Hyperfibrinolysis in Liver Disease

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KEYWORDS

- Hyperfibrinolysis • tPA • Liver disease • Variceal bleeding
- Liver transplantation • Aprotinin

The association between liver disease and accelerated fibrinolysis was described more than 80 years ago when the rapid reliquidification of incubated, clotted blood from cirrhotic patients was noted.[1] In the current literature the occurrence of hyperfibrinolysis in patients who have cirrhosis has been suggested but is still debated.[2] The reasons for this uncertainty probably lie in the lack of appropriate laboratory tests for the evaluation of hyperfibrinolysis.[3] Thus, the assay of individual components rather than evaluation of the overall fibrinolytic activity has been investigated.[3–5] Nonetheless, there is a relative consensus that hyperfibrinolysis may complicate the clinical course of patients who have cirrhosis or liver failure.[6–9] In a previous study the incidence of hyperfibrinolysis, diagnosed by abnormal euglobulin lysis time, was 36%,[10] comparable to most,[7,11] but not all, previous reports[12] in patients who underwent liver transplantation. Hyperfibrinolysis correlated positively with the severity of underlying liver disease (the Child-Pugh classification),[10,13–15] and low-grade systemic fibrinolysis was found in 30% to 46% of patients who had end-stage liver disease.[16] Therefore the debate regarding hyperfibrinolysis in liver disease focused essentially on the mechanism of hyperfibrinolysis and its role, if any, in the bleeding disorders complicating the clinical course of liver cirrhosis.

PATHOPHYSIOLOGY OF HYPERFIBRINOLYSIS IN LIVER DISEASE
Imbalance of the Fibrinolytic System

All the proteins involved in fibrinolysis, except for tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1), are synthesized in the liver.[17] Reduced plasma levels of plasminogen,[18] alpha2-antiplasmin,[19–21] histidine-rich-glycoprotein,[22,23] and factor XIII[24] are found in cirrhosis. There is general agreement that patients who have liver cirrhosis have increased values of tPA[13,25–27] that

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probably result from reduced hepatic clearance,[28,29] but the measure of plasminogen activator inhibitor type 1 (PAI-1) gives conflicting results[3,25,30,31] and seems to be influenced greatly by the characteristics of the patients screened. Thus, circulating levels of PAI-1 are elevated in patients who have chronic liver disease,[13,32] but they are depressed in severe liver failure.[13,33] It has been suggested that, in patients who have severe liver failure, hyperfibrinolysis occurs when plasminogen activation by tPA is accelerated on the fibrin surface, and decreased levels of PAI-1 and alpha2-antiplasmin fail to balance it. In contrast, there are high levels of the acute-phase reactant PAI-1, leading to a shift toward hypofibrinolysis in acute liver failure.[8]

In the last few years, another plasma protein, thrombin-activatable fibrinolysis inhibitor (TAFI), has been identified. It is synthesized by the liver and plays an important regulatory role in fibrinolysis.[34–36] Upon activation by thrombin or plasmin, it is converted to an enzyme (TAFIa) with carboxypeptidase B–like activity that inhibits fibrinolysis through the removal of C-terminal lysines from partially degraded fibrin.[37,38] Particular attention has been focused on TAFI on the assumption that its decreased levels might account for hyperfibrinolysis in cirrhosis.[39] Lisman and colleagues[40] tested this hypothesis by measuring the individual components of fibrinolysis and by using a global test to assess the overall plasmatic fibrinolytic capacity. They concluded that the deficiency of TAFI in cirrhotic patients is not associated with increased plasma fibrinolysis resulting from the concomitant reduction of profibrinolytic factors. Colucci and colleagues,[41] however, showed TAFI antigen and activity levels are reduced markedly in cirrhotic patients and concluded that in vitro plasma hyperfibrinolysis is caused largely by defective TAFIa generation resulting from low TAFI levels. These different results probably can be explained by the different designs of the global fibrinolysis assays performed in the two studies. A recent report described a new method for assessing the global fibrinolytic capacity of both the extrinsic and the intrinsic pathway and confirmed the presence of hyperfibrinolysis in chronic liver disease.[42]

At the origin of hyperfibrinolytic state in liver cirrhosis, physiologic stress, including infection, may be involved through the increased release of tPA.[43] Extravascular activation of the fibrinolytic system also has been suggested as playing a role. Ascites has fibrinolytic activity,[44] and its absorption could affect systemic fibrinolysis. Thus, because ascites fluid re-enters the systemic circulation via the thoracic duct (a natural peritoneovenous shunt with up to 20 L reabsorbed daily), this phenomenon could be a trigger for accelerated fibrinolysis.

Accelerated Intravascular Coagulation and Fibrinolysis

The significance of low-grade disseminated intravascular coagulation in liver cirrhosis is another debated issue.[33,45–49] As with hyperfibrinolysis, the variable characteristics of the patients screened may explain the divergent results. Thus, with the use of highly sensitive tests such as prothrombin fragment 1+2 (a marker of in vivo thrombin generation), D-dimer (a product of thrombin and plasmin activation), high-molecular-weight fibrin/fibrinogen complexes, or soluble fibrin, a particular profile, accelerated intravascular coagulation and fibrinolysis (AICF), was detected in about 30% of cirrhotics, depending on the degree of liver failure.[2,49,50] AICF seems to occur predominantly in patients who have moderate-to-severe liver failure but is not detected in compensated patients[51] AICF probably results from the formation of a fibrin clot that is more susceptible to plasmin degradation because of elevated levels of tPA or the presence of dysfibrinogen. A reduced release of PAI to control tPA and lack of alpha2-antiplasmin to quench plasmin activity promotes secondary hyperfibrinolysis.

An additional stress, such as infection, may influence these processes with a consequent imbalance of the clotting and fibrinolytic system.[3] In patients who have acute or chronic liver disease, an impairment of the reticuloendothelial system and/or the presence of portosystemic shunts may lead, in the absence of sepsis, to enhanced endotoxemia into the systemic circulation.[52] In decompensated liver cirrhosis, high levels of circulating endotoxin were correlated with monocyte expression of tissue factor mRNA, prothrombin factor 1+2, and D-dimer, suggesting a direct relationship between clotting activation and endotoxemia.[53,54] This hypothesis was supported by the decrease of clotting and fibrinolytic activation after the reduction of endotoxemia obtained with nonabsorbable antibiotics.[54]

HYPERFIBRINOLYSIS AND BLEEDING

Bleeding is a frequent and often severe complication of liver cirrhosis.[55] Variceal hemorrhage occurs at a yearly rate of 5% to 15%. The most important predictor of hemorrhage is the size of varices. Patients who have large varices are at the highest risk of first hemorrhage (15% per year).[56] Other predictors of hemorrhage are decompensated cirrhosis and the endoscopic presence of red wale marks.[56] Bleeding from esophageal varices is associated with a mortality of at least 20% at 6 weeks,[57–59] and late rebleeding occurs in approximately 60% of untreated patients, generally within 1 or 2 years of the index hemorrhage.[60,61] Hemodynamic alterations secondary to portal hypertension are considered the main cause of gastrointestinal bleeding in cirrhotics.[62,63] The role played by the coagulopathy of cirrhosis in gastrointestinal bleeding is still unclear.[64,65] Coagulopathy does not seem to play a major role in initiating bleeding, but a relationship between severity of bleeding and coagulation defects has been postulated.[13] Variceal bleeding is more severe, more difficult to control, and more likely to recur in patients who have advanced liver failure, which presents as defects of primary and secondary hemostasis.[66,67] Otherwise, the recent literature indicates the hemostatic changes either impair or promote hemostasis, thus suggesting a rebalanced hemostatic system in liver disease.[17]

Previous studies suggested that hyperfibrinolysis may be a good predictor of gastrointestinal bleeding.[68,69] Consistent with these preliminary reports, the authors demonstrated that fibrinogen degradation products in the serum increase the risk of bleeding in cirrhosis;[70] however, the methodologic problems related to this assay rendered these data difficult to interpret.[46] In another report, hyperfibrinolysis, as assessed by high values of D-dimer and tPA activity, was found to be a predictor of the first episode of upper gastrointestinal bleeding in cirrhotic patients who had portal hypertension.[71] Hyperfibrinolysis was associated closely with the degree of liver failure and ascites and constituted a further risk, in addition to variceal size, in predicting gastrointestinal bleeding.[71] The interference of hyperfibrinolysis with clotting activation and platelet function might account for this association. Thus, as a consequence of hyperfibrinolysis, clotting activation may be delayed because of the consumption of clotting factor and inhibition of fibrin polymerization.[72] Hyperfibrinolysis also reduces platelet adhesion and aggregation by degradation of von Willebrand's factor and fibrinogen platelet receptors (glycoprotein Ib and IIb/IIIa).[73,74] Finally, hyperfibrinolysis may provoke clot lysis by inducing platelet disaggregation and disruption of the hemostatic plug.[75]

These arguments suggest that when esophageal varices rupture, hyperfibrinolysis may delay primary hemostasis or clotting activation or induce disruption of the hemostatic plug, thereby aggravating variceal bleeding and increasing the likelihood of recurrence.[73,76]

HYPERFIBRINOLYSIS IN LIVER TRANSPLANTATION

In earlier studies, up to 75% of liver transplantations required a blood transfusion, and the mortality and morbidity at 1 year were related closely to the quantity of blood components required.[77] Although refinements in surgical techniques have reduced the need for blood transfusions, this population remains at a significant risk of bleeding problems. Since the 1960s, alterations in hemostatic system and activation of fibrinolysis pathway have been considered to be responsible for a hemorrhagic diathesis.[78] The risk of bleeding in the preanhepatic stage is related directly to the preoperative hemorrhagic risk related to the underlying liver disease. During this phase, in fact, there usually are no changes in the hemostatic profile, and there are no significant differences between liver transplantation and other abdominal interventions in cirrhotic patients.

During the second anhepatic stage, a veno-venous bypass maintains venous return, and most vessels are clamped off; so there is no hepatic function and no risk of surgical bleeding. Life-threatening blood loss may occur, however. Many studies have reported enhanced fibrinolytic activity during this period,[79] and the lack of tPA clearance and the reduction of α2-antiplasmin may be responsible for enhanced primary fibrinolysis.[49]

Reperfusion of the liver during the postanhepatic phase is the crucial point of the intervention; although the surgical trauma is comparable to the previous stages, the amount of blood loss is completely different. Some patients may present with uncontrollable diffuse bleeding within a few minutes after reperfusion. Primary fibrinolysis seems to play a pivotal role in this phase also.[49,78] Porte and colleagues[12] demonstrated that the rise of tPA during the anhepatic phase is followed by a dramatic increase after reperfusion in almost three quarters of patients who undergo liver transplantation. Usually hyperfibrinolysis subsides within an hour, but in damaged donor liver a sustained increased fibrinolytic activity may be observed.[80] The endothelium of the donor liver is an important source of tPA; the ischemic damage to the graft during preservation may explain the dramatic increase in plasminogen activators. In the postoperative period, a reduction in platelet count is related to blood loss. Both thrombopoietin plasma levels and an increase in platelet consumption contribute to the development of thrombocytopenia. The platelet count usually normalizes after 2 weeks.[81]

The monitoring of coagulation and fibrinolysis activity is an essential element of care during liver transplantation. Among the diagnostic tests usually performed (listed in **Table 1**), thromboelastography highlights alterations at every step in the cascade from clot formation to its lysis (see also the article by A. Tripodi in this issue). Thus with thromboelastography it is possible to know if bleeding results from a failure to provide adequate surgical hemostasis, whether there are platelet dysfunction or anomalies in coagulation proteases or their inhibitors, and whether the blood loss is associated with early, excessive fibrinolysis. Finally, thromboelastography allows a rational approach to the correct used of blood components in transfusion or drug therapy.[82]

THERAPY

Antihyperfibrinolytic therapy is an important component of hemostatic therapy in hepatic diseases (see also the article by Shah and Berg in this issue). Both ϵ–aminocaproic acid (EACA) and tranexamic acid interfere with the plasminogen binding to the fibrin, reducing the conversion of plasminogen to plasmin; although EACA and tranexamic acid have been used widely to prevent blood loss during liver

Table 1
Diagnostic tests in hyperfibrinolysis

Laboratory Test	Methodology	Normal Range	Limitation
Clot lysis time	In vitro clot dissolution	30–60 minutes	High interindividual variability
Euglobin lysis time	In vitro clot dissolution without plasmin inhibitors	5–27 hours	High interindividual variability
D-dimer assay	Determination by latex immunoagglutination assay	0.0–0.4 μg fibrinogen equivalent/mL	Low specificity
Fibrinogen degradation products assay	Determination by latex immunoagglutination assay	< 5 μg/mL	Low specificity
tPA assay	Binding to the wells of a microtiter plate by anti-tPA monoclonal antibodies	0.2–2.0 IU/mL	Requires specific tube
Thromboelastogram clot lysis index	Thromboelastography	Amplitude at 60 minutes as a percentage of the maximal amplitude (< 40%)	Requires a thromboelastogram

transplantation, the evidence base for their efficacy is limited. Only a single random-ized trial, performed 20 years ago,[11] demonstrated the efficacy of EACA in reducing blood cell transfusion; moreover studies testing the usefulness of tranexamic acid have reported divergent results; trials that used high dosage (40 mg/kg/hour), reported a significant reduction of bleeding,[83] but no efficacy was found when this drug was used at lower dosages.[84] Thromboembolic complications may occur with a high-dose regimen, and the optimal dose of tranexamic acid for orthotopic liver transplan-tation is still unknown.

Aprotinin is a serin-protease inhibitor that reduces fibrinolytic activity by inhibiting plasmin and kallicrein.[85] This drug has been used in liver transplantation since 1990. Because randomized trials have shown a reduction in the need for blood transfusion of about 30%,[86] aprotinin now is the most widely used antifibrinolytic drug during liver transplantation. It is usually administered as 2×10^6 units over 30 minutes followed by continuous infusion of 0.5×10^6 units/hour. Aprotinin and other antifibrinolytic agents are potentially associated with two important complications: the development of thromboembolic events and the induction of acute renal tubular necrosis. A recent meta-analysis that included almost 1500 patients, however, demonstrated that the administration of antifibrinolytic therapy during liver transplantation is not significantly associated with an increased risk of thromboembolism.[87] Similarly, a recent random-ized trial that enrolled about 1000 patients demonstrated that aprotinin is associated with a major risk of developing transient renal dysfunction during the first days after orthotopic liver transplantation, but it is not associated with a long-term renal disease or increased mortality.[88]

SUMMARY

Although it has been difficult to assess its overall magnitude, and debate remains, there is a relative consensus that hyperfibrinolysis can complicate the overall clinical course of liver cirrhosis, especially in cases of moderate-to-severe liver failure. Primary imbalance of the fibrinolytic system seems to be related to higher circulating levels of tPA, but accelerated intravascular coagulation with secondary hyperfibrinolysis also has been reported overall in patients who have liver failure. Hyperfibrinolysis may delay primary hemostasis, thereby aggravating variceal bleeding and making recur-rence more likely. Liver transplantation may be associated with a dramatic increase in fibrinolytic activity, especially during the reperfusion phase; thus, some patients may present with uncontrollable bleeding, requiring blood transfusion and specific antifibrinolytic therapy. At present, aprotinin, a plasmin inhibitor, is the most widely used antifibrinolytic drug, because it reduces the need for blood transfusion by about 30%; moreover, although the use antifibrinolytic drugs may be related to thromboem-bolic events and the occurrence of renal tubular necrosis, recent evidence has demonstrated that the use of aprotinin is not associated with these adverse events.

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