysis onset time (LOT)  $< 45$  min or clot lysis index after 45 minutes ( $CLI_{45}$ )  $< 85\%$ ) and a late lysis (LOT 45–60 min or  $CLI_{45} > 85\%$  and  $CLI_{60} < 85\%$ ). It is also important to consider the phase, in

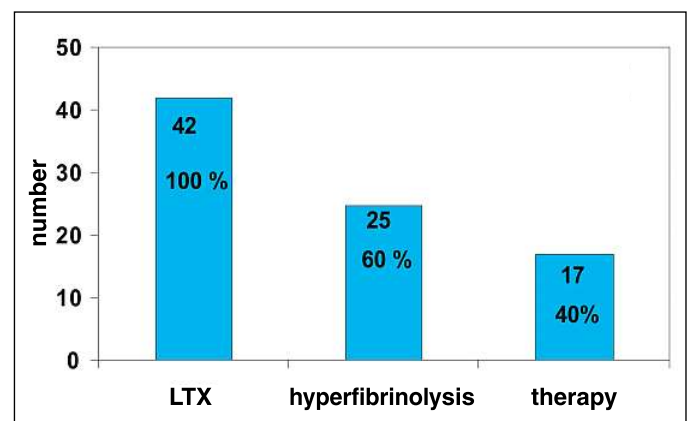
which the lysis occurs during surgery (preanhepatic, anhepatic or after reperfusion) and to know about the primary disease of the patient (figure 8). Essential for the decision to administer an antifibrinolytic drug or not is the ongoing clinical situation, in particular the presence of diffuse bleeding at the operation site or at catheter insertions.

In the preanhepatic or early anhepatic phase, hyperfibrinolysis should always be treated if maximal lysis (ML)  $> 15\%$  within 60 min ( $CLI_{60} < 85\%$ ), because otherwise there will be a massive increase of the pre-existing hyperfibrinolysis during the anhepatic phase.

In the late anhepatic phase, fulminant hyperfibrinolysis with a ML  $> 50\%$  within 30 min ( $CLI_{30} < 50\%$ ) has to be treated with fibrinolysis inhibitors. On the other hand, fulminant hyperfibrinolysis with an ML  $> 50\%$  within 30 min ( $CLI_{30} < 50\%$ ) after reperfusion of the liver graft should only be treated in presence of clinically relevant bleeding or if fibrinolysis increases during remaining surgery (Fig. 8). In case of good graft function, hyperfibrinolysis in this phase of transplantation is usually self-limiting and doesn't require any specific therapy (23) (Fig. 9).

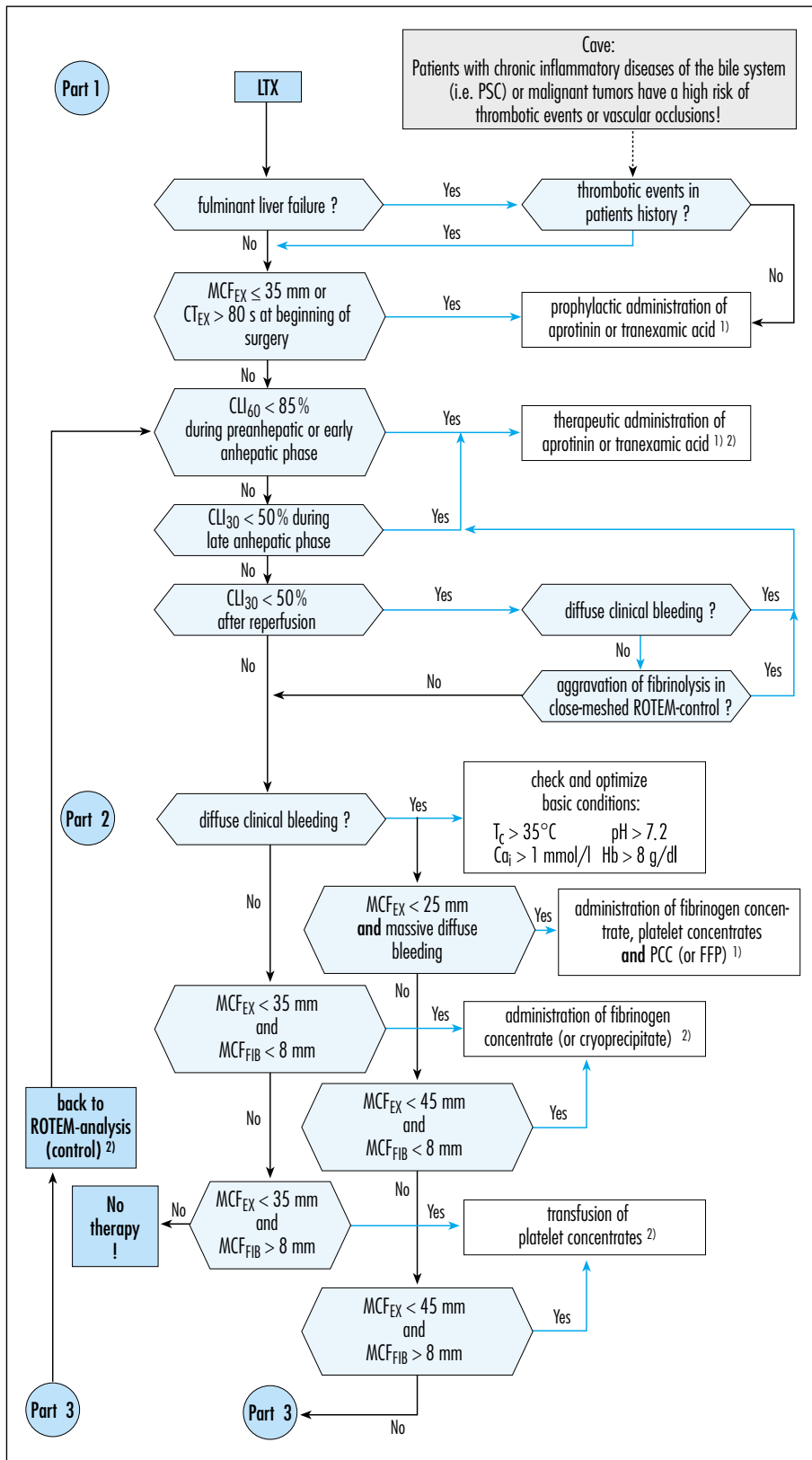
### Enhancement of clot firmness

Measures to increase clot firmness are only indicated in cases of clinically relevant diffuse bleeding or in cases of borderline reduction in clot stability in connection with expected further surgical blood loss and further requirement for volume substitution (see figure 6, Part 2).



**Fig. 5** Incidence of hyperfibrinolysis during liver transplantation (LTX) in Essen (January to May 2003)





**Fig. 6** Algorithm for ROTEM®-based perioperative coagulation management during liver transplantation: management of hyperfibrinolysis (**Part 1**) and clot firmness (MCF) (**Part 2**)

Reasons for reduction of maximum clot firmness are fibrinogen deficiency, fibrin polymerisation disorders, thrombocytopenia, and platelet function disorders. Fibrin polymerisation disorders caused by interactions with colloids can be detected by ROTEM® analysis. In fibrinogen measurement according to Clauss colloids can effect false high values because of elevated opacity of plasma (20, 31). On the other hand, platelet function disorders are only partly detected by ROTEM® analysis, since platelets are stimulated in ROTEM® tests by thrombin generated after addition of activators. This means that the effect of platelet aggregation inhibitors such as acetylsalicylic acid, clopidogrel or ticlopidine, is overcome by thrombin and thus is not detectable in ROTEM® (8).

In cases of differences between manifest clinical bleeding without pathological findings in ROTEM® results, the possibility of platelet function disorders should be taken into account and performance of further tests with platelet function analysers (e. g. impedance aggregometry with Multiplate® analyser) can be helpful (Fig. 4).

If clot firmness is reduced in ROTEM®, comparison of MCF in EXTEM and FIBTEM can differentiate between fibrinogen deficiency or fibrin polymerisation disorders and thrombocytopenia or platelet function disorders on the other hand (44).

### Administration of fibrinogen

In dilutional coagulopathy, normally fibrinogen is the first coagulation factor, which achieves a critical level (21, 32, 54, 76). In case of liver transplantation, it must be recognised that many patients have a complex coagulopathy even before surgery, with reduction of coagulation factors and a reduced platelet count. In addition, these patients often have an increased turnover of coagulation factors and platelets (e.g. in hypersplenism or latent activation of the coagulation system), while replenishment is reduced (e.g. because of bone marrow depression or liver cirrhosis). Contemporary differentiation between these haemostatic disorders is significantly relieved by point-of-care testing with ROTEM (35). Administration of fibrinogen is indicated in case of

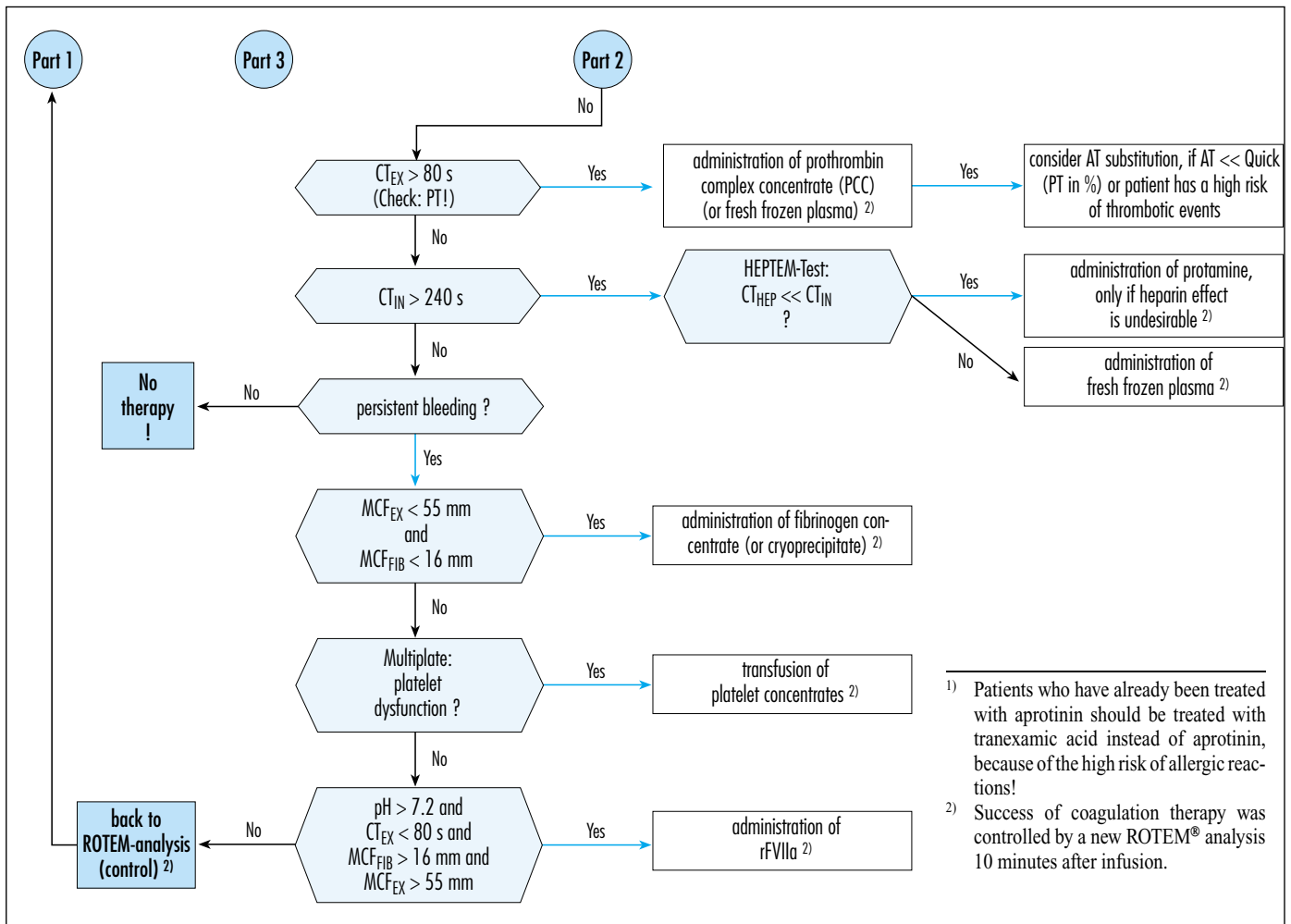


Fig. 6, Part 3 Management of clot firmness (MCF)

diffuse bleeding with  $MCF_{EX} < 45$  mm and  $MCF_{FIB} < 8$  mm (23).

The **dosis** depends on the altitude of  $MCF_{FIB}$ . At  $MCF_{FIB} < 8$  mm, a dosage of 25 mg fibrinogen per kg body weight (2 g fibrinogen/80 kg body weight) is required to balance fibrinogen deficiency, compared with 50 mg fibrinogen per kg body weight (4 g fibrinogen/80 kg body weight) at  $MCF_{FIB} < 4$  mm.

Without diffuse bleeding, fibrinogen should only be given if the  $MCF_{EX} < 35$  mm and  $MCF_{FIB} < 8$  mm and if further surgical blood loss is expected.

In case of hyperfibrinolysis, further consumption of fibrinogen during the time of measurement has to be taken into account. Thus, the indication for fibrinogen substitution should be determined more generously in this situation and higher doses have to be

given. It should also be considered that in cases of hyperfibrinolysis  $MCF_{AP}$  should be used for evaluation of clot firmness rather than  $MCF_{EX}$ . This also applies to the indication of platelet substitution. Before the application of fibrinogen, however, hyperfibrinolysis should be stopped with antifibrinolytic drugs, because otherwise the generation of fibrin and fibrinogen degradation products will be amplified by fibrinogen administration and coagulation disorder may be exacerbated.

It is difficult to achieve a sufficient increase in plasma fibrinogen level by therapy with fresh frozen plasma (FFP) (79). The mean fibrinogen concentration in FFP, obtained naturally from healthy donors without acute or chronic inflammation, is 2.5 g/l (14). Thus, the increase in fibrinogen con-

centration in plasma can only be obtained by using large amounts of fresh frozen plasma (20–30 ml/kg body weight, corresponding to 8–12 units of 200 ml for an 80 kg patient) (10). It is not possible to increase the fibrinogen concentration in the patient's plasma above 2.5 g/l because of the low fibrinogen concentrations in FFP.

Especially in case of transfusion of large amounts of FFP citrate accumulation has to be taken into account, which may result in citrate anticoagulation and hypocalcaemia. Large amounts of virus inactivated S/D plasma also present the risk of increasing hyperfibrinolysis because of the inactivation of alpha-2 antiplasmin during SD-process (5, 13, 28). On the other hand, quarantined plasma carries the risk of transfusion related acute lung injury (TRALI)

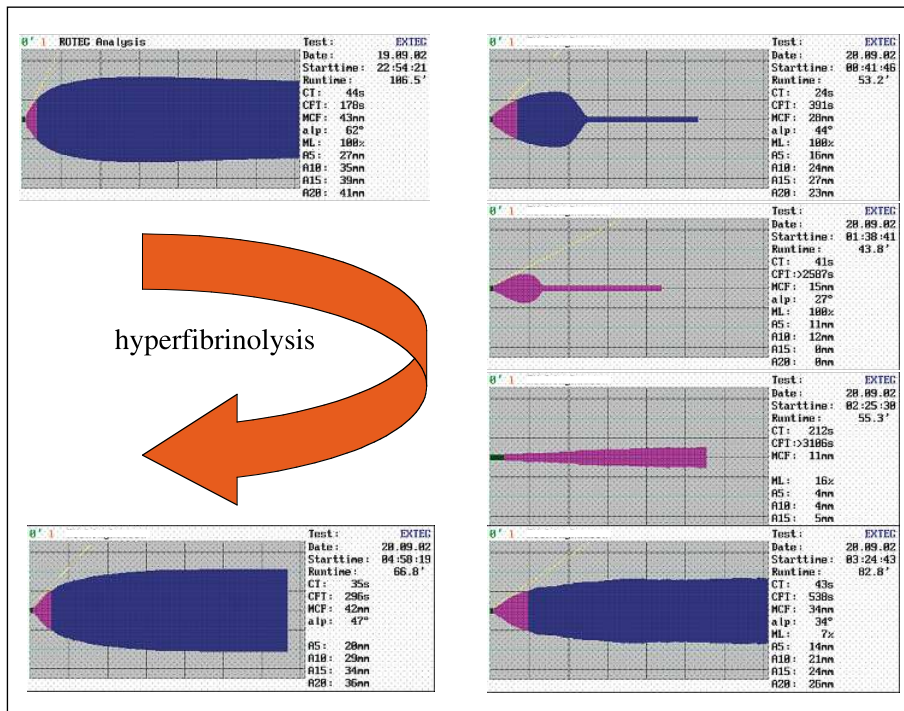


Fig. 7 Case study: Hyperfibrinolysis during liver transplantation

(83). The incidence of TRALI after quarantined plasma transfusion is 1:5,000 with a mortality of 5%. At 15%, TRALI is the second most common reason of transfusion related death (73). It has not been seen after giving S/D plasma or coagulation factor concentrates (71).

### Administration of platelet concentrates

Besides fibrinogen clot firmness is most dependent upon platelets. In cases of diffuse bleeding with  $MCF_{EX} < 45$  mm and  $MCF_{FIB} > 8$  mm administration of platelet concentrates is indicated. These patients often have

a prolonged clot formation time too ( $CFT_{EX} > 300$  s or  $CFT_{IN} > 300$  s), without detection of any heparin effect ( $CT_{HEP} \approx CT_{IN}$ ).

In absence of diffuse bleeding platelets are only given if  $MCF_{EX} < 35$  mm and  $MCF_{FIB} > 8$  mm and further blood loss during surgery is expected.

Whether the trigger for platelet transfusion can further be shifted in the direction of fibrinogen replacement is the subject of further studies. It has to be taken into consideration that platelet transfusion is associated with clinically relevant risks. Primary, the incidence of bacterial contamination of platelet concentrates is 1:1000 to 1:3000 and thus significantly higher than other blood products, because of the need for storage of platelet concentrates at room temperature. This means that platelet concentrates carry the highest risk of transfusion-associated infections. Transfusion of bacterially-contaminated platelet concentrates results in clinical sepsis in 6–20% (overall incidence 1:15000) and leads to death in about 1.5–5% (overall incidence 1:60000) (9, 56). The risk of bacterial contamination in pooled platelet concentrates in comparison with apheresis platelet concentrates is 2 to 6-fold higher. In platelet concentrates older than four days the risk of bacterial contamination rises by the factor of 5 additionally (60, 61, 88).

Furthermore, the risk/benefit estimation for administration of platelet concentrates must also take into account that during reperfusion of the graft activated platelets are thought to be responsible for microembolisation of the pulmonary circulation (25, 72).

It has to be taken into account that in cases of massive diffuse bleeding and  $MCF_{EX} < 25$  mm a combined administration of fibrinogen and platelet concentrates often is required – supplemented with prothrombin complex concentrate (PCC) or FFP if necessary (Fig. 6, part 3).

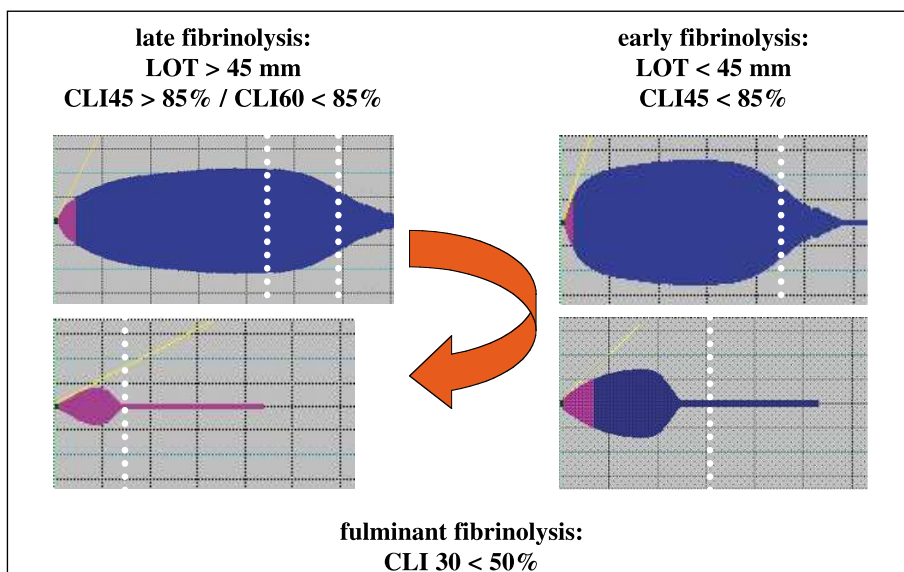


Fig. 8 Severity of hyperfibrinolysis

### Shortening of coagulation time

Whereas fibrinogen concentration and the platelets are the most important determinants of clot firmness, the other clotting factors are responsible for the rate of thrombin generation. Deficiency in enzymatic coagulation



factors cause a prolongation of the coagulation time (CT) in EXTEM and/or INTEM. However, there is only a minor correlation between  $CT_{EX}$  and PT or between  $CT_{IN}$  and aPTT. The need for a therapy with coagulation factor concentrates or FFP can be expected if  $CT_{EX} > 80$  s or  $CT_{IN} > 240$  s. Yet, in these cases a prolongation of coagulation time due to heparin effects has to be excluded ( $CT_{HEP} \approx CT_{IN}$ ) (58) (Fig. 6, part 3).

### Administration of prothrombin complex concentrate (PCC) or FFP

Prolongation of  $CT_{EX} > 80$  s suggests reduced activity of vitamin K dependent coagulation factors and can be treated with PCC. The  $CT_{EX}$  allows only rough estimation of PT and not the calculation of the amount of PCC needed for replacement therapy. If a certain PT has to be obtained, measurement of PT is essential. To achieve a clinical improvement in the activity of vitamin K dependent coagulation factors (increase in PT of about 20%) it is usually necessary to administer adults about 1,500 IU PCC (20 IU/kg body weight) or alternatively a transfusion of 8 to 12 units of FFP (20–30 ml/kg body weight).

The thrombogenic risk of modern PCC concentrates is low, since they do not contain an excess of prothrombin (15, 48, 70). In patients with liver cirrhosis and reduced antithrombin levels, administration of antithrombin prior to the PCC should be considered (84). However, FFP therapy may lead to hypervolaemia, which may lead to a reduction in one year survival rate of LTX patients, as it has been shown in a study of Massicotte (52).

If  $CT_{IN}$  is prolonged  $> 240$  s administration of FFP must be considered, since factor VIII is not contained in prothrombin complex concentrates (PCC). At least 20 to 30 ml FFP per kg body weight must be given to achieve a clinically relevant improvement in haemostasis (10).

Alternatively, factor VIII concentrate can be given, if there has been detected an isolated prolongation of CT in INTEM. A heparin effect should be excluded as the cause of CT prolongation ( $CT_{HEP} \approx CT_{IN}$ ). In hyperfibrinolysis, however, production of fibrin and fibrinogen split products as well as

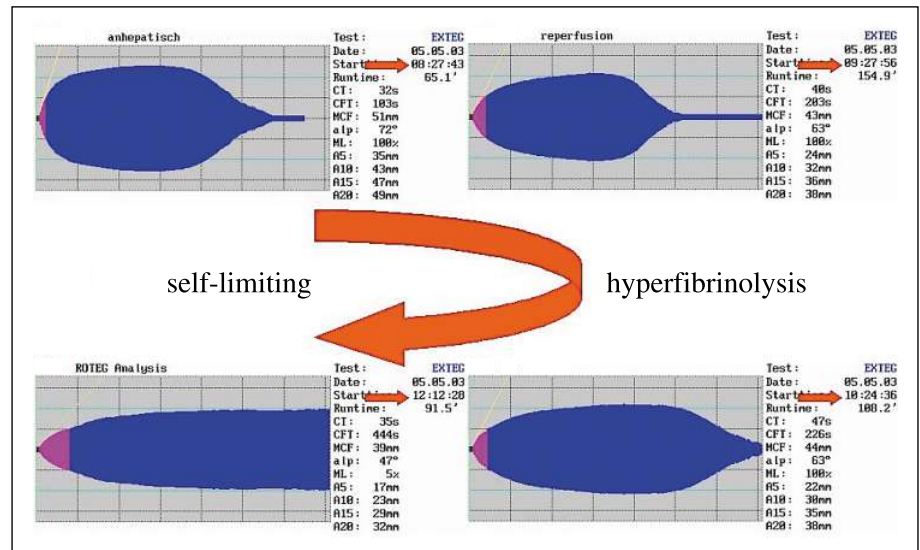


Fig. 9 Case study: Self-limiting hyperfibrinolysis after reperfusion of the liver graft

consumption of factor XII can lead to a prolongation of  $CT_{IN}$ , without clinically relevant effects on haemostasis.

Furthermore, high dose administration of aprotinin leads to inhibition of Factor XI

and thus to prolongation of CT in INTEM (62). Therefore, therapy with coagulation factor concentrates or FFP is only indicated because of CT prolongation in cases of clinically relevant bleeding.

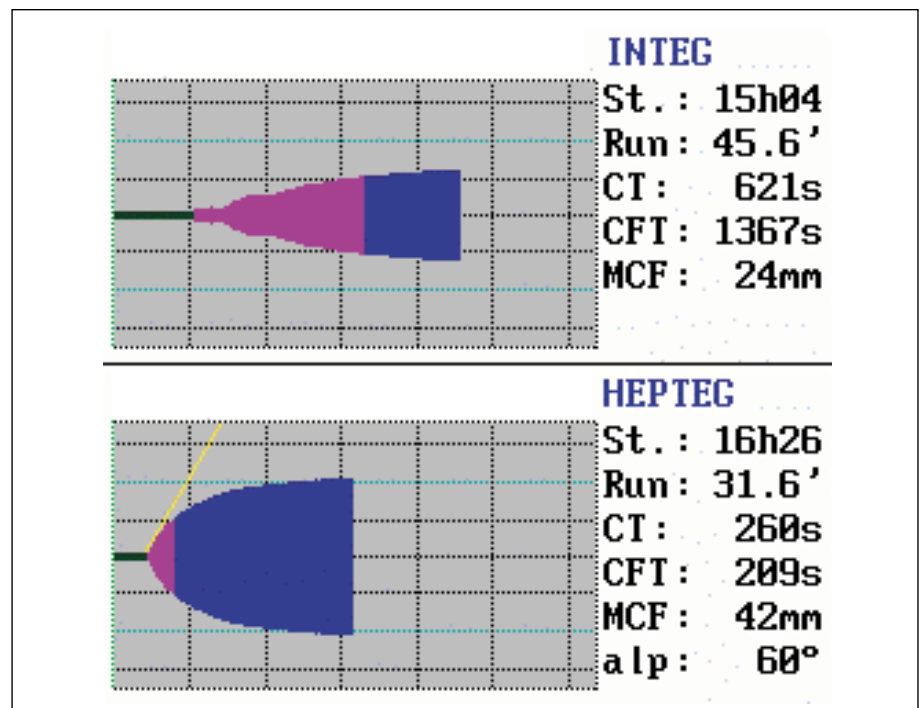


Fig. 10 Detection of endogenous heparinoids by ROTEM® analysis after reperfusion of the liver graft



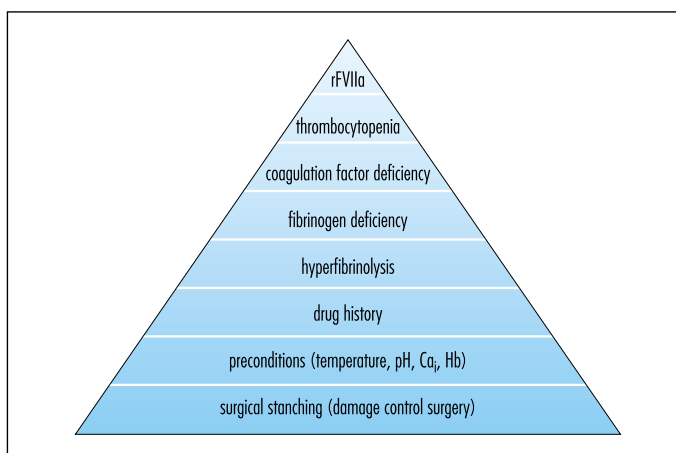
### Administration of protamine\*

During liver transplantation, heparin-related disturbances of haemostasis can be expected (27, 40) (Fig. 10). Endogenous heparinoids can be released on reperfusion of the liver graft. Heparin filled catheters (patients from the ICU requiring dialysis or haemofiltration), rinsing solutions used by the surgeons, and cell saver blood (especially during emergency wash program) have to be taken into account as sources for exogenous heparinoids. Typical sign of a heparin effect is a  $CT_{IN} > 240$  s in association with a significantly shorter coagulation time in HEPTTEM ( $CT_{HEP}/CT_{IN} < 0.75$ ) (58).

Although heparin induced prolongation of the  $CT_{IN}$  is commonly observed during liver transplantation, it seldom requires treatment. If there is no clinically relevant bleeding, the heparin effect can be allowed to fade away. However, it is reasonable to clarify the reason of the prolongation of  $CT_{IN}$  to avoid unnecessary replacement of coagulation factors.

Especially in case of a flatline in INTEM, a heparin effect should first be excluded or confirmed by measuring CT in HEPTTEM, before starting treatment with coagulation factors or platelets. This can only be neglected if a fulminant hyperfibrinolysis has already been detected.

\* Only if heparin effect is undesired and in presence of diffuse bleeding!



**Fig. 11**  
Pyramid of therapy of coagulopathies

### Administration of antithrombin

The indications for administration of antithrombin (AT) cannot be determined by ROTEM®. Antithrombin replacement in patients with liver cirrhosis can be considered in the following circumstances:

- $AT \ll PT$  (%) ( $PT$  (%) –  $AT > 20\%$ ),
- replacement therapy with high doses of PCC (if  $PT$  (%)  $\geq AT$ ).

In cases of coadministration of antithrombin, fibrinogen and PCC, antithrombin should be given first, then fibrinogen and finally PCC in order to minimise the risk of thromboembolic events (84).

### Specific reduction of single coagulation factors (e. g. FVIII)

By adding single coagulation factors into ROTEM® tests, it is possible to investigate whether any impairment of haemostasis, detected in ROTEM®, can be affected by targeted administration of a single coagulation factor. The following constellation may indicate factor VIII deficiency:

- $CT_{IN} > 240$  s and  $CT_{HEP} \approx CT_{IN}$  and normalisation of the  $CT_{IN}$  after addition of 0.2 IU factor VIII (e. g. Haemate® HS) in the INTEM test.

If a positive effect can be demonstrated in ROTEM®, therapy with factor VIII concentrate (20–40 IU per kg body weight) or with FFP (30 ml per kg body weight) can be conducted.

### Evidence of factor XIII deficiency

A reduction in clot firmness over time that cannot be inhibited by addition of aprotinin, and which is stabilised by addition of Factor XIII in EXTEM test, can be interpreted as an evidence of factor XIII deficiency:

- $MCF_{EX} < 45$  mm and  $CLI60_{EX} < 88\%$  and  $CLI60_{AP} < 90\%$  and significant improvement of  $CLI60_{EX}$  after addition of 0.2 IU factor XIII (e. g. Fibrogammin®) in ROTEM.

Treatment with factor XIII concentrate (15–30 IU per kg body weight) or with FFP (30 ml per kg body weight) can be conducted, when a positive effect in ROTEM® can be demonstrated (81).

### Administration of recombinant factor VIIa (NovoSeven®)

Besides the classical indications for therapy with recombinant factor VIIa (rFVIIa) – haemophilia with inhibitors and Glanzmann's thrombasthenia – rFVIIa is used in off-label status in clinical situations with manifest diffuse bleeding, which can not be stopped by standard therapy (2, 26, 39, 66). A dosage of 90 µg/kg body weight or 4.5 KIU/kg body weight is recommended. If the treatment is not sufficient, repetition of administration is required after 15 minutes. Caused by the short half-life time of rFVIIa it is sometimes necessary to repeat the treatment after 1 to 3 hours.

Despite a very promising pilot study, a positive effect of prophylactic administration of rFVIIa on transfusion requirements could not be proved in liver transplantation (29, 47, 65).

Since the use of rFVIIa has been associated with very high costs, the conditions for its successful use should be fulfilled in order to minimize the risk of treatment failure. Preconditions for the off-label use of rFVIIa are:

- massive diffuse bleeding,
- pH  $> 7.2$ ,
- no heparin effect ( $CT_{HEP} \approx CT_{IN}$ )
- no hyperfibrinolysis ( $CLI30_{EX} > 85\%$ )
- $MCF_{FIB} \geq 8$ –10 mm (fibrinogen  $> 150$  mg/dl)
- $MCF_{EX} \geq 30$  mm (platelets  $\geq 20000/\mu l$ ).

According to the concept of coagulation management used in Essen, rFVIIa is administered only, if diffuse bleeding does not stop even after optimisation of the coagulation by standard therapy (Fig. 6, part 3 and Fig. 11). The absence of heparin and hyperfibrinolysis is essential. The criteria for this “last-ditch” use of rFVIIa are:

- pH >7.2 (55),
- no heparin effect ( $CT_{HEP} \approx CT_{IN}$ )
- no hyperfibrinolysis ( $CLI30_{EX} >85\%$ )
- $MCF_{FIB} >16$  mm (fibrinogen >300 mg/dl)
- $MCF_{EX} >55$  mm (platelets  $\geq 80\,000/\mu l$ ),
- $CT_{EX} <80$  s (PT >50%),
- nevertheless, persistent massive diffuse bleeding ( $\geq 4$  units PRBC/h).

It has to be taken into consideration that the clinical effects of rFVIIa do not correlate well with changes detectable in the ROTEM test in vitro (16, 22, 34).

## Non-surgical bleeding

As ROTEM<sup>®</sup> does not detect all kinds of coagulation disorders, clinical important bleeding can occur in normal ROTEM<sup>®</sup> tests. In these cases vasculopathies, von-Willebrand-disease and platelet function disorders (e. g. caused by antiplatelet drugs or phytopharmaca) should be considered. These platelet function disorders are not detected by ROTEM<sup>®</sup> analysis, since platelets in ROTEM<sup>®</sup> tests are stimulated by large amounts of thrombin. Thus, inhibition of individual activation pathways – such as arachidonic acid, ADP or collagen – is hidden. Possibly, the Multiplate<sup>®</sup> – a new platelet function analyser based on impedance aggregometry – may fill this diagnostic void (Fig. 4).

Besides, hypothermia, acidosis, hypocalcaemia and anaemia deteriorate the preconditions of haemostasis significantly. This can lead to clinically relevant dysfunction of the coagulation system (Fig. 11). Thus, hypothermia at a body core temperature below 35°C, which can occur quickly in infants and children, has to be avoided and treated consequently. Determination of classical coagulation parameters is usually performed at 37°C and thus the effect of hypothermia is not considered. In contrast to

this measurement in ROTEM<sup>®</sup> system can be carried out at patient's temperature (30–40°C). This allows evaluation of coagulation status at the patient's body temperature.

Since many coagulation factors have their optimum pH in alkaline conditions, acidosis leads to a significant reduction in thrombin generation (51, 55, 86). During liver transplantation, acidosis with a pH <7.2 frequently occurs in patients with fulminant liver failure, with protracted shock and after reperfusion of organs with long time of ischaemia. As known from patients with multiple trauma, a combination of hypothermia, acidosis and coagulopathy interferes survival (11, 17, 37). This has led to the term „trauma triad of death” (12, 57, 77).

Anaemia with a haemoglobin concentration below 8 g/dl can influence primary haemostasis significantly. It is caused by two facts. On the one hand red blood cells ensure that platelets are in the marginal stream of the vessels enabling the interaction between platelets and the exposed subendothelium of the damaged vessel wall (1, 36, 85). On the other hand, erythrocytes integrated in the clot seem to provide platelets with arachidonic acid, ADP and phospholipids and thus enhance platelet function (30, 82). Therefore, patients with manifest, diffuse bleeding should have at least a haemoglobin level of 8–10 g/dl.

Finally, it should be considered that – especially in patients with liver insufficiency – transfusion of large amounts of FFP may lead to hypocalcaemia with a concentration of ionised calcium ( $Ca_i$ ) of less than 1 mmol/l due to citrate overload. Beside an anticoagulational effect, it can impact the cardiovascular system essentially, too (3, 42, 43, 50).

These pathophysiological conditions can be counteracted by the following therapeutic options (Fig. 11):

- Pay attention to preconditions: avoidance and treatment of hypothermia <35°C, acidosis <7.2, hypocalcaemia  $Ca_i <1$  mmol/l and anaemia with Hb <10 g/dl,
- Administration of DDAVP (0.3 µg/kg body weight over 30 minutes) if required in combination with aprotinin (or tranexamic acid); in acquired thrombocyto-

pathy (acetylsalicylic acid, uraemia) or von-Willebrand-disease type I; DDAVP does not have any effect on clopidogrel and ticlopidine induced platelet dysfunction!

- Administration of platelet concentrates in case of clopidogrel and ticlopidine induced platelet dysfunction,
- administration of Haemate HS (20–40 IU/kg body weight in von-Willebrand-disease type II or III or in distinctive factor VIII deficiency (7),
- administration of PCC in patients with oral anticoagulation with vitamin K antagonists or other causes of PT <30%; possibly in combination with antithrombin,
- administration of Factor XIII concentrate (15–30 IU per kg body weight) in acquired Factor XIII deficiency (particularly in patients with Child-C-cirrhosis) (81),
- administration of recombinant Factor VIIa unless otherwise uncontrollable bleeding (26).

### Conflict of interest

The author points at associations with the following companies: Dr. K Görlinger held scientific lectures on fee basis for Novo Nordisk and CSL Behring.

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