

Andre M. De Wolf

## Introduction

Liver transplantation (LTx) continues to result in significant transfusion requirements, although less so than in previous decades. Blood transfusion is associated with increased morbidity and mortality, emphasizing the need to further reduce the need for blood product transfusion [1]. The current almost ubiquitous use of the piggyback technique and overall better surgical techniques [2–4], and the recently introduced restrictive use of fluids to avoid increases in central venous pressure [5], have helped to reduce blood loss, but better management of hemostasis should allow a further reduction of transfusion requirements. Not surprisingly, there is significant inter-institutional variability in the need for blood transfusion, with some patients requiring no blood product transfusion at all [6].

Liver disease has for a long time been the prime example of acquired coagulopathy. However, this view is changing rapidly because it is now realized that the consequences of severe liver disease on the coagulation system are more complex than previously thought. There is now growing evidence that the coagulopathy is not as severe as the traditional coagulation tests suggest [7, 8]. Instead, the current view is that there is a new precarious balance between the pro- and anti-coagulant systems [9–11].

Since the traditional coagulation tests give an incomplete picture of the overall coagulability, we will have to adjust our interpretation of these tests. While all LTx centers use intraoperative coagulation monitoring based on traditional coagulation tests, many centers also use viscoelastic tests of clot kinetics since the introduction of thromboelastography into clinical practice by Kang in the early 1980s [12]. The inter-

pretation of these viscoelastic tests allows for a better coagulation management, including a more optimal use of blood products and a more directed pharmacologic intervention such as the use of antifibrinolytics to correct hyperfibrinolysis.

Hypercoagulability is now recognized as a potential problem in patients with severe liver disease. For example, anticoagulants are now considered in an attempt to prevent and/or treat portal vein thrombosis despite prolonged prothrombin time [11, 13–16]. However, hypercoagulability has also been observed during LTx, sometimes resulting in intracardiac thrombosis (ICT), an uncommon but frequently lethal complication [17]. The viscoelastic tests allow the early detection of hypercoagulability, and therefore guide us in the prevention and/or treatment of ICT during LTx.

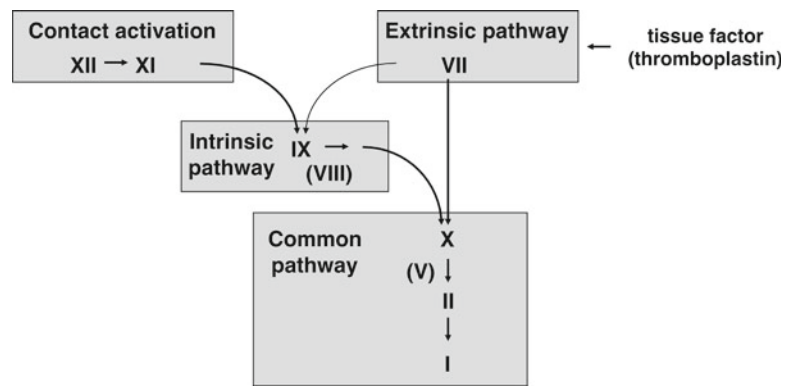
## Brief Review of Hemostasis

Hemostasis is essential to stop blood loss from a damaged vessel, and consists of vasoconstriction, platelet plug formation, and blood coagulation. The platelet plug formation and blood clot formation are closely tied together, potentiate each other, and occur simultaneously. In other words, this is an intricate interplay between platelets, coagulation factors, and components of the vessel wall [18–20]. Summarized, damage to blood vessel and/or endothelium results not only in the exposure of tissue factor (thromboplastin; expressed by fibroblasts and smooth muscle cells and under pathologic conditions [e.g., endotoxemia] also by endothelial cells and leukocytes), leading to activation of factor VII (factor VIIa; extrinsic pathway), but also in platelet adhesion to the subendothelial tissue by the von Willebrand factor (vWF, produced by endothelial cells, megakaryocytes, and subendothelial connective tissue) that binds to the platelet at the glycoprotein Ib/IX receptors, while there is also direct binding of platelets to subendothelial tissue through binding of glycoprotein Ia/IIa receptors to collagen (Figs. 36.1 and 36.2).

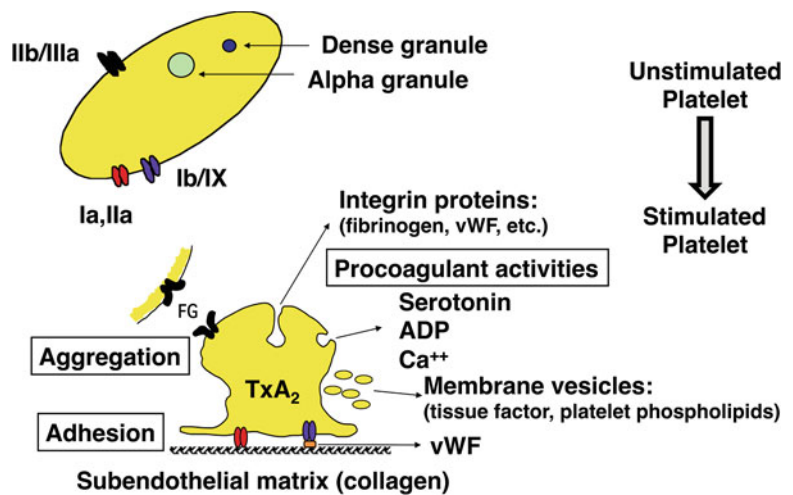
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**Fig. 36.1** Coagulation pathways. Activation of the extrinsic pathway (through activation of factor VII by tissue factor) and the intrinsic pathway (through contact activation of factor XII) ultimately results in the formation of fibrin (factor I), the building block of the clot. Most steps require the presence of  $\text{Ca}^{++}$  and platelet phospholipid. See text for details



**Fig. 36.2** Platelet activation. Platelet activation results in aggregation of platelets and several procoagulant activities. See text for details

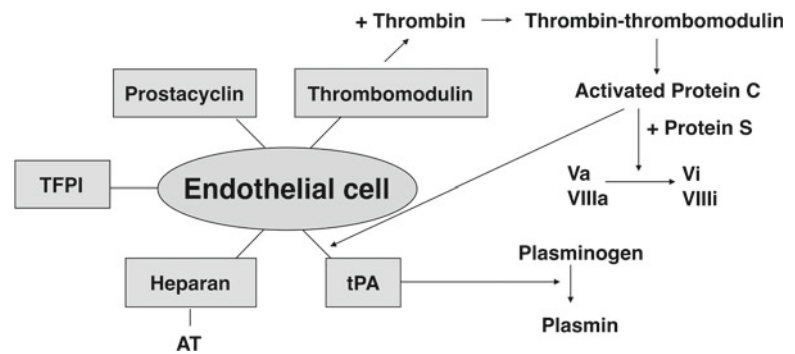


Platelet activation follows, resulting in a change in its shape (increase in surface area), the development of pseudopods, the shedding of microparticles expressing tissue factor and procoagulant phospholipids, the increased expression of membrane receptors, and the release of procoagulant factors from alpha granules (fibrinogen, vWF, thrombospondin [a platelet aggregate stabilizer]) and dense granules (ADP, serotonin, calcium) (Fig. 36.2). Thrombin and collagen intensely and massively activate platelets; this results in the further release of thromboxane  $\text{A}_2$  (vasoconstrictor as well as platelet activator) functioning as a positive feedback loop in the activation of platelets. Moderate platelet activators include ADP and thromboxane  $\text{A}_2$ , while weak platelet activators include epinephrine,  $\text{PGE}_2$ , serotonin, and ATP [20]. Aggregation of platelets is the result of fibrinogen, fibronectin, vitronectin, and vWF bridges between glycoprotein IIb/IIIa receptors on adjacent activated platelets. In addition, factor XII is activated (intrinsic pathway) by exposure to subendothelial tissue (collagen) especially in the presence of activated platelets through their release of polyphosphate, resulting again in activation of factor X and further production of thrombin (Fig. 36.1). Thrombin not only results in the activation of fibrinogen and platelets but also of factors V

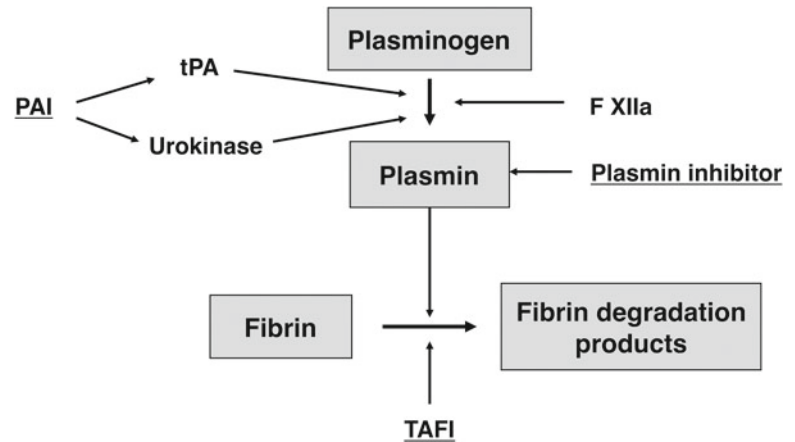
and VIII (positive feedback loop). The result is platelet plug formation and the promotion of clot formation (conversion of fibrinogen to fibrin) [11, 18, 20]. Finally factor XIII is activated by thrombin and enhances platelet adhesion to damaged endothelium, stabilizes the formed fibrin clot through cross-links increasing its resistance to lysis, and stimulates tissue granulation and eventually repair.

The processes described in the previous paragraph are quite complex and are influenced by procoagulant as well as anticoagulant factors while there are also feedback mechanisms with amplifying and inhibiting loops. Although it is clear that clot formation has to be efficient, it is important that these processes are localized and regulated at the same time in order to limit clotting to the site of vessel injury. Indeed, this is essential in order to preserve life because clot formation that goes unchecked would result in massive intravascular clotting. There are several potent mechanisms that normally limit the clot formation to the site of vascular injury, preventing thrombosis in healthy vessels (Fig. 36.3). When thrombin is formed near healthy endothelium, it binds to thrombomodulin expressed on endothelium and thereby activates protein C. With protein S as a cofactor, protein C (both synthesized in the liver and vitamin K dependent) then

**Fig. 36.3** Anticoagulant pathways. The normal endothelial cell plays a crucial role in limiting the clot formation to the site of vessel injury. See text for details. *TFPI* tissue factor pathway inhibitor; *AT* antithrombin; *tPA* tissue plasminogen activator



**Fig. 36.4** Fibrinolytic system. Activators and inhibitors of the fibrinolytic system. Inhibiting factors are underlined. *PAI* plasminogen activator inhibitor; *tPA* tissue plasminogen activator; *TAFI* thrombin-activatable fibrinolysis inhibitor. See text for details



inactivates factors Va and VIIIa. Protein S has other anticoagulant activities as well [20]. Antithrombin (AT) neutralizes most of the enzymes generated during activation of the clotting cascade, especially thrombin and factors Xa and IXa. The irreversible complex that is formed by the binding of AT and thrombin is thrombin-antithrombin (TAT) and is a sensitive marker of thrombosis. Heparin increases the activity of AT by at least 1000-fold. Heparinoids and heparan (expressed by healthy endothelium) have similar effects as heparin. Prostacyclin and nitric oxide, released by healthy endothelium, inhibit platelet activation, and tissue factor pathway inhibitor (TFPI), secreted by and expressed by endothelial cells, inhibits factors VIIa and Xa. Finally, plasminogen is activated to plasmin by the release of tissue plasminogen activator (tPA) by healthy endothelium (activated protein C promotes this), and by thrombin, fibrin, and factor XIIa, lysing any fibrin that would have been produced in healthy vessels. Plasmin not only lyses fibrin but also inactivates factors Va, VIIIa, and XIIa. Thus, normal endothelium prevents clot formation by the expression of heparan (activating AT), thrombomodulin (activating protein C), and TFPI, and by the release of prostacyclin, tPA, and TFPI (Fig. 36.3). ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs), synthesized in hepatic stellate cells, cleaves the very large (“hyperactive”) vWF multimers. Deficiency of ADAMTS13 (as a result of severe liver

disease or consumption) results in increased platelet activity and various microangiopathies [21]. Disturbances in this complex hemostatic balance can result in hypocoagulation or hypercoagulation.

Fibrinolysis of the formed clot is essential in the eventual restoration of blood flow. This is done through the activation of plasminogen into plasmin, and this process is also controlled by various activators and inhibitors (Fig. 36.4). Activators include tPA, urokinase plasminogen activator, and factor XIIa, and inhibitors include tPA inhibitor (plasminogen activator inhibitor or PAI, released by endothelium), plasmin inhibitor, and thrombin-activatable fibrinolysis inhibitor (TAFI). Here too, disturbances of this balance may result in hyperfibrinolysis (hemorrhage), or hypofibrinolysis (increased risk of thrombosis).

### Coagulation Changes in Chronic Liver Disease (Cirrhosis)

For many years, the impaired synthesis of clotting factors (factors I, II, V, VII, IX, X, XI, XII) by the dysfunctional liver and thrombocytopenia has been considered to result in severe coagulopathy [22]. Vitamin K malabsorption contributes to the coagulopathy through impaired production of factors II, VII, IX, and X. The platelet count is reduced mainly

due to splenic sequestration, decreased production (reduced synthesis of thrombopoietin in the liver, hepatitis C infection, folic acid deficiency, and chronic alcohol abuse), and thrombin-mediated platelet consumption [9, 11, 23–25]. There is some evidence of impaired platelet aggregation, reduced adhesiveness, and impaired procoagulant properties of platelets as a result of reduced production of thromboxane  $A_2$  and defective signal transduction [26]. Others however have found no evidence of platelet dysfunction [27, 28]. Reduced concentration of factor XIII is seen in a minority of patients with severe liver disease (21 %), and may contribute to increased bleeding [29]. Also, low factor XIII concentration has been associated with increased mortality [29]. The clinical significance of fibrinogen abnormalities (dysfibrinogenemia) is currently unclear [24].

On the other hand, there are changes that enhance thrombus formation: there is a reduction in the concentration of inhibitors of the coagulation system such as protein C, protein S, AT, and tissue factor pathway inhibitor (TFPI) [9, 11, 30, 31], and elevated levels of factor VIII (produced by endothelial cells in kidney, spleen, lungs, and brain) and vWF [32, 33]. Deficiency of ADAMTS13 as a result of severe liver disease results in increased platelet clumping [21]. ADAMTS13 is present in fresh frozen plasma, which is the only available source of ADAMTS13. Here too the increased vWF concentration and reduced ADAMTS13 are rebalanced by a reduction in platelet count (and possibly reduction in platelet function); therefore platelet transfusion should only be done based on bleeding complications, NOT on platelet count [34]. There is evidence for adequate thrombin generation in patients with severe liver disease or undergoing LTx, validating the concept of the rebalancing of the pro- and anti-coagulant systems [8, 35].

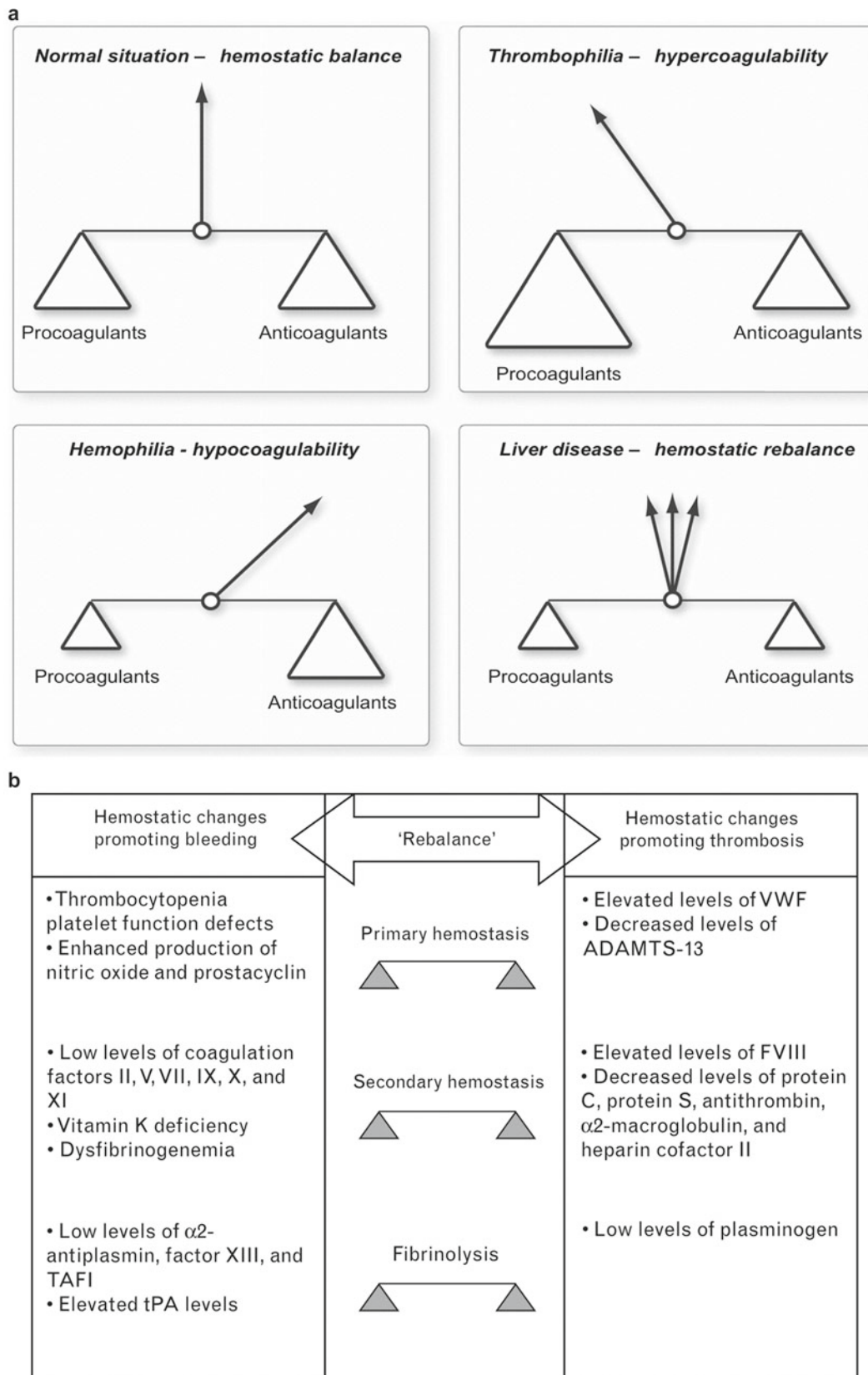
Changes in the fibrinolytic system mimic the changes in the coagulation system. There is a reduction of both pro- and antifibrinolytic factors: there are decreased levels of plasminogen and  $\alpha_2$ -antiplasmin, but increased levels of tPA and its inhibitor PAI [36]. Although tPA is synthesized by endothelial cells, it is metabolized by the liver, resulting in increased concentrations in liver disease [11, 37]. In most patients this results in a new balance, but in a minority of patients there is increased tPA activity. Some feel that a hyperfibrinolytic state in chronic liver disease, at least in part due to a decrease in thrombin activatable fibrinolysis inhibitor (TAFI, synthesized in the liver) concentration, may contribute to bleeding [38]. Bacterial infection plays a role by stimulating the release of tPA, contributing to a hyperfibrinolytic state [39]. The hyperfibrinolytic state can be documented by the presence of D-dimers [40].

Overall, the simultaneous and opposing changes in both the coagulation and fibrinolytic systems in patients with liver disease are now felt to result in a new balance (Fig. 36.5) [31, 41, 42]. This fragile coagulation balance can be tipped into a

state of severe hemorrhage or, less frequently, thrombosis. We have all observed that patients with severe liver disease have episodes of hemorrhage, most frequently intestinal hemorrhage mainly caused by portal hypertension. Also, bleeding may be provoked by stressing factors such as infection or renal failure [42, 43]. In addition, endogenous heparinoids may be released from the endothelium in the presence of bacterial endotoxins, and their clearance may be reduced [44]. Similarly, a state of hyperfibrinolysis can be triggered by inflammatory mediators and endotoxins. However, patients with cirrhosis also have a higher incidence of peripheral thrombosis with thromboembolism and portal vein thrombosis despite abnormal PT or INR [24, 42, 45, 46]. Obviously reduced flow in the portal vein contributes to this complication, but under the right circumstances and with the right triggers, some of these patients become truly hypercoagulable; after all these patients have reduced concentrations of the inhibitors of the coagulation system and increased concentrations of vWF and factor VIII. The release of platelet-derived microparticles by endotoxemia or systemic inflammation may be such a trigger and result in a procoagulant effect by expressing phospholipids and tissue factor; this process is associated with systemic complications and adverse outcome in patients with acute liver failure [47–50]. Intracardiac thrombosis (ICT) has been observed during LTx, reflecting a state of hypercoagulability [17]. It is important to recognize that these patients are not “autoanticoagulated,” as frequently thought in the past [11, 42]. Also, certain types of liver disease are associated with a prothrombotic state. In patients with hepatocellular carcinoma this may be the result of hyperhomocysteinemia [51]. Patients with mild or moderate chronic cholestatic liver disease (primary biliary cirrhosis, primary sclerosing cholangitis) have a mild hypercoagulable state, likely the result of better platelet function (enhanced  $g_{pIb}/V/IX$  expression), higher fibrinogen concentrations, and lower degree of hyperfibrinolysis [26, 52].

Patients with severe liver disease may have, at the same time, grossly abnormal coagulation tests, signs of accelerated intravascular coagulation, and evidence of fibrinolysis [42]. Although tests frequently suggest the presence of disseminated intravascular coagulation (DIC), clinically evident DIC is rarely seen, and autopsy results indicate that fibrin depositions are uncommon [53]. It is possible that the high concentrations of D-dimers are the result of the formation of fibrin clot that is more susceptible to fibrinolysis, the increased levels of tPA, or the presence of abnormal fibrinogen; once again, endotoxemia may play a significant role [24, 54, 55].

So, the combination of the reduced concentration of coagulation factors, thrombocytopenia, changes that enhance thrombus formation, and the complex changes in the fibrinolytic system results in a new fragile equilibrium (Fig. 36.5). What are the clinical implications of this new understanding?



**Fig. 36.5** (a) New balance of coagulation in liver disease. Severe liver disease results in a new but more fragile balance of the coagulation system. Relatively small stimuli can result in a state of severe coagulopathy

or in hypercoagulability. (b) Changes in pro- and anticoagulant factors in liver disease. Concentrations in both pro- and anticoagulant factors are changed, resulting in a new balance of the hemostatic system



First, there is a poor relationship between the degree of coagulopathy as determined by the traditional laboratory tests and the occurrence of gastrointestinal bleeding or duration of bleeding after liver biopsy [11, 56]. It is now felt that bleeding from esophageal varices is to a large degree related to a mechanical cause (portal hypertension), while coagulopathy does contribute. Also, blood loss during LTx is poorly related to the degree of abnormality of the traditional coagulation tests [57]. In addition, administration of recombinant factor VIIa shortens the PT results but has minimal clinical benefit during LTx [58]. Thus, coagulation management is better guided by the clinical picture and non-conventional coagulation tests than by the traditional coagulation tests.

### Changes in Traditional Coagulation Tests in Severe Liver Disease

The *prothrombin time (PT)* tests the extrinsic pathway of the coagulation system: it measures the time for the plasma to clot after addition of tissue factor of different origins. PT depends on factors I, II, V, VII, and X, and is a good indicator of severity of liver disease (especially acute liver disease because the extrinsic pathway is dependent on factor VII that has a short half-life). The international normalized ratio (INR) was meant to standardize the effect of the added tissue factor, but there is still inter-laboratory variability. The reduced synthesis of coagulation factors in severe liver disease is reflected in the prolongation of the PT, which is used as an independent marker of severity of liver disease and as a prognostic indicator. The *activated partial thromboplastin time (aPTT)* tests the contact activation (intrinsic) pathway; it is initiated by activation of the contact factors of plasma. The aPTT is also prolonged in patients with severe liver disease, but usually not as much as the PT. However, both PT and aPTT are poor predictors of bleeding in these patients because of the presence of compensatory mechanisms [41]. Also, these tests are not very sensitive regarding the effects of reduced concentrations of anticoagulants such as AT, protein C, and protein S, and don't take into account the interactions of the coagulation factors with platelets and the reduced concentration of factor XIII.

*Platelet count* is reduced in patients with severe liver disease, a result of diminished production in the bone marrow (bone marrow depression and altered thrombopoietin metabolism) and hypersplenism. *Platelet function* has been assessed by several tests in vitro, but their clinical usefulness has been disappointing [59]. *Bleeding time* assesses platelet function in vivo, but is highly influenced by factors such as vascular smooth muscle dysfunction in liver disease as well as by variability among those who perform the test. Thus, prolonged bleeding time is observed in up to 40% of

patients with cirrhosis [60], but its clinical relevance remains unclear [9, 28].

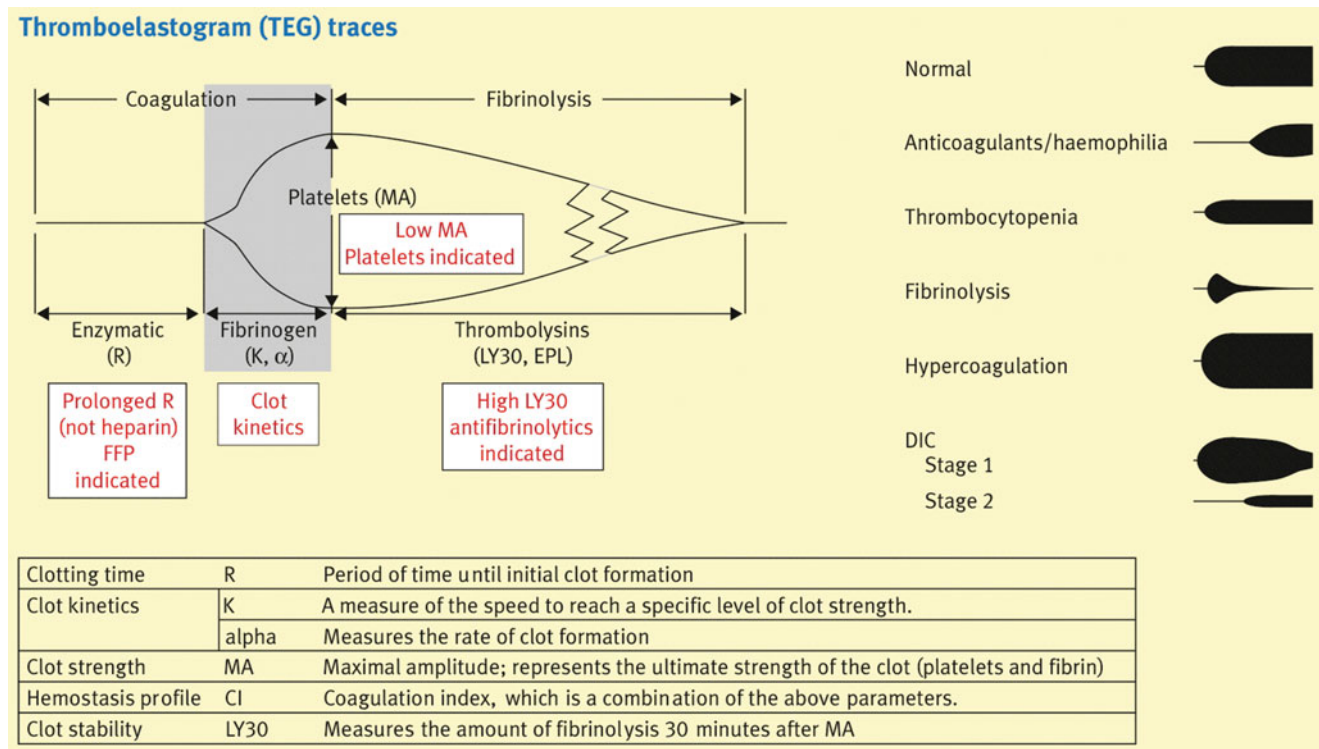
Measurements of *individual coagulation factors* can help in obtaining a more accurate diagnosis, but only the measurement of fibrinogen is of clinical significance to most anesthesiologists. *Fibrin degradation products and D-dimers* are present in both severe liver disease (as a result of a hyperfibrinolytic state and reduced clearance) and disseminated intravascular coagulation (DIC).

Overall, the conventional coagulation tests (PT, aPTT, INR, platelet count) do not reflect the compensatory mechanisms that play a major role. Therefore, despite abnormal coagulation tests, these patients do not necessarily bleed excessively clinically. Consequently, interventions attempting to normalize these tests may not be required before invasive procedures and during LTx [9].

### Monitoring of the Coagulation System During Liver Transplantation

Routine coagulation tests are performed at all transplant centers during LTx, and include at least PT, aPTT, platelet count, and fibrinogen concentration. Many centers use additional tests based on viscoelasticity measurements of clot strength to obtain a better, more complete view of the coagulation system; these tests include thromboelastography (TEG<sup>®</sup>), thromboelastometry (ROTEM<sup>®</sup>), and Sonoclot<sup>®</sup> [61–63]. The main advantage of these viscoelastic tests is that they monitor the coagulation from fibrin formation to clot retraction and fibrinolysis. In addition, these tests are performed on whole blood, allowing the interaction between the plasmatic pathways and platelets, and they can demonstrate the presence of hypercoagulability [64, 65]. TEG<sup>®</sup> and ROTEM<sup>®</sup>, and probably also Sonoclot<sup>®</sup>, provide valuable information on the fibrinolytic process [66].

TEG<sup>®</sup> and ROTEM<sup>®</sup> are clotting tests that determine the overall whole-blood coagulability by analyzing the viscoelasticity of the clot during its formation and dissolution [64, 65]. The TEG<sup>®</sup> analysis includes the effects of most of the factors that affect clot formation, with the endothelium as the only exception. The TEG<sup>®</sup> tracing displays the torque on a pin that is dropped in a cup containing whole blood that is oscillated 4° 45' in either direction every 4.5 s at 37 °C (Fig. 36.6). Without clot, the oscillation of the cup has no effect on the torsion wire, and the result is a straight line on the TEG<sup>®</sup> tracing. When there is clot formation, the maximum rotation of the torsion wire is recorded as the TEG<sup>®</sup> outline (thromboelastogram). Derived parameters include reaction time (*r* time; time to 2 mm amplitude, normal range 5–7 min), clotting time (*k* time; time from 2 to 20 mm amplitude, normal range 1.5–3 min), speed of clot propagation



**Fig. 36.6** Basics of TEG. Typical thromboelastography tracings for several coagulation abnormalities are presented, and specific therapeutic options for certain TEG abnormalities are suggested

(angle,  $\alpha$ , normal range 54–67°), maximum amplitude (MA, normal range 55–73 mm), and clot lysis index (amplitude 60 min after MA is achieved divided by MA, expressed in %). MA reflects the strength of the clot, and a gradual, small reduction in amplitude occurs following the development of the MA and reflects clot retraction, the result of fibrin-platelet interaction in which the platelet's actin cytoskeleton plays a major role. Clot retraction should be distinguished from hyperfibrinolysis, the result of premature breakdown of the clot by plasmin [67, 68]. The principles of the ROTEM® technique are similar except for a stationary cup and rotating pin, an optical detector system, and the inclusion of an electronic pipette [64, 65]. However, the terminology to describe the tracings is different. Also, because of the different materials that are used, the reference ranges of the TEG® and ROTEM® tracings are not the same [64, 65].

TEG® and ROTEM® allow global assessment of the coagulation system within 20–30 min, including clot initiation (platelet aggregation, platelet-fibrin interaction, fibrin cross-linkage), clot strengthening, clot stability, and eventually clot lysis [69]. Just by looking at the TEG® tracings it can be determined whether the patient has a normal coagulation profile or has hypocoagulability, hypercoagulability, or hyperfibrinolysis. A prolongation of  $r$  usually indicates inadequate coagulation factor concentration; a decreased  $\alpha$  is usually the result of low fibrinogen and to a lesser degree

platelet count or function; and a decreased MA mainly reflects inadequate platelet count or function and to a lesser degree low fibrinogen. Hypercoagulability is reflected by short  $r$  time, increased  $\alpha$  angle, and increased MA. Hyperfibrinolysis is seen as the rapid narrowing of the TEG tracing (Fig. 36.6). The interpretation of the TEG® can be improved by the addition of specific agents: hyperfibrinolysis in the blood sample can be blocked by adding a small dose of epsilon-aminocaproic acid, while heparin effect can be eliminated by adding heparinase or protamine; the resulting TEG® tracings can then be compared to the native TEG® tracing, allowing detection of hyperfibrinolysis or heparin effect in the patient. The clotting process can be accelerated by adding activators such as celite or tissue factor, and this allows a faster assessment of the coagulation system. However, the interpretation of the test then has to be based on adjusted normal ranges. Celite acts as a contact surface, activating factor XII, and platelets.

Several studies have investigated the relationships between TEG® parameters and traditional coagulation tests; overall the results have been poor [70, 71]. This is to be expected because of the completely different technologies that are used (tests on plasma or isolated platelets vs. whole blood); for example, PT and PTT tests end when fibrin starts to develop. However, when TEG® analysis is performed on platelet-inhibited whole blood or purified fibrinogen

solutions, good relationships are found between clot strength (TEG<sup>®</sup> variable MA) and fibrinogen concentration [72]. Management of the coagulation system has to be based not just on traditional coagulation tests and viscoelastic tests, but should be driven by the clinical need to intervene. Although TEG<sup>®</sup> and ROTEM<sup>®</sup> results do not always correlate well with the impression obtained from the surgical field, TEG<sup>®</sup> and ROTEM<sup>®</sup> are particularly helpful in determining how to improve clinical coagulopathy.

The viscoelastic tests have several advantages. These are rapid tests, providing us with a good overview of overall coagulability in 20–30 min. They allow the rapid detection of factor deficiency or inadequate platelet count or function, fibrinolysis, and heparin effect. Another advantage is that TEG<sup>®</sup> includes the effects of factor XIII on clot formation rate and strength ( $r$ ,  $\alpha$ , MA) while the traditional coagulation tests do not [73]. TEG<sup>®</sup> also allows us to determine the presence of hypercoagulability that cannot be discovered by traditional coagulation tests [70]. Finally, an increase in clot formation rate (as documented by a shortening of the  $r$  time on TEG<sup>®</sup>) has been observed as a result of reduced AT concentration, supporting the concept of the establishment of a new coagulation balance in patients with severe liver disease [74].

Another viscoelastic test is the Sonoclot<sup>®</sup>. A hollow, open-ended plastic probe is placed in a cuvette with the blood sample. The probe then oscillates vertically in the sample, and the clotting process is reflected in the gradually increasing impedance to movement [64]. Cuvettes with activators or inhibitors are available. Overall there is less experience with the Sonoclot<sup>®</sup> than with the other viscoelastic tests during LTx [66, 75, 76].

### **Intraoperative Changes in Coagulation and Their Management**

The main causes of bleeding during LTx include portal hypertension, inadequate surgical hemostasis, hypothermia, dilutional and/or consumption coagulopathy, hyperfibrinolysis, effects of synthetic colloids, and release of heparin-like substances and inflammatory mediators from the graft and other tissues. Clamping of portal vein and inferior vena cava (complete or partial) results in an increase in hydrostatic pressure distally in these vessels, contributing to blood loss. The concentration of platelets and most factors affecting coagulation (including fibrinolytic system and inhibitors) will reduce as a result of dilution and/or consumption. It seems logical that severity of liver disease influences transfusion requirements, related to more severe portal hypertension and coagulopathy. However, there is conflicting information on this [77, 78]. A lower transfusion requirement was observed in patients undergoing living donation LTx compared to cadaveric donation LTx, although many

factors besides MELD score and degree of coagulopathy could be responsible for this, such as better quality of the graft [79].

Proper coagulation monitoring is essential to manage the coagulation system perioperatively. Certain coagulation problems are associated with the stage of the LTx procedure. For example, surgical bleeding is more common in stages I and II, while hyperfibrinolysis is seen especially towards the end of stage II and early stage III. The most important blood products that are used to correct coagulopathy during LTx include platelets, fresh frozen plasma, and cryoprecipitate. There is limited experience with other blood products such as prothrombin complex and fibrinogen concentrates [80].

### **Immediate Preoperative Management and Stage I (Dissection)**

Because the bleeding risk is not nearly as bad as suggested by the traditional coagulation tests, it is not recommended to attempt to correct abnormal traditional coagulation tests immediately preoperatively or at the beginning of the LTx procedure. To the contrary, the routine administration of fresh frozen plasma, cryoprecipitate, or platelets at that time is expected to increase central venous and portal venous pressure, resulting in increased bleeding caused by increased hydrostatic pressure in the transected vessels [57, 78, 81]. Rather, a low CVP management is chosen by some, necessitating the use of vasoconstrictors to maintain systemic blood pressure [82]. Most anesthesiologists, myself included, however prefer to maintain normovolemia in order to maintain hemodynamic stability, thereby reducing the risk of renal impairment by maintaining its perfusion [83, 84]. Gradual correction of the coagulopathy should be started when intraoperative bleeding occurs and should be guided by coagulation monitoring. If bleeding occurs without evidence of oozing, i.e., surgical bleeding, an argument can be made for the administration of FFP in equivalent amounts to the administration of red blood cells to restore normovolemia and to maintain the fragile, new coagulation balance. Fresh frozen plasma contains not only coagulation factors but also inhibitors of the coagulation system (protein C, protein S, AT, TFPI). Platelet and cryoprecipitate administration are infrequently necessary at this stage, although their administration should be guided by platelet count, TEG/ROTEM, and observation of the surgical field. There is limited experience with prothrombin complex concentrate in liver transplantation [80]. This purified concentrate contains not just factors II, VII, IX, and X, but also protein C, protein S, and AT. Although the administration of prothrombin complex concentrate can normalize PT in patients with liver disease, its efficacy and safety during LTx have not yet been established [80]. Its main potential advantage would be its low volume.



## Management of Hyperfibrinolysis

Hyperfibrinolysis is usually seen towards the end of stage II and early stage III and is the direct result of increased concentrations of tPA in the presence of decreased concentrations of its inhibitors. tPA is released by the graft and mesenteric vessels on reperfusion, possibly related to ischemic damage of the endothelial cells [40, 85]. Although some centers routinely use prophylactic antifibrinolytics during LTx, others only administer antifibrinolytics when fibrinolysis is clearly present on TEG and there is evidence of significant oozing in the surgical field [86, 87]. Small doses are usually sufficient (e.g.,  $\epsilon$ -aminocaproic acid 250–500  $\mu$ g) but mild fibrinolysis in the absence of clinical bleeding does not require pharmacological intervention because it is usually self-limiting. The prophylactic use of antifibrinolytic agents has resulted in reduced transfusion requirements; most experience has been obtained with aprotinin, but since its withdrawal from the market in 2007 (due to renal toxicity and increased incidence of myocardial infarction), there is less interest in this practice. There seems to be a shift away from prophylactic use of antifibrinolytics towards a practice of administration of antifibrinolytic agents when fibrinolysis is clearly documented by TEG/ROTEM and when there is evidence of oozing in the field [88].

## Management of Heparin Effect

Heparin effect may be seen after graft reperfusion and is usually caused by the release of heparin that was part of the preservation solution [89]. If it is felt to result in clinical oozing, it can be antagonized with a small dose of protamine (25–50 mg or 1 mg/kg) [90].

## Use of Factor VIIa

Although VIIa administration improves PT and INR, there is no evidence that it results in a reduction in transfusion requirements; however it could be of value as a rescue therapy in uncontrollable bleeding [58, 91].

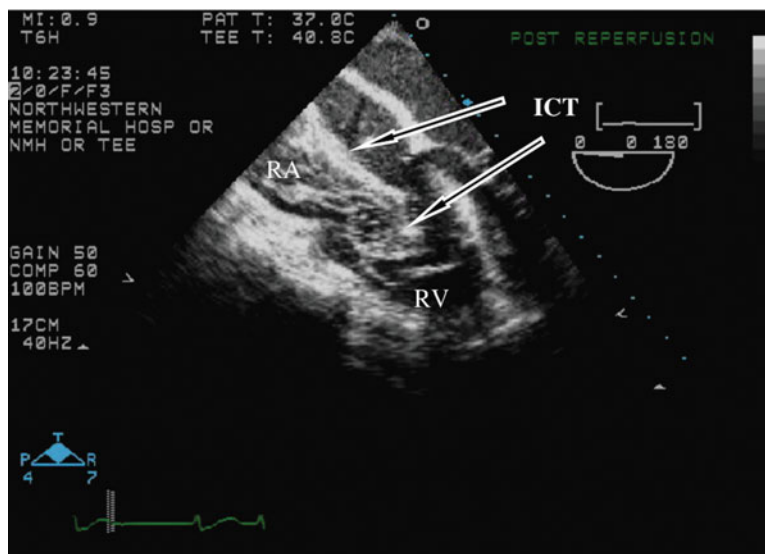
## Management of Hypercoagulability and Intracardiac Thrombosis (ICT)

Massive intracardiac thrombosis (ICT) has been documented during LTx, initially early after graft reperfusion, but later during all stages [17, 92, 93]. Remarkably this complication in the form of pulmonary thromboembolism during LTx associated with a hypercoagulable TEG had already been described by von Kaulla in 1966, although it is not clear whether this was truly ICT [94]. The estimated incidence is about 1–4%, and the mortality is likely about 50% [17, 93, 95]. ICT has to be differentiated from peripheral venous thrombosis with embolism to the heart: monitoring with transesophageal echocardiography has made it clear that during the development of ICT there is de novo clot formation in the heart, usually attached to the valves and pulmonary artery catheter (Fig. 36.7), but in extreme cases clots can be observed attached to the mitral or aortic valve, clearly not a result of embolization [17, 95]. Although the initial report on ICT described its occurrence immediately after graft reperfusion, it is now clear that ICT can happen unexpectedly at any time during LTx [17, 95, 96]. Sometimes the ICT spontaneously disappears, probably the result of secondary fibrinolysis [97].

It has been discussed already that in general clot formation in patients with severe liver disease is better than suggested

**Fig. 36.7** TEE of intracardiac thrombosis (ICT).

Transesophageal echocardiography (four-chamber view) in a patient with ICT. Clots can be observed in the right atrium (RA) and right ventricle (RV). Note the leftward shift of the interatrial and interventricular septa (from Boone et al. [92], with permission)



by traditional coagulation tests (reduced concentrations of protein C, protein S, and AT, and increased concentrations of vWF and factor VIII). However, some patients become overtly hypercoagulable in the presence of the right triggers especially because of the fragile balance of the coagulation system. Extensive surgery may release an overwhelming amount of tissue factor, with the diseased or absent liver unable to clear tissue factor or other activated coagulation factors. Release of endotoxins, possibly related to an ischemic insult to the intestines during portal vein clamping, and release of activators from leukocytes may further activate the coagulation system [98]. It is known that endotoxemia and severe systemic inflammation cause the expression of tissue factor on circulating monocytes, microparticles, and endothelial cells in the microvascular system, resulting in widespread activation of the coagulation system [20]. Despite some case reports linking the use of antifibrinolytics to ICT, there is no convincing evidence that their use increases the risk of ICT [95, 99].

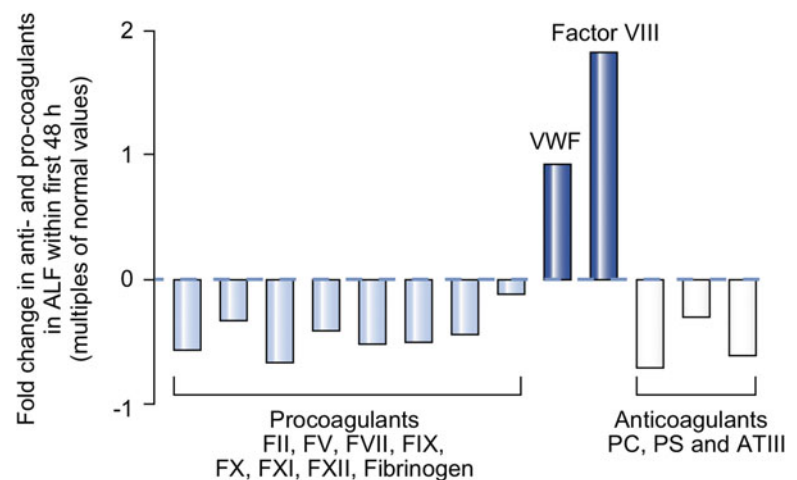
A hypercoagulable TEG tracing (very short reaction time, wide maximum amplitude), clotting of the TEG blood sample before it could be analyzed, and even clotting of a heparinized blood sample (indicating very low AT concentrations) have all been observed in several of these patients [17, 93]. However, ICT has been observed in the absence of hypercoagulability on TEG, probably because the patient can suddenly and at any time become hypercoagulable [100]. A flat-line TEG is, in my opinion, likely the result of hypercoagulability followed by severe secondary fibrinolysis [93, 101]. Early and correct diagnosis of ICT depends on routine transesophageal echocardiography and pulmonary artery pressure monitoring [92]. Early diagnosis allows immediate intervention with low-dose tPA (2–4 mg) that may be effective because it is administered very early in the clotting process before solidification of the clots [92]. Usually a small dose of heparin is administered as well. The

potential for rapid lysis of intracardiac clots is supported by a case report where the ICT was not present anymore during autopsy [102]. Higher dose tPA may be successful also but may be associated with more significant blood loss [103–105]. Supportive therapy consists of the administration of routine resuscitation drugs, including epinephrine, and cardiac compression [17, 93]. Thrombectomy has been tried, although it is frequently but not always futile [17, 96, 105]. In my opinion, prevention may include the use of low-dose heparin (3000–5000 U) in combination with FFP administration before clamping of the major vessels or whenever hypercoagulability is observed on TEG. Hypercoagulability has also been observed in other critically ill patients such as during ARDS, multiple organ failure, and severe tissue trauma, and is associated with increased tissue factor concentrations [70, 106].

### Management of Coagulopathy in Acute Liver Failure

Overall, the coagulation changes seen in patients with acute liver failure are similar to those seen in cirrhosis, with a proportional reduction (re-balancing) of procoagulant and anticoagulant proteins (Fig. 36.8) [107–109]. As a result, recent studies suggest that hemostasis in most of those patients is well preserved, despite abnormal traditional coagulation tests [108, 110, 111]. One exception is the reduced fibrinolytic potential in acute liver failure, the result of increased levels of PAI [108]. However, because PT and other conventional coagulation tests suggest significant coagulopathy, invasive procedures are frequently preceded by the administration of fresh frozen plasma and platelets. While these transfusions may not be needed at all, it may actually worsen intracranial hypertension as a result of an increase in central venous pressure. Some therefore prefer recombinant factor

**Fig. 36.8** Changes in concentration of pro- and anticoagulants in acute liver failure. Both procoagulants and anticoagulants are reduced to a similar extent, while vWF and factor VIII are elevated, resulting in a re-balancing of the coagulation system



VIIa, although it remains unclear whether this reduces the risk of bleeding [112]. Nevertheless, it is understandable that correction of coagulopathy is attempted before doing a high-risk procedure (placement of intracranial pressure monitor) because of the devastating consequences of intracranial bleeding [28].

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