Tests of Coagulation in Liver Disease

Armando Tripodi, PhD

Cirrhosis is characterized by a complex hemostatic defect including primary hemostasis, coagulation, and fibrinolysis. This defect is considered responsible for the bleeding problems that often are associated with the disease, and the causal relationship between abnormal tests and bleeding has become an accepted paradigm. Accordingly, hepatologists order laboratory testing to assess the risk of bleeding and rely on the results to make decisions about the management of the coagulation disturbances, using procoagulant drugs as prophylactic or interventional measures (reviewed in Ref.2). Recent data, however, indicate that this presumed association might not be valid. This article reviews and appraises the clinical value of the main testing procedures related to coagulation, fibrinolysis, and thromboelastography.

COAGULATION

Cirrhosis is characterized by an impaired synthesis of all coagulation factors, except for factor VIII and von Willebrand’s factor. This defect usually is documented by the measurement of individual coagulation factors or by the prolongation of such global tests as the prothrombin time (PT) and the activated partial thromboplastin time (aPTT).

**Prothrombin Time**

The PT, also called “tissue factor–induced coagulation time,” is a test developed by Armand Quick in 1935 for investigating patients with liver disease. The test result consists of the time needed for the platelet-poor plasma to clot after the addition of tissue extracts (thromboplastin) and calcium chloride. The PT is responsive to congenital or acquired deficiencies of factors VII, X, V, and II and fibrinogen. The type of thromboplastin is the main determinant of the responsiveness of the test to the coagulation defect. Results can be expressed as simple coagulation times (in seconds) or as

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percentage activities interpolated from a dose–response curve constructed by testing increasing dilutions of a normal pooled plasma to which an arbitrary activity of 100% is assigned. Other ways of expressing results are the ratio (patient-to-normal coagulation time) and the international normalized ratio (INR), in which the ratio is raised to a power equal to the international sensitivity index (ISI) of the measuring system used for testing.

The INR is not a test but rather is a scale of values for the PT test that was introduced in 1983 as a means of harmonizing PT results across laboratories. The regular INR is expected to harmonize PT results only for patients taking vitamin K antagonists, because the ISI needed to convert results usually is determined by means of plasma from patients taking vitamin K antagonists. The use of the INR scale to harmonize results for patients who have liver disease requires appropriate determination of the relevant ISI value for this category of patients.

Activated Partial Thromboplastin Time

The aPTT, developed in 1953 and modified in 1961, is the time (in seconds) needed for the platelet-poor plasma to clot when mixed with a particulate or soluble activator of the contact coagulation factors (factor XII, pre-kallikrein, and high-molecular-weight kininogen) and negatively charged phospholipids as platelet substitutes. The aPTT is responsive to congenital or acquired deficiencies of all coagulation factors except factors VII and XIII. The type, concentration, and combination of activators and phospholipids determine the responsiveness of the test. The results, which usually are expressed as a coagulation time or a ratio (patient-to-normal coagulation time), vary according to the commercial measuring system used for testing; no standardization scheme has been devised to harmonize results across laboratories.

Clinical Value of Prothrombin Time and Activated Partial Thromboplastin Time in Cirrhosis

The PT and aPTT are used ostensibly to investigate patients who have cirrhosis even though these tests are known to be poor predictors of bleeding in this category of patients. To explain this apparent paradox, it has been argued that the PT and aPTT might be inadequate to reflect the balance of coagulation as it occurs in vivo, especially in cirrhosis, a condition in which the levels of such naturally occurring anticoagulants as protein C and antithrombin are reduced in parallel with the procoagulants. It also should be noted that protein C in vivo is activated by thrombin in cooperation with its endothelial receptor, thrombomodulin. Plasma and reagents needed to perform PT and aPTT do not contain sufficient amounts of thrombomodulin. As a consequence, the activation of protein C is limited, and it cannot exert its full anticoagulant activity. Therefore, it is reasonable to assume that PT and aPTT are responsive only to the thrombin generated as a function of procoagulants but are much less responsive to the inhibition of thrombin mediated by the anticoagulants. Accordingly, PT and aPTT should be regarded as suitable tests to investigate congenital deficiencies of procoagulants but not congenital deficiencies of anticoagulants or acquired deficiencies of both pro- and anticoagulants, as occurs in cirrhosis. These reasons may be why the global coagulation tests are poor predictors of bleeding in patients who have cirrhosis. Indeed, the balance of pro- and anticoagulants in stable cirrhosis was found to be normal when assessed by thrombin generation measured in the presence of thrombomodulin, and this balance was seen even though the PT and aPTT were prolonged. Platelets contribute to the generation of thrombin; therefore the occurrence of thrombocytopenia and/or thrombocytopenia often found in cirrhosis theoretically could affect the generation of thrombin in this condition. A recent study,
however, showed that thrombin generation, when measured in platelet-rich plasma from stable cirrhotics in the presence of thrombomodulin, was indistinguishable from that of control subjects under the same experimental conditions, provided that the platelet levels were higher than \(6 \times 10^9/L\).\(^{24}\)

The conclusion drawn from these studies is that coagulation in patients who have stable cirrhosis is normal if the platelet levels are sufficiently high to sustain the normal thrombin generation elicited by plasma. This conclusion might explain the poor efficacy shown by such antihemorrhagic agents as recombinant activated factor VII when used for patients who have chronic liver disease,\(^{25-27}\) even though this agent shortens the PT. As a corollary, one may conclude that conventional coagulation tests are of little value for predicting bleeding in cirrhosis or for guiding decisions about the appropriate management of bleeding events in cirrhotic patients. If a test is needed at all in this condition, one of the leading candidates is thrombin generation assessed in the presence of thrombomodulin, provided there is sufficient fibrinogen.

**Thrombin Generation Test**

The thrombin generation test is a global test in which plasmatic coagulation is activated with small amounts of tissue factor as a trigger and phospholipids that act as platelet substitutes.\(^{28,29}\) The thrombin generation curve (ie, the thrombin concentration versus time) (Fig. 1) is characterized by the lag phase, which occurs soon after the activation of coagulation, the peak of thrombin, the time to peak, and the area under the curve, which is called the “endogenous thrombin potential.” The endogenous thrombin potential may be considered a measure of the amount of thrombin that a given plasma sample may generate under the specified experimental conditions and represents the balance between the pro- and anticoagulant proteins operating in plasma. The test mimics more closely than any other what occurs in vivo. It can be useful to assess the risk of bleeding in patients who have cirrhosis, but further clinical studies are needed to substantiate this hypothesis, especially for patients whose condition is complicated by bacterial infections or endothelial dysfunction. Until the results of such studies are available, clinicians responsible for patients who have cirrhosis should rely more heavily on their clinical judgment (history of previous bleeding,

![Fig. 1. Thrombin generation (nM thrombin versus time) curve. The area under the curve represents the endogenous thrombin potential.](image-url)
hemodynamic alterations subsequent to portal hypertension, renal failure, and endothelial dysfunction) and less on the results of conventional global coagulation tests.

The Prothrombin Time as an Index of Prognosis in Cirrhosis

The PT also has been used over the years in combination with other clinical and laboratory parameters to calculate such prognostic indexes as the Child-Pugh\textsuperscript{30} or the model of end-stage liver disease (MELD).\textsuperscript{31} The MELD, in particular, has gained wide acceptance as an index of survival\textsuperscript{31} and has been used to prioritize patients listed for liver transplantation.\textsuperscript{32} The observations summarized in the previous paragraph on the unsuitability of the PT to predict bleeding do not subsume its usefulness in the prognosis of cirrhosis, which remains intact, provided results are expressed in the appropriate scale to ensure harmonization of results across laboratories.\textsuperscript{33} More information on this topic is provided in the articles by Trotter and Kamath in this issue.

FIBRINOLYSIS

As shown in Fig. 2, fibrinolysis is a tightly regulated mechanism by which the proenzyme plasminogen is converted into the enzyme plasmin. The literature and textbooks state that cirrhosis is characterized by hyperfibrinolysis. This complex defect is documented at present by measuring the individual plasmatic components of fibrinolysis and, more rarely, through global tests. The measurement of the individual components cannot give a clear picture of the balance of fibrinolysis because of the complex interplay between activators and anti-activators that regulates the plasminogen–plasmin conversion. Reports in the literature show that cirrhotics may have increased levels of tissue plasminogen activator and its inhibitor but also can have decreased levels of plasminogen, antiplasmin, and factor XIII (reviewed in Ref.\textsuperscript{2}).

Recent attention has focused on thrombin-activatable fibrinolysis inhibitor (TAFI), and researchers have speculated that its deficiency, a typical feature of cirrhosis, may explain the hyperfibrinolytic state often described in this condition. Recent investigations on this topic gave conflicting results, however. According to Lisman and colleagues,\textsuperscript{34} deficiency of TAFI is not associated with increased plasma fibrinolysis, because the reduction of TAFI is counterbalanced by the concomitant decrease of the profibrinolytic factors. Conversely, according to Colucci and colleagues,\textsuperscript{35} the deficiency of TAFI is associated with increased plasma fibrinolysis. A possible explanation for these conflicting findings may be the different designs of the global assays.

Fig. 2. Schematic representation of fibrinolysis. Solid and broken arrows represent profibrinolytic and antifibrinolytic factors, respectively. TAFI, thrombin activatable fibrinolysis inhibitor.
used by the two investigators to assess the balance of fibrinolysis. No commercial
global assays for fibrinolysis are available, and standardization of homemade assays
is difficult and beyond the expertise of the average clinical laboratory. In conclusion,
these observations suggest that the measurement of individual components of the
fibrinolytic pathway is unlikely to help; simple global tests representing the balance
operating in vivo should be the developed and investigated in clinical trials to assess
their value in predicting bleeding in patients who have cirrhosis.

THROMBOELASTOGRAPHY

Thromboelastography is a technique that can provide continuous observation and
tracing of all the hemostatic functions that lead to clot formation and dissolution. It
was developed many years ago as a means to investigate patients who had hemor-
rhagic disease and can be considered, at least in theory, as the prototype of a global
test for hemostasis because it (allegedly) takes into account primary hemostasis, co-
agulation, and fibrinolysis. In the past, the use of this technique was limited somewhat
by poor standardization, poor reproducibility, and the difficulty of interpreting the trac-
ings and parameters.

Recently, the concepts of thromboelastography have been revisited and coupled
with new computer technology. This combination, together with the design of new
materials and equipment, has made modern thromboelastography more popular as
a bedside tool, especially during such major surgical interventions as liver transplan-
tation and cardiovascular procedures. More recently, thromboelastography has
been used to provide evidence for the generation of endogenous heparinoids as
possible contributors to the coagulopathy in patients who have liver disease. In
this application thromboelastography using native blood could be useful in clinical
practice to detect the anticoagulant effect of endogenous heparinoids and the asso-
ciated hemorrhagic events. To be consistent with in vivo conditions, however, it
should incorporate thrombomodulin to secure optimal protein C activation. Further
work is urgently needed to explore the clinical application of this combined technology
to optimize the use of potentially helpful therapeutics and to avoid unnecessary and
potentially dangerous use of blood products and procoagulants.

SUMMARY

Although not yet entirely conclusive, all the observations presented here are consis-
tent with the concept that the abnormality of coagulation in stable cirrhosis is more
a myth than a reality. This understanding helps explain the apparent paradox of the
prolonged global coagulation tests and their apparent poor prediction of bleeding in
this setting and raises questions about the usefulness of conventional testing.
Alternative tests mimicking more closely what occurs in vivo should be developed
and investigated in appropriate clinical trials to determine their value in the manage-
ment of bleeding in cirrhosis.

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