LETTER

Role of portal venous platelet activation in patients with decompensated cirrhosis and TIPS

We read with interest the recent study by Lv *et al*,[1] who pointed out that transjugular intrahepatic portosystemic shunt (TIPS) placement is feasible for prevention of variceal rebleeding in the majority of cirrhotic patients with portal vein thrombosis and that it is more effective than endoscopic band ligation plus propranolol. Moreover, association with a higher probability of portal vein recanalisation and a lower risk of subsequent rethrombosis was described. However, even after TIPS, in eight out of 24 patients, either portal or superior mesenteric vein thrombosis persisted or reoccurred. While development and progression of splanchnic venous thrombotic events implicate disease progression in cirrhosis,[2] their pathogenesis remains unclear. According to Virchow's triad, pathological coagulation/platelets, decreased flow and impaired vascular wall are the drivers of thrombosis. In TIPS, flow is restored and, to a large extent, also the shear stress (the vascular wall compenent) due to decompression of portal hypertension. However, the prothrombotic milieu (platelet and plasmatic coagulation) has not been investigated to date. One hypothesis for this is the platelet activation due to lipopolysaccharide (LPS)-linked inflammation in the portal venous vascular bed.[3]

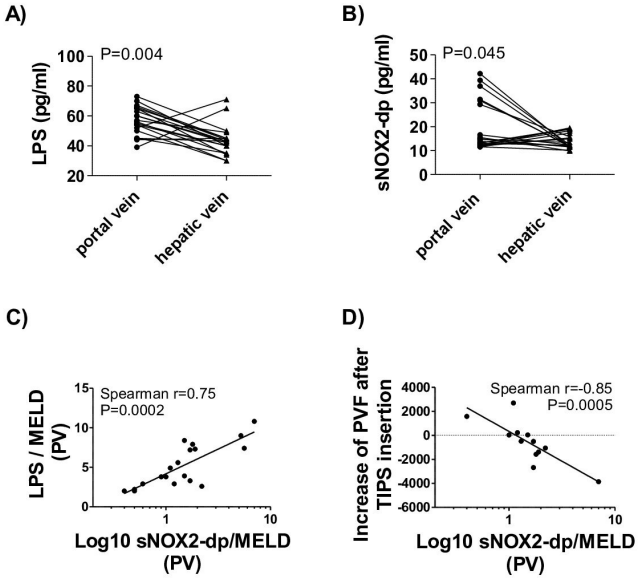

Figure 2 Differences of portal and hepatic vein levels of LPS (A) and sNOX2- dp (B), their correlation in the PV (C) and association of sNOX2-dp and portal venous flow at control angiography after TIPS insertion (D). P-values <0.05 were considered statistically significant. Patients: A-B, N=20; C, N=19; D, N=12. LPS, lipopolysaccharide; MELD, model for end-stage liver disease; PV, portal vein; PVF, portal venous flow; s NOX2-dp: soluble NOX2-derived peptide.

Moreover, recent data have demonstrated that the gut microbiome is related to hepatocellular carcinoma, which is also associated with decreased platelets.[4] Therefore, the interaction between platelet activation in the portal venous compartment and the microbiome might be a mechanism, as recently confirmed in various diseases.[3 5] To address this hypothesis, TIPS insertion provides a unique opportunity to access portal circulation. In 20 patients with decompensated cirrhosis, we measured portal and hepatic vein levels of LPS, soluble glycoprotein VI, soluble P-selectin and soluble NOX2-derived peptide (sNOX2-dp) as representatives of bacterial translocation, in vivo platelet activation and oxidative stress as previously described[6] (see online supplementary 1). Here, platelet activation occurred increasingly more often in the portal than in the hepatic vein, and this was associated with disease severity (Model for End-Stage Liver Disease score), even in the presence of thrombocytopenia (see figure 1). Indeed, aggregation of platelets in cirrhosis might lead to obliteration and parenchymal extinction depending on disease severity.[7] As a potential cause for platelet activation, we detected increased levels of LPS in the portal vein, reflecting bacterial translocation. Furthermore, we found high oxidative stress levels in the portal vein detected by markers of NOX2 activation (sNOX2-dp), deriving from activated immune cells as a readout for inflammation, suggesting that this LPS inflammation possibly contributes to platelet activation (see figure 2). Extended bacterial translocation in advanced liver disease, as a trigger for activation of inflammatory cells in the portal vein[7] and potentially of platelets, is biologically plausible and provides further insights into the development of thrombotic events in liver cirrhosis, even in case of thrombocytopenia and TIPS insertion.

In the majority of our patients, an invasive procedure was performed to re-evaluate

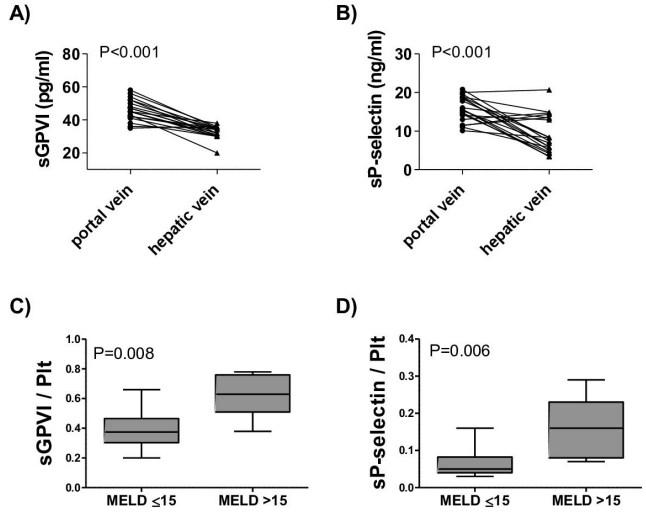

Figure 1 Differences in portal and hepatic vein levels of sGlycoprotein VI (A), sP-selectin (B) and their association to disease severity (C-D). P-values <0.05 were considered statistically significant. A-B, N=20; C-D, N=19. MELD, model for end-stage liver disease; Plt: platelets; sGPVI, soluble glycoprotein VI; sP-selectin, soluble P-selectin.

function and position of TIPS. Indeed, baseline sNOX2-dp levels, even after adjustment for disease severity, showed a strong correlation to reduced portal venous flow in control angiography (See figure 2), as an indirect sign for a prothrombotic milieu in the portal vein.

In conclusion, decompensated liver cirrhosis leads to enhanced platelet activation in the portal vein. Bacterial translocation and/or oxidative stress may contribute to this and possibly increase the risk of thrombogenesis in decompensated liver cirrhosis.

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Correction notice This article has been corrected since it published Online First. The affiliations for Roberto Carnevale and Francesco Violi have been corrected.

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