

The Fibrinolytic Status in Liver Diseases

Frank W. G. Leebeek, MD, PhD¹ Dingeman C. Rijken, PhD¹

¹Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

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Address for correspondence Frank W. G. Leebeek, MD, PhD, Department of Hematology, Erasmus University Medical Center, 'S Gravendijkwal 230, 3015 CA Rotterdam, The Netherlands (e-mail: f.leebeek@erasmusmc.nl).

Abstract

The liver is the main site of synthesis and/or clearance of proteins involved in fibrinolysis. Therefore, chronic liver disease, including cirrhosis, leads to altered plasma levels of fibrinolytic proteins. Historical studies using in vitro clot lysis assays suggested that patients with chronic liver disease had accelerated fibrinolysis. Subsequent studies measured levels of individual pro- and antifibrinolytic proteins and showed that levels of tissue-type plasminogen activator are elevated. Plasma levels of plasminogen activator inhibitor-1 may also be altered, which leads to a shift in balance in the fibrinolytic system. Despite the fact that a more recent study using a plasma clot lysis assay challenged the existence of hyperfibrinolysis, other recent studies detected hyperfibrinolysis in a considerable number of patients with cirrhosis. Therefore, it is now recognized that hyperfibrinolysis may occur in 30 to 50% of patients with end-stage liver disease. A causal role of hyperfibrinolysis in bleeding is difficult to establish because also other concomitant changes in hemostasis occur. Treatment of hyperfibrinolysis consists of the use of fibrinolysis inhibitors, such as tranexamic acid. In this review we summarize current insights of the role of the liver in fibrinolysis, changes in fibrinolytic proteins, the potential clinical implications, and management of hyperfibrinolysis in liver disease.

Keywords

- fibrinolysis
- liver
- cirrhosis
- acute liver failure
- plasminogen activator
- α_2 -antiplasmin

In patients with acute liver failure or chronic liver disease, various changes in the fibrinolytic system may occur. The liver is the main site of synthesis of many factors involved in fibrinolysis, both pro- and antifibrinolytic proteins, such as plasminogen, α_2 -antiplasmin (α_2 -AP), and thrombin-activatable fibrinolysis inhibitor (TAFI). A reduced synthesis function of the liver leads to reduced levels of these factors in the circulation. In addition, the liver is involved in the clearance of tissue-type plasminogen activator (t-PA) and many protease-inhibitor complexes from the circulation. Therefore levels of t-PA and plasminogen activator inhibitor-1 (PAI-1) may also be altered in liver disease. Theoretically, ongoing fibrinolysis may also lead to decreased levels as a result of consumption. These changes may lead to a shift in the balance of the fibrinolytic system. Patients with liver disease have frequent bleeding episodes, mainly in the gastrointestinal tract such as variceal bleeding. It has been a long-standing dogma that patients with liver disease have a high risk of bleeding due to the hemostatic changes, including

hyperfibrinolysis. In this review we summarize the current insights on fibrinolysis in liver disease and the possible clinical implications and management of these patients.

The Liver and the Regulation of Fibrinolysis

The central step in the fibrinolytic system (► **Fig. 1**) is the conversion of the inactive proenzyme plasminogen into the active enzyme plasmin, which degrades fibrin into soluble fibrin degradation products.¹ Two immunologically distinct physiologic plasminogen activators catalyze the conversion of plasminogen: t-PA and urokinase-type plasminogen activator (u-PA).² The most important plasminogen activator for fibrin degradation is t-PA. In the absence of fibrin, t-PA has a low plasminogen activator activity. However, in the presence of fibrin, this activity is two orders of magnitude higher as a result of the binding of both t-PA and plasminogen to fibrin and the formation of a cyclic ternary complex.³

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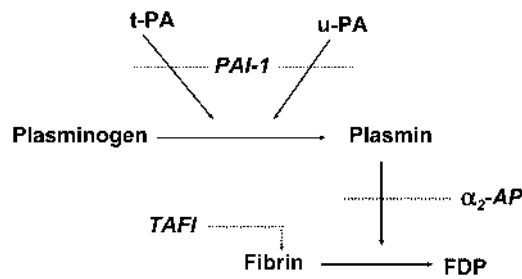


Fig. 1 Fibrin degradation by the fibrinolytic system. Plasminogen is converted into plasmin by tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA), which is regulated by plasminogen activator inhibitor-1 (PAI-1). Plasmin degrades fibrin into soluble fibrin degradation products (FDP) and is regulated by α_2 -antiplasmin (α_2 -AP). The fibrinolytic system is also regulated by thrombin-activatable fibrinolysis inhibitor (TAFI), which modifies the fibrin substrate.

Inhibition of the fibrinolytic system may occur both at the level of plasminogen activation, mainly by PAI-1⁴ and at the level of plasmin, mainly by α_2 -AP.⁵ Both inhibitors are members of the serine protease inhibitor (serpin) superfamily. An important mechanism of α_2 -AP involves its cross-linking to fibrin by the action of activated coagulation factor XIII.⁵ Fibrin degradation is additionally inhibited by TAFI. TAFI is the most recently discovered fibrinolysis inhibitor and represents a link between coagulation and fibrinolysis.⁶ The inhibitor is slowly activated by thrombin, but the activation is accelerated 1,250-fold by thrombomodulin. The activated form (TAFIa) is a plasma carboxypeptidase B and is relatively unstable under physiological conditions (half-life ~10 minutes). The antifibrinolytic activity of TAFIa is ascribed to the elimination of C-terminal lysine and arginine residues from partially degraded fibrin. This results in a strongly reduced binding of plasminogen on partially degraded fibrin and a concomitant reduction in the activation of plasminogen.⁷

The liver is strongly involved in the regulation of fibrinolysis in the circulation, because many fibrinolysis factors in blood are either synthesized or cleared by the liver. For instance, plasminogen, α_2 -AP, TAFI and fibrinogen, the precursor of fibrin are all predominantly synthesized by the liver. By contrast, t-PA is synthesized, stored, and secreted by vascular endothelial cells. Changes in the release of t-PA into the blood stream are achieved by two mechanisms: (1) a rapid, short-term release of t-PA, which occurs within minutes (acute release, regulated secretion) and (2) a long-term change in the rate of synthesis and constitutive secretion of t-PA.⁸ Storage pools have not yet been conclusively identified, but may include a t-PA/type 2 organelle for unstimulated secretion as well as Weibel-Palade bodies for stimulated secretion of t-PA.⁹ The origin of PAI-1 in blood involves a variety of cells.¹⁰ Under physiologic conditions liver (endothelial) cells, smooth muscle cells, adipocytes, and platelets could contribute to the levels of PAI-1 in blood. Under pathological conditions, additional cells may secrete large amounts of PAI-1, such as tumor cells, endothelial cells in response to inflammatory cytokines, and other inflammation-activated cells.

The role of the liver in the clearance of fibrinolytic proteins is most evident for the short-living proteins t-PA and PAI-1. The plasma half-life of t-PA in humans is only approximately 5 minutes, due to the recognition of t-PA probably by the mannose receptor on the liver endothelial cells and the low-density lipoprotein receptor-related protein (LRP) on the liver parenchymal cells.^{11,12} The plasma half-life of PAI-1 is somewhat longer than that of t-PA, but the liver represents also the main site of clearance.¹³ Because PAI-1 interacts with LRP in vitro, this protein is considered as a candidate receptor responsible for the in vivo clearance of PAI-1.¹⁴ However, more recent studies show that not LRP but other still unidentified receptors from the low-density lipoprotein receptor family are involved in the in vivo clearance of PAI-1.¹⁵

The liver is also involved in the clearance of reaction products of fibrinolysis (e.g., t-PA-PAI-1 complex, plasmin- α_2 -AP, fibrin degradation products). Although the products are not strongly involved in the regulation of fibrinolysis, they are sometimes used to detect ongoing fibrinolysis in vivo. Abnormal clearance of reaction products in cirrhosis might provide incorrect information about the fibrinolytic system in vivo.

Assays to Study Fibrinolytic Capacity

Fibrinolytic factors can be measured in plasma by antigen or activity assays. However, because in liver diseases multiple factors are disturbed simultaneously, global assays reflecting the balance of all factors are required to assess the fibrinolytic capacity. In healthy subjects the fibrinolytic activity is low and spontaneous lysis of blood or plasma clots in vitro is slow and not easy to determine. Several methods have been developed in the past to circumvent this problem by eliminating the effects of fibrinolysis inhibitors. Well-known examples are the dilute whole blood clot lysis time (DWBCLT) in which inhibitors are partially eliminated by a 10-fold dilution of the blood samples, and the euglobulin clot lysis time (ECLT) in which inhibitors are partially eliminated by a euglobulin fractionation of plasma at a low pH and ionic strength. In addition, these assays usually contain no or insufficient calcium ions for the activation of TAFI or for the cross-linking of α_2 -AP to fibrin. The assays therefore reflect only a part of the fibrinolytic system. More recent assays were developed to better reflect the fibrinolytic system in the circulating blood. Three examples will be discussed in a greater detail: the turbidimetric plasma clot lysis assay, thromboelastography (TEG), and our new test for the global fibrinolytic capacity in whole blood. A useful review of new fibrinolytic assays and their clinical application was recently published by Pepperell et al.¹⁶

Turbidimetric plasma clot lysis assay¹⁷: Platelet-poor plasma is added to the wells of a microtiter plate containing a buffer with tissue factor, CaCl_2 , and phospholipid vesicles to induce clotting and purified t-PA to induce lysis. The optical density is measured at regular time intervals for a couple of hours. The clot lysis time (CLT) is the time from the midpoint

of minimum turbidity to maximum turbidity, which represents clot formation, to the midpoint of maximum turbidity to minimum turbidity, which represents clot lysis. The CLT amounts to 60 to 100 minutes for normal plasma, but depends on the added amount of t-PA.¹⁸ The CLT reflects several factors and mechanisms of the fibrinolytic system in plasma, except the level of endogenous t-PA in the circulating blood because an excess of t-PA is added to the system. It might be more appropriate to consider the CLT as a measure of fibrin clot resistance to exogenous t-PA than as fibrinolytic capacity or fibrinolytic potential. The fibrin clot resistance could, however, be a physiologically relevant parameter as clots could not only lyse by t-PA present in the circulation but also (and possibly primarily) by t-PA that is locally released by the vascular endothelial cells.

Several variants of the assay have been published, including the overall hemostatic potential (OHP) assay that assesses not only the lytic phase but also the clotting phase.¹⁹

Thromboelastography (TEG): This is an old technique that monitors coagulation and lysis on the basis of viscoelastic properties of whole blood clots.²⁰ The assay has regained interest by the development of robust analyzers, such as the TEG (Haemonetics, Braintree, MA) and ROTEM (Tem International GmbH, Munich, Germany). One of the advantages is that the assay can be performed with whole blood and thus includes both plasma proteins and blood cells including platelets. TEG is primarily used to assess coagulation and clot properties, but severe hyperfibrinolysis can also be detected. However, studies in trauma patients showed that this assay is relatively insensitive to hyperfibrinolysis, as compared with biochemical assays of reaction products of fibrinolysis.²¹ An additional problem is that blood is usually collected in citrate and stored for some time before analysis starts. This is acceptable for the coagulation phase, but not for the lytic phase. It can be calculated that endogenous t-PA activity in normal plasma is already inhibited for 50% by PAI-1 within 5 minutes.¹

To eliminate the insensitivity of TEG to endogenous fibrinolytic activity, purified t-PA can be added to the blood sample immediately before the assay is started. As in the turbidimetric plasma clot lysis assay, the readouts may reflect more blood clot resistance to exogenous t-PA than endogenous fibrinolytic capacity of the blood. Although experience and standardization is still limited, this approach could provide interesting information.

Global fibrinolytic capacity in whole blood²²: In this test blood is collected in a tube containing thrombin and the resulting clot is incubated for 3 hours at 37°C. Then serum is prepared and the generated fibrin degradation products are determined by an immunoassay. This test is fully dependent on t-PA (and possibly u-PA) in the blood sample and on the potential effects of blood cells. In vitro inhibition of t-PA by PAI-1 before the assay starts is minimized because the clot is formed immediately after blood collection in thrombin. The low extent of blood clot lysis under normal conditions in healthy subjects (around 0.1% in 3 hours) is easily detected by the immunoassay. A practical drawback is that the assay cannot be performed on stored samples.

Another global fibrinolytic capacity assay in plasma has a similar design.²³ However, plasma is used and a small amount of purified t-PA is added to induce lysis.

Historical Studies on Fibrinolysis in Cirrhosis

As early as over a century ago, Goodpasture reported spontaneous lysis of plasma clots of patients with liver cirrhosis using in vitro clot lysis assays.²⁴ Over several decades other studies using clot-lysis experiments of plasma of patients with various liver diseases confirmed these findings.^{25,26} Van de Loo and Schmiessing summarized more than 20 studies on fibrinolysis and concluded that most of these studies showed enhancement of fibrinolysis in liver disease patients.²⁷ An increased fibrinolytic activity was, however, not observed by all investigators.^{28,29} In addition, in the studies reporting hyperfibrinolysis, this was not observed in all patients and most often encountered in patients with a more severe degree of cirrhosis.

The mechanism of enhanced fibrinolysis was studied by Fletcher et al who injected nicotinic acid in patients with cirrhosis, which elicited a rise in t-PA. They observed an abnormal fibrinolytic response that was ascribed to a defective clearance of plasminogen activators by the diseased liver.³⁰ Also, an exercise-induced increase in t-PA in patients with cirrhosis resulted in enhancement of fibrinolysis that lasted longer than in healthy individuals, because of reduced clearance of t-PA.^{28,31} Most of the studies used ECLT or whole blood clot lysis tests.³² Hu et al studied ECLT in a group of 86 patients with liver disease, mostly cirrhotics and observed a shortened ECLT in around 30% of the patients, especially in those with a high Child-Pugh score.³³

To unravel the cause of hyperfibrinolysis, several studies examined the individual fibrinolytic proteins in liver disease patients. Levels of plasminogen were reduced in patients with a reduced liver synthesis capacity, which is dependent upon the severity of disease.³⁴ α_2 -AP was also reduced in cirrhosis as demonstrated by Aoki et al and others.^{34,35} This was strongly associated with the residual synthesis function of the liver.³⁶ Booth et al. demonstrated increased plasma concentration of t-PA (antigen) levels in cirrhosis.³⁷ Although they suggested that this might reflect increased synthesis or release of t-PA by endothelial cells, it is more likely that this is caused by a reduced clearance of t-PA or of t-PA-PAI-1 complexes in circulation.³⁸

Over the years, more groups studied the balance between various pro- and antifibrinolytic factors to study the net effect of these changes.^{34,39} Inhibitors such as α_2 -AP and TAFI are reduced in cirrhosis, whereas PAI-1 may be normal, decreased, or even increased in patients with liver disease.^{34,40–43} The increase in PAI-1 is not observed in all patients and does not seem to be dependent on the cause and the severity of cirrhosis.⁴³ The fibrinolytic balance in cirrhosis may be disrupted if the increase in t-PA is not fully counteracted by the increase of PAI-1. In cirrhotic patients with relatively low PAI-1 levels, increased plasminogen activator activity is observed. This indicates that PAI-1 plays a critical role in the pathogenesis of accelerated fibrinolysis.^{34,44}

Several fibrinolysis studies have focused on measuring plasma levels of protease-inhibitor complexes or fibrin (ogen) degradation products to obtain evidence of *in vivo* hyperfibrinolysis. Many studies have shown increased plasmin- α_2 -AP complexes and fibrin degradation products (D-dimer) in plasma of cirrhotic patients.⁴⁵ D-dimer levels are especially high in patients with more severe cirrhosis (Child-Pugh C) and with decompensated cirrhosis.⁴⁶ Despite the fact that increased levels of these markers suggest hyperfibrinolysis, they may also be elevated by reduced clearance of these fibrinolytic markers by the diseased liver. The increase in D-dimer levels may also be indicative of low-grade disseminated intravascular coagulation. This may be a cause of the occurrence of enhanced, so-called secondary, fibrinolysis. Violi et al clearly showed that endotoxemia in cirrhosis is a powerful activator of both coagulation and fibrinolysis, which may also indicate that hyperfibrinolysis results from clotting activation.⁴⁷ Another possible mechanism of hyperfibrinolysis in cirrhosis may be the presence of ascites.²⁶ The high fibrinolytic activity of ascites may be a trigger for the hyperfibrinolysis in circulation.

Recent Studies on Fibrinolysis in Cirrhosis Using New Global Assays

Papatheodoridis et al applied TEG on blood samples from 30 patients with decompensated cirrhosis and found no evidence of fibrinolysis in samples taken on admission. Only two patients during hospitalization developed detectable fibrinolysis after 5 days of ongoing sepsis.⁴⁸ Roullet et al similarly found that only 2 out of 23 patients undergoing orthotopic liver transplantation showed hyperfibrinolysis by ROTEM analysis before, during, or after surgery.⁴⁹ In a larger, but not fully published study, Stravitz found no lysis by applying TEG(Ly-30) on blood samples from 273 patients with cirrhosis, whereas Jairath et al reported that ROTEM analysis detected hyperfibrinolysis in 26 out of 106 (25%) patients with cirrhosis.^{50,51} Taken together, these studies indicate that only a minority of cirrhotic patients (at most 25%) show hyperfibrinolysis using TEG. However, it should be realized that TEG is relatively insensitive to hyperfibrinolysis by endogenous t-PA, as stated earlier. ROTEM analysis of blood samples to which purified t-PA is added shows an apparently unaltered resistance to clot lysis in patients with cirrhosis.⁵² Apparently this modification of the standard procedure of TEG does not result in the detection of more signs of hyperfibrinolysis in cirrhosis.

As with TEG, it is questionable whether hyperfibrinolysis in cirrhosis is detected with the turbidimetric plasma clot lysis assay (with exogenous t-PA). Lisman et al found no difference in CLT between patients with Child-Pugh A, B, or C and healthy controls (~20 subjects per group).⁴¹ TAFI levels are decreased in cirrhosis, but the percent activation of TAFI by thrombin in the assay is probably increased because thrombin is less efficiently inactivated by the reduced levels of antithrombin in the patients. These findings lead to the concept of a rebalanced fibrinolytic system, in which a reduction in antifibrinolytic factors may be compensated

by a concomitant reduction in profibrinolytics.⁵³ The study by Lisman et al was not confirmed by Colucci et al.^{40,41} These authors confirmed the reduced TAFI levels in cirrhotic patients, but found increased fibrinolysis in a similar plasma clot lysis assay. The study by Lisman et al was also not confirmed by Rijken et al.^{41,54} They reported hyperfibrinolysis (defined by a shorter plasma CLT than the CLT in 30 healthy controls) in 40% of 75 cirrhotic patients.

In the latter study, patients were also tested with an assay of the global fibrinolytic capacity in whole blood, which is fully dependent on the endogenous fibrinolytic system. Hyperfibrinolysis was detectable in 43% of the patients. Combining the results of the two assays indicated that hyperfibrinolysis, in at least one of the two global assays, is detectable in 60% of the patients. This is in line with the finding of hyperfibrinolysis in small groups of patients with cirrhosis or other chronic liver diseases by using another global fibrinolytic capacity assay in plasma.⁵⁵ A rebalanced fibrinolytic system may occur in approximately 40% of cirrhotic patients.

In conclusion, it seems that it is essential to use new global assays, which involve the whole fibrinolytic system. In general, they show less evidence of hyperfibrinolysis than the old global assays, but somewhat depending on the assay used and the definition of hyperfibrinolysis, in a substantial percentage of patients with cirrhosis hyperfibrinolysis can be demonstrated.

Clinical Implications and Treatment of Hyperfibrinolysis in Cirrhosis

From the aforementioned studies with more recently developed assays, it is evident that hyperfibrinolysis is encountered in 30 to 50% of patients with chronic liver disease. The question remains whether this is associated with bleeding complications. This is because some patients with liver disease also have a compromised primary and secondary hemostatic function.^{53,56} In addition, patients may bleed for nonhemostatic reasons, such as in variceal bleeding or other gastrointestinal bleedings, which may not be directly related to disorders of hemostatic function. This life-threatening bleeding complication of liver disease results from local vascular abnormalities or portal hypertension and not primarily from deranged hemostasis or fibrinolysis. Hyperfibrinolysis may contribute to easy bruising, purpura, epistaxis, gingival bleeding, menorrhagia, and gastrointestinal bleeding.^{32,57} Violi et al found that hyperfibrinolysis, defined as positive fibrinogen degradation products, was associated with the risk of gastrointestinal bleeding observed over 3 years of follow-up in patients with cirrhosis.⁵⁸ In a follow-up study by the CALC group in 112 cirrhotic patients with hyperfibrinolysis, defined as concomitantly high values of D-dimer and t-PA activity, hyperfibrinolysis was the only marker predictive of bleeding with a hazard ratio of 42.5.⁵⁹ Interestingly it was suggested that variceal bleeding, whose incidence peaks in the evening and in the early morning, may be related to the circadian rhythm of the fibrinolytic activity.⁶⁰

However, this may only explain the evening peak, since PAI-1 is high in the early morning.⁶¹ In a recent study in 75 cirrhotic patients we did not find an association between gastrointestinal bleeding complications observed within 1 year after including the study and hyperfibrinolysis, assessed with two fibrinolysis assays. However, this was a relatively small study with limited duration of follow-up.⁵⁴ Based on the limitations of the clinical studies, it has now been recognized that there is no clear evidence that hyperfibrinolysis is associated with gastrointestinal bleeding.⁶² In individuals with generalized mucosal bleeding symptoms, which may be indicative of hyperfibrinolysis, treatment with fibrinolysis inhibitors such as tranexamic acid or epsilon aminocaproic acid should be considered. Both these fibrinolysis inhibitors reduce the binding of plasminogen to fibrin, thereby decreasing the activation of plasminogen to plasmin. Tranexamic acid is also recommended in case of interventional procedures such as dental extractions due to the high fibrinolytic activity in the oral mucosa.

Fibrinolysis in Acute Liver Failure

Also, patients with acute liver failure have profound abnormalities in their hemostatic function. In patients with acute liver failure increased levels of PAI-1 and reduced levels of plasminogen are found, which is consistent with a hypofibrinolytic state. Although it is difficult to measure reduced fibrinolysis with most currently used tests, the imbalance between pro- and antifibrinolytic proteins are indicative of a reduction in the fibrinolytic capacity. Indeed in a recent study, Lisman et al found no lysis in 74% of patients with acute liver failure versus 3% in a healthy control group using a plasma clot lysis assay.⁶³ Spontaneous bleeding is not frequently encountered in patients with acute liver failure and an association of bleeding and changes in fibrinolysis have not been observed.

Fibrinolysis in Liver Transplantation

Liver transplantation performed in patients in acute or chronic liver failure has always been complicated by significant and sometimes life-threatening bleeding problems requiring massive use of coagulation factor concentrates or plasma and erythrocyte transfusion. Especially after removal of the diseased liver, the so-called anhepatic stage, significant hemostatic changes occur. Because activated coagulation factors are not cleared from the circulation, disseminated intravascular can develop, with consumption of platelets and coagulation factors and secondary hyperfibrinolysis. Hyperfibrinolysis may occur due to a reduced clearance of t-PA. Release of tissue factor and t-PA from the reperfused graft may cause disseminated intravascular coagulation with primary or secondary fibrinolysis. Several studies have focused on the bleeding complications during liver transplantation and the role of the fibrinolytic system. During the anhepatic phase, t-PA is not cleared, which may result in hyperfibrinolysis.⁶⁴ Therefore, hyperfibrinolysis is

thought to contribute significantly to impaired hemostasis during the anhepatic and reperfusion phases. Use of synthetic antifibrinolytic agents, such as tranexamic acid (a lysine analogue) and aprotinin (a serine protease inhibitor) results in reduced red cell and plasma transfusion. This may not be necessary in patients with primary biliary cirrhosis undergoing liver transplantation because these patients have less fibrinolytic activation during the anhepatic phase.⁶⁵

Conclusion

In many patients with chronic liver disease, such as cirrhosis, the fibrinolytic activity in plasma is increased. This has now been well established using newly developed and optimized fibrinolysis tests. This is especially encountered in patients with end-stage liver disease, such as patients with Child-Pugh C cirrhosis. Primary fibrinolysis may occur due to increased levels of t-PA and (relative) reduction in inhibitors of fibrinolysis, including PAI-1, TAFI, and α_2 -AP. Secondary fibrinolysis is likely to occur due to low-grade disseminated intravascular coagulation. It is still debatable whether hyperfibrinolysis contributes to bleeding complications. In case of bleeding in these individuals, treatment with fibrinolysis inhibitors may be indicated. Fibrinolysis inhibitors have also been successfully used to decrease blood loss during liver transplantation.

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