To the Editor:

In an elegant and comprehensive review of the literature, Violi and coworkers conclude that primary hemostasis may not be defective in patients with cirrhosis, and that a low platelet count in these patients should not necessarily be considered as a bleeding risk [1]. Whilst we concur with these conclusions, we wish to make additional comments on platelet function in patients with cirrhosis.

(1) Whereas routine diagnostic tests of platelet function such as the skin bleeding time and suspension aggregometry are frequently abnormal, in vivo platelet function may be adequate as pointed out by Violi et al. Although intrinsic platelet function under physiological flow conditions has been shown to be preserved, defective platelet–vessel wall interactions due to anemia and thrombocytopenia are present [2]. A dysbalanced von Willebrand factor (vWF)/ADAMTS13 balance may (in part) compensate for these indirect platelet defects. The net effect of all possible changes in primary hemostasis in patients with cirrhosis appears to be a system which is in physiological hemostatic balance [3]. Nevertheless, the balance in primary hemostasis in these patients is presumably precarious, and patients may experience either bleeding or thrombotic complications as a result of poorly understood mechanisms that upset the balance in the primary hemostatic system. We agree with Violi and coworkers that studies testing the predictive value of different platelet function tests for either bleeding or thrombosis are required. However, until results of such studies are available, we argue against routine use of platelet function tests, including bleeding time and suspension aggregometry, in the diagnostic work-up of hemostasis of patients with cirrhosis, as it is at present unclear how these test results should be interpreted. Even the interpretation of the platelet count in a patient with cirrhosis is difficult, as potential compensatory mechanisms may be present. A recent study showed that ultrasound-guided thoracentesis can be safely performed in patients with platelet counts below 50,000/μl [4], although a platelet count below this level is considered a contraindication for small invasive procedures such as thoracentesis, as pointed out by Violi and coworkers. These findings reinforce the need for prospective clinical studies on safety of invasive procedures in patients with cirrhosis and a moderate to severe thrombocytopenia.

(2) Platelet transfusions are frequently administered before or during larger invasive procedures (including liver transplantation) in patients with cirrhosis. We have recently demonstrated that platelet function is preserved throughout liver transplantation [5], although profound hemostatic changes, including further changes in levels of coagulation proteins and the potential occurrence of hyperfibrinolysis, are known to occur during this procedure. Moreover, a hyper-reactive VWF system characterized by substantially elevated levels of VWF and a temporary ADAMTS13 deficiency develops during liver transplantation [6]. Not only may this hyper-reactive primary hemostatic system constitute a risk for development of intra- or post-operative thrombosis (such as hepatic artery thrombosis), these findings also reinforce that a restrictive platelet transfusion policy is warranted, given the detrimental effects of perioperative platelet transfusions. Importantly, routine diagnostic tests of platelet function do not take alterations in the VWF/ADAMTS13 balance into account. Also during liver transplantation, the interpretation of available platelet function tests should be performed with care, and platelet tests other than a platelet count may have little value in guiding hemostatic management.

(3) Although platelet function in patients with cirrhosis is presumably sufficient to support hemostasis, and platelet reactivity may in some cases be such that it even precipitates thrombosis, little is known about the function of cirrhotic platelets in processes other than cessation of bleeding. It is well recognized that platelets have multiple extra-hemostatic functions in processes including inflammation, host defense, angiogenesis, tumor metastasis, and wound healing. In liver biology, the extra-hemostatic functions of platelet may do both good and harm [7]. A variety of molecules stored within platelet granules play a role in the above mentioned processes. Furthermore, it may be that de novo synthesis of proteins by platelets contributes to extra-hemostatic functions of platelets [8]. The competence of platelets to perform these extra-hemostatic functions in patients with cirrhosis is incompletely known and requires further study. It has been established that important platelet-derived molecules including 5-hydroxytryptamine (serotonin) are deficient in patients with cirrhosis [9]. Given the important role of serotonin in repair of damaged liver tissue [10], platelets may be defective in repair as a result of reduced serotonin content. It is not unthinkable that also de novo platelet protein synthesis is compromised in platelets from patients with cirrhosis.

In conclusion, although the available literature strongly supports that defects in primary hemostasis in patients with cirrhosis are more fiction than fact, many open questions remain. Future studies should not only focus on the role of platelets in bleeding and thrombosis, but also extra hemostatic functions of platelets should be considered.

Conflict of interest

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Letters to the Editor

References

To the Editor:
We thank Drs. Lisman and Porte for their very interesting comments concerning our review on the presence or absence of platelet dysfunction in liver cirrhosis. We agree that extrinsic and intrinsic factors may contribute to maintain a normal primary hemostasis in cirrhosis, despite potential defects due to thrombocytopenia and anemia. Among the extrinsic factors, we agree that the enhanced ratio von Willebrand factor/ADAMTS13 may have a role. However, we have recently demonstrated the existence of a novel intrinsic factor that could contribute to maintain a normal hemostasis. We demonstrated that, upon stimulation, platelets produce physiologic amounts of isoprostanes [1], which are chemically stable eicosanoids derived from arachidonic acid interaction with reactive oxidant species (ROS) [2]. In virtue of these chemical characteristics, isoprostanes are useful in the late phase of platelet activation, where they serve to propagate platelet aggregation via activation of the glycoprotein IIb/IIa [1]. We have recently discovered that the enzyme NADPH oxidase, one of the most important cellular producers of ROS, has a key role in the formation of platelet isoprostanes. Thus, in patients with hereditary deficiency of the enzyme, platelet formation of isoprostanes is down-regulated. In particular, platelets from these patients have impaired platelet activation, reinforcing the formation of isoprostanes as a relevant intracellular pathway for platelet function [1]. On the basis of these findings, we analyzed the behavior of platelet isoprostanes and NADPH oxidase activation in a population affected by cirrhosis. We found that platelet production of isoprostanes was increased coincidentally with an up-regulation of platelet NADPH oxidase, suggesting a cause-effect relationship between them [3]. These changes were more evident in patients with Child-Pugh’s classes B and C, indicating the platelet over-expression of this pro-aggregating molecule typically occurs in patients with severe liver failure. This finding was associated with systemic signs of platelet activation such as enhanced soluble CD40L, corroborating the concept that in liver cirrhosis platelets are more prone to be activated.

The fact that platelets possess all the armamentarium to activate NADPH oxidase [4,5] is of relevance, not only for the hemostatic system, but also for the extra-hemostatic effects potentially played by platelets. The important issue raised by Drs. Lisman and Porte is still to be adequately addressed, even if there is evidence of a role of platelets in tumor metastasis, wound healing and, overall, inflammation. Our data contribute to further expand the knowledge on the pro-inflammatory role of platelets in as much as NADPH oxidase is an enzyme of the innate immune system with a crucial role for the bacterial killing via the production of ROS [6]. In this regard, platelets may represent another important component of the innate immune system, potentially involved in the atherosclerotic process [7,8]. Thus, ROS generation by NADPH oxidase is used by platelets to oxidize LDL which are ultimately taken up by macrophages via scavenger receptors [9]. Such an extra-hemostatic effect may implicate a key role for platelets in the inflammatory process that initiates atherosclerotic disease. The impact of this phenomenon in liver cirrhosis remains, however, to be established.

How the complexity of these platelet functions relates to the progression of liver cirrhosis, including bleeding and thrombosis, is still a matter of debate and needs further investigation. For this reason, we fully agree with Drs. Lisman and Porte that, currently, the use of routine in vivo and ex vivo tests to explore global platelet function in cirrhosis is not useful for clinicians. However, future research may identify new platelet biomarkers that will help better understand the role of platelets in the bleeding and thrombotic events that complicate the clinical course of cirrhosis.

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