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INVITED COMMENTARY

Hepatic artery thrombosis after liver transplantation: more than just a surgical complication?

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Thrombosis of the hepatic artery is one of the major complications following liver transplantation and is associated with morbidity and graft loss. Hepatic artery thrombosis (HAT) may occur early after transplantation, but can also occur years after surgery. It is generally believed that early HAT is mainly a surgical complication and a result of technical difficulties with the construction of the arterial anastomosis. However, some studies have shown that early HAT is also associated with nonsurgical factors, including donor age [1]. Therefore, it remains unclear whether HAT is truly a pure surgical complication and it cannot be excluded that excessive activation of the hemostatic system contributes to the risk of early HAT.

Although a patient with liver disease is generally considered to have a defective hemostatic system, for example evidenced by a prolonged prothrombin time, there is increasing evidence that these coagulation tests may not reflect the bleeding tendency. The classical coagulation tests only measure the procoagulant route of the hemostatic system. With the realization that in a patient with liver disease both pro- and anticoagulant pathways are defective, the concept of a rebalanced hemostatic system in these patients has arisen [2,3]. Thus, a patient with liver disease has a more or less competent hemostatic system, but the hemostatic balance is less stable compared with healthy individuals, and the balance may be turned to hypo- or hypercoagulation when the hemostatic system is challenged, which may occur for example during liver transplantation.

Small studies and case reports have suggested that a (relative) hypercoagulable state, for example induced by genetic factors such as factor V_{leiden}, may be associated with the occurrence of HAT [4,5]. Furthermore, acquired temporary hemostatic defects leading to increased hemostatic potential may predispose to early HAT. A dysbalance in pro- and antihemostatic systems leading to a hypercoagulable state is seen in the first days after liver transplantation [6]. Furthermore, a temporary lack of capacity to dissolve clots, a phenomenon referred to as 'postoperative fibrinolytic shutdown' that occurs immediately after surgery may contribute to excessive clot formation [7]. Finally, the tissue near the anastomoses is damaged by ischemic insults and surgical handling, and the damaged or activated endothelium in vessels may trigger activation of the hemostatic system. Thus, a reactive hemostatic system may respond to activating signals in the vicinity of the arterial anastomosis resulting in HAT.

In this issue of *Transplant International*, Bispo *et al.* retrospectively report their experience with early HAT [8]. In their series, a relatively large proportion of

patients (39%) was transplanted for familial amyloidotic polyneuropathy (FAP), which has a high prevalence in Portugal. Surprisingly, patients with FAP had an almost eightfold increased incidence of early HAT compared with patients transplanted for other indications. In a multivariate analysis, FAP was shown to be an independent risk factor for HAT. As arterial reconstructions in patients with FAP are generally straightforward because of the absence of disturbed liver architecture as is encountered in the typical patient with end-stage cirrhosis, a surgical cause for this highly increased incidence of HAT is unlikely. An important indirect conclusion from the study by Bispo *et al.*, therefore, seems to be that the study provides evidence that HAT after liver transplantation is not only related to surgical factors, but may also have a nonsurgical pathogenesis, such as hemostatic factors.

Patients with FAP have a fully competent synthetic capacity of the liver, and therefore the typical alterations in the hemostatic system that are encountered in a patient with compromised liver function are absent in FAP patients. In fact, our experience with patients with FAP is that they show signs of hypercoagulability when hemostatic capacity is tested by thromboelastography. However, the presence of a hypercoagulable state in patients with FAP is, to our knowledge, not recognized in articles published in literature, and our experience is with a limited number of patients only. Patients with many types of amyloidosis in general suffer from focal or generalized bleeding complications as a result of excessive activation of the fibrinolytic system and reduced activity of the coagulation system, although thrombotic episode may also occur [9,10]. Only one paper examined bleeding symptoms in patients with FAP, and concluded that bleeding in patients with FAP, and abnormalities in the coagulation system are uncommon [11]. We have no explanation for the hypercoagulable state we observed in our patients, but a possible explanation is the capacity of proteins with amyloid structure to act as activators of blood platelets [12]. As mutant transthyretin is found in circulation in patients with FAP [13], it is conceivable that these amyloid structures slightly activate platelets resulting in 'primed', hyper-reactive platelets in circulation.

During and after liver transplantation, patients with FAP have a normal or even hypercoagulable hemostatic status, while a patient transplanted for liver cirrhosis typically is thrombocytopenic and may have extremely low circulating levels of proteins involved in coagulation and fibrinolysis [14]. The better preserved hemostatic capacity of patients with FAP is also reflected by the substantially reduced transfusion requirements (red cell transfusion in the FAP patients was approximately half of the nonFAP group in the series presented by Bispo), although reduced transfusion requirements may also be explained by the fact that liver transplantation in a FAP patient is technically much easier because of absence of portal hypertension, venous collaterals or perihepatic inflammatory adhesions.

The observation that patients with FAP are more prone to early HAT suggests that this complication is not only a surgical complication, but is at least partially also related to nonsurgical factors. In addition, it raises the question whether early prophylaxis with anticoagulant therapy might help reduce the incidence of HAT after liver transplantation. In view of the 'postoperative fibrinolytic shutdown' and other phenomena leading to a dysbalanced hemostasis right after liver transplantation, a consideration of early initiation of anticoagulant treatment (preferably already at post operative day 1) seems justified. The choice of anticoagulant or combination of anticoagulants is still an open question as most of the experience on prophylactic anticoagulation following liver transplantation is not based on (randomized) studies. However, one recent retrospective study showed aspirin to substantially reduce the occurrence of late HAT [15], and as the thrombus in HAT is presumably rich in platelets, an antiplatelet agent might be the strategy of choice to prevent this particular type of thrombosis. A combination with low molecular weight heparin, as suggested by the authors, is common practice in our institution in patients with high thrombotic risk. However, (temporary) use of other classes of antiplatelet drugs, such as inhibitors of P2Y12 or αIIbβ3 (Plavix or ReoPro), alone or in combination with aspirin might also be considered.

In conclusion, the results of Bispo *et al.* show a substantially increased incidence of HAT in patients undergoing liver transplantation for FAP compared with patients transplanted for end-stage liver disease. As technical issues are unlikely to explain this difference, the data suggest that HAT is more than just a surgical complication, and nonsurgical factors, such as changes in the hemostatic system may play a clinically relevant role as well.

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