

Hemostasis abnormalities in liver cirrhosis: myth or reality?

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Abstract: Chronic liver disease is characterized by a global hemostatic defect that includes platelet-vessel wall interaction (primary hemostasis), fibrinolysis and coagulation causing abnormalities of the relevant laboratory tests. The causal relationship between abnormal tests and bleeding has been widely accepted, despite the fact that abnormal tests are poorly associated with bleeding. Recent evidence from the literature disputes the above paradigm and open new directions for laboratory and clinical research in this field.

Key words: chronic liver disease, coagulation, coagulopathy, liver transplantation, prognosis

Chronic liver disease is characterized by a complex hemostatic defect that involves primary hemostasis, fibrinolysis and coagulation. Over the years, this complex defect has been considered responsible for the bleeding problems that are often associated with the disease and this has become a sort of paradigm. However, the recent literature shows evidence that this might not be the case. The aim of this review is to focus on the main aspects of primary hemostasis, fibrinolysis and coagulation that may be used as arguments to dispute this paradigm.

Primary hemostasis

It is well known that chronic liver disease is characterized by variable thrombocytopenia and thrombocytopathy [1]. The former being due to increased platelets destruction or increased splenic and hepatic sequestration and the latter being due to defective thromboxane A₂ synthesis, storage pool deficiency, defects of platelet glycoprotein Ib or others. Presumably, because of these defects the bleeding time (BT) which has long been regarded as the global test for primary hemostasis is prolonged in up to 40% of cirrhotics [2]. However, it is of interest to see whether this prolongation is a matter of concern from a clinical standpoint. In their study Boberg and coworkers showed that a prolonged BT (more than 12 minutes) was associated with a 5-fold increased risk of hemoglobin reduction after liver biopsy, but the association with

clinical bleeding was not evaluated [3]. However, subsequent studies assessing the value of correcting the prolonged BT with desmopressin in patients with cirrhosis gave positive results [4,5], thus supporting the hypothesis that the BT may play a role. On the other hand, studies with clinical end points that assessed the risk of bleeding after desmopressin infusion and BT shortening gave negative results [6,7], thus casting doubts on the value of the BT prolongation in predicting the risk of bleeding. Furthermore, in a recent study of platelet adhesion in cirrhosis assessed under flow conditions, Lisman et al. [8], found that highly elevated levels of von Willebrand factor, which are typically found in patients with cirrhosis, contribute to the induction of primary hemostasis. Accordingly, increased von Willebrand factor may compensate for the defect of platelet numbers and functions in these patients [8].

So that, we may conclude that although defects of primary hemostasis in cirrhotics may have a causative role in the occurrence of bleeding, the BT once regarded as the test of choice to investigate primary hemostasis is probably not predictive of bleeding and should be abandoned. The logical conclusion is that if one wishes to rely on laboratory testing for primary hemostasis to predict bleeding in chronic liver disease methods should go beyond the BT. Results from the literature showed also little clinical value on the use of such other surrogate tests for the BT in this setting as the platelet function assay.

Fibrinolysis

The literature and text books describe that cirrhosis is characterized by hyperfibrinolysis and that this complex defect can be documented in plasma through global fibrinolytic tests or through the measurement of the individual components [1]. However, the measurement of the individual components

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cannot give us a clear picture of the balance of fibrinolysis because of the complex balance where there are activators and anti-activators which regulate the conversion of plasminogen to plasmin. As a matter of fact reports from the literature show that cirrhotics may have increased levels of tissue plasminogen activator and its inhibitor, but also decreased levels of plasminogen, anti-plasmin and factor XIII [1]. Recently, attention has also been put on thrombin activatable fibrinolysis inhibitor (TAFI). Research workers speculated that its deficiency may explain the hyperfibrinolytic state often described in cirrhosis. Two recent studies on this topic gave conflicting results. According to Lisman et al. [9], deficiency of TAFI is not associated with increased plasma fibrinolysis because the reduction of profibrinolytic factors is counterbalanced by the concomitant reduction of antifibrinolytic factors. Whereas, according to Colucci et al. [10], the deficiency of TAFI is associated with increased plasma fibrinolysis. The explanation for these conflicting results rests probably on the different assay design used by the two investigators to assess the balance of fibrinolysis.

In conclusion, the role played by hyperfibrinolysis in the occurrence of bleeding in cirrhotics is still unclear and the measurement of individual components of the fibrinolytic pathway is unlikely to help. Simple global tests representing the balance operating *in vivo* should be developed and investigated in clinical trials.

Coagulation

Chronic liver disease is characterized by an impaired synthesis of coagulation factors [11]. This complex defect is conventionally documented through the measurement of individual coagulation factors, or through the prolongation of such global tests as the prothrombin time (PT) and the activated partial thromboplastin time (APTT). On the other hand, it is known that global tests are not predictive of bleeding in patients with cirrhosis [12]. Recently, it has been surmised that global tests such as PT and APTT might be inadequate to reflect the balance as it occurs *in vivo* especially in cirrhosis, a condition where the naturally occurring anticoagulants protein C, antithrombin and tissue factor pathway inhibitor are reduced in parallel with procoagulants. Furthermore, protein C *in vitro* is activated to a limited extent in the absence of thrombomodulin and therefore it cannot exert its full anticoagulant activity [13]. It should be noted that plasma and reagents needed to perform PT and APTT do not contain thrombomodulin. Therefore, it is reasonable to assume that PT and APTT are responsive only to the thrombin generated as a function of procoagulants, but much less to the inhibition of thrombin mediated by the anticoagulants. According to this concept PT and APTT should be regarded as suitable tests to investigate congenital deficiency of procoagulants (conditions where the anticoagulants are normal), but they are unsuitable to investigate congenital deficiency of anticoagulants or acquired deficiency of both pro- and anti-coagulants as it occurs

in cirrhosis [13]. Interestingly, the balance of pro- and anti-coagulants in cirrhosis was found to be normal when assessed as thrombin generation monitored over time in the presence of thrombomodulin [13]. This happened notwithstanding that PT and APTT were prolonged [13]. Platelets are important contributors to the generation of thrombin [14]. Hence, the occurrence of thrombocytopenia and/or thrombocytopathy in patients with cirrhosis may at least in theory affect thrombin generation in these patients. A recent study showed that thrombin generation in the presence of thrombomodulin when measured in platelet-rich plasma from patients with cirrhosis was indistinguishable from that of healthy subjects under the same experimental conditions, provided that the numbers of platelets were higher than $60 \times 10^9/l$ [15].

The tentative conclusion stemming from these studies is that coagulation in patients with liver cirrhosis is normal provided that the numbers of platelets are sufficiently high to sustain the normal thrombin generation elicited by plasma. This conclusion might explain the poor efficacy of such procoagulant agents as activated factor VII when used for patients with chronic liver disease [16-18] and may justify clinical trials to see whether platelets transfusion or treatment with recombinant human thrombopoietin [19] are effective in those patients with severe thrombocytopenia when they bleed spontaneously or when they undergo such risky procedures as surgery or liver biopsy.

SUMMARY

Although not yet conclusive all the above observations are consistent with the concept that the abnormality of hemostasis in stable chronic liver disease is more a myth than a reality and that the culprits for the bleeding problems occasionally seen in these patients should be searched elsewhere. Together with severe thrombocytopenia other potential candidates responsible for bleeding are the hemodynamic alterations subsequent to portal hypertension, endothelial dysfunction (reduced vascular tone), bacterial infections and renal failure [1]. Interventions aimed at correcting these alterations might be more effective to stop bleeding than correcting the hemostatic derangement.

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