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Mechanisms of enhanced thrombin-generating capacity in patients with cirrhosis

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See also Sinegre T, Duron C, Lecompte T, Pereira B, Massoulier S, Lamblin G, Abergel A, Lebreton A. Increased factor VIII plays a significant role in plasma hypercoagulability phenotype of patients with cirrhosis. This issue, pp 1132–40.

The liver is the site of synthesis of many proteins involved in hemostasis, including procoagulant and anticoagulant proteins, profibrinolytic and anti-fibrinolytic proteins, and thrombopoietin. Consequently, patients with liver disease acquire complex changes within their hemostatic system [1]. Historically, these changes were thought to result in a bleeding diathesis. Although bleeding complications are common in patients with chronic liver disease, the most common bleeding complication, variceal bleeding, is a consequence of portal hypertension, rather than hemostatic failure. Notably, the severity and outcome of variceal bleeding were not different between patients with cirrhosis who did or did not use anticoagulant drugs at the time of the bleed, confirming that variceal bleeding is unrelated to hemostatic failure [2]. Severe bleeding was previously common during large invasive procedures such as liver transplant surgery. However, improvements in perioperative management have led to a substantial decline in bleeding severity during the transplant procedure. Now, a substantial proportion of patients undergo transplant surgery without the requirement for any perioperative blood product transfusion [3]. These clinical observations, combined with laboratory analyses of global hemostatic capacity, have led to the concept of rebalanced hemostasis [4]. Patients with liver disease appear to have a reset in their hemostatic balance, owing to simultaneous declines in procoagulant and anticoagulant drivers. This new hemostatic balance, however, is much more fragile than the balance in healthy individuals, and may abruptly tip to either a hypocoagulable or hypercoagulable phenotype.

Although, historically, bleeding was a major concern in patients with liver disease, the focus has now shifted to thrombotic complications. Recent studies, including meta-analyses, have demonstrated that chronic liver diseases constitute a risk factor for venous thrombosis [5]. However, the prevention and treatment of venous thrombosis are complex, as it is not established how to best anticoagulate a patient with a profoundly altered hemostatic system at baseline [6]. Another frequent thrombotic complication in patients with advanced chronic liver disease is portal vein thrombosis (PVT). PVT in the patient with advanced cirrhosis is often discovered incidentally during imaging. There is debate about whether PVT is simply a reflection of the severity of liver disease [7], or whether PVT drives progression of disease [8]. Consequently, it is unclear whether treatment of asymptomatic PVT is required. Notably, some of the asymptomatic thrombi resolve spontaneously [7], and prolonged anticoagulant treatment leads to recanalization in only a proportion of patients [9]. A single small randomized controlled trial has demonstrated that prophylactic low molecular weight heparin (LMWH) safely and effectively prevents the development of PVT in a very select group of patients with cirrhosis [10]. Interestingly, LMWH also decreased the rate of decompensation and death, indicating that anticoagulant therapy might delay disease progression, and that prevention rather than (considering) treatment of PVT should be the focus of treatment paradigms.

The concept of rebalanced hemostasis states that all components of hemostasis are in a new balance, with
Limited plasma levels of antithrombin (AT) associated with reduced plasma levels of factor VIII. Recent studies by multiple independent laboratories have demonstrated increased thrombin generation in patients with cirrhosis [13–16]. An article by Sinegre et al. in this issue of the Journal of Thrombosis and Haemostasis addresses the question of which factors determine enhanced thrombin-generating capacity in patients with cirrhosis [13]. Previous studies have demonstrated that regulation of thrombin generation by the protein S pathway is decreased in patients with cirrhosis, and that normal to increased thrombin generation in thrombomodulin-modified thrombin generation tests relates to resistance to the anticoagulant action of thrombomodulin [17]. This thrombomodulin resistance is a result of both decreased plasma levels of protein C and increased plasma levels of factor VIII [18,19]. Recently, the ratio between the results of thrombin generation tests performed in the absence and in the presence of thrombomodulin, or the ratio between FVIII and protein C levels, have been used to indicate a hypercoagulable status in patients with cirrhosis [17,20]. However, as these ratios are not necessarily related to overall thrombin-generating capacity, it may be more appropriate to assess the results of the thrombomodulin-modified thrombin generation test in determining the hemostatic capacity of plasma from patients with cirrhosis. Sinegre et al. did exactly this, and demonstrated increased thrombin generation in patients with cirrhosis as compared with healthy controls, with thrombin-generating capacity increasing with increasing disease severity. The authors addressed the roles of elevated FVIII and decreased protein C levels in the hypercoagulable state of patients with cirrhosis by normalizing plasma levels in individual patient samples. Protein C levels were normalized by the addition of purified protein C, and FVIII levels were normalized by a
very elegant approach in which some of the plasma FVIII was inactivated by an antibody against FVIII, which was titrated so that residual FVIII activity was close to 100%. The authors showed that the increased thrombin generation in patients was only partly normalized when only protein C or only FVIII was normalized, but full normalization occurred when protein C and FVIII levels were normalized simultaneously. The authors carefully conclude that enhanced thrombin generation in patients with cirrhosis is explained by opposite changes in plasma levels of FVIII and protein C. Although high FVIII and low protein C levels clearly contribute to enhanced thrombin generation in patients with cirrhosis, this is probably only part of the story.

Thrombin-generating capacity is the net result of plasma levels of procoagulant and anticoagulant proteins, all of which (perhaps except for levels of tissue factor pathway inhibitor) are altered in patients with cirrhosis. To demonstrate that high FVIII and low protein C levels are not the only contributors to enhanced thrombin generation in patients with cirrhosis, we studied thrombomodulin-modified thrombin generation in 15 patients with cirrhosis and decreased antithrombin plasma levels before and after normalization of antithrombin levels. As shown in Fig. 1A, antithrombin levels were substantially decreased in patients as compared with 44 healthy individuals, and levels were normalized after in vitro addition of antithrombin concentrate. Figure 1B shows elevated thrombin generation in patients as compared with controls, which was fully normalized when antithrombin plasma levels were normalized. These data are almost identical to the data in Figure 4 of the Sinegre et al. article, and illustrate that enhanced thrombin generation in cirrhosis is the result of multiple complex changes in the plasma levels of procoagulant and anticoagulant proteins that not limited to high FVIII and low protein C levels.

Thus, Sinegre et al. confirm and extend previous findings on the mechanisms underlying enhanced thrombin generation in plasma from patients with cirrhosis by showing that not only low protein C levels [18], but also high FVIII levels contribute to the hypercoagulable state. However, as the coagulation potential in cirrhosis depends on the interaction between all procoagulants and anticoagulants, isolated assessment of FVIII or protein C levels in these patients yields incomplete information. Rather, global tests such as thrombomodulin-modified thrombin generation should be used to estimate the hemostatic status of these patients.

Notwithstanding the complexity of the mechanisms underlying the enhanced in vitro thrombin generation in patients with cirrhosis, the data of Sinegre et al. help us to better understand the mechanisms underlying this particular hypercoagulable feature in the hemostatic system with complex alterations in patients with cirrhosis. Future studies will have to address whether enhanced thrombin generation in patients with cirrhosis contributes to the elevated risk of important clinical outcomes, such as venous thrombosis and/or PVT, and what steps should be taken to safely neutralize this hypercoagulable phenotype in order to avoid these potentially devastating thrombotic events in this patient population.

Addendum
T. Lisman drafted the manuscript and supervised the experiment. S. Bos and N. M. Intagliata provided intellectual input and commented on the initial draft. S. Bos included patients and controls.

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Disclosure of Conflict of Interests
The authors state that they have no conflict of interest.

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