

Superimposed Coagulopathic Conditions in Cirrhosis: Infection and Endogenous Heparinoids, Renal Failure, and Endothelial Dysfunction

Jasper H. Smalberg, MSc^a, Frank W.G. Leebeek, MD, PhD^{a,b,*}

KEYWORDS

- Cirrhosis • Hemostasis • Infection
- Heparinoids • Renal failure • Endothelial dysfunction

Liver failure is accompanied by multiple changes in the hemostatic system.¹ These changes are mainly caused by a reduced synthesis of coagulation factors and altered clearance of activated coagulation factors. In addition, hyperfibrinolysis and thrombocytopenia are frequently encountered.¹ In this article, the authors discuss three additional pathophysiologic mechanisms that influence the coagulation system in patients who have liver disease. First, they discuss the influence of infections and endogenous heparinoids (see the related article elsewhere in this issue). Second, they discuss renal failure, a condition that is frequently encountered in patients who have liver cirrhosis. Finally, the dysfunction of the endothelial system is reviewed, including testing of endothelial function in liver disease.

^a Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

^b The Netherlands Organisation for Scientific Research (NWO), Den Haag, The Netherlands

* Department of Hematology, Erasmus University Medical Center, Room L-435, P.O. Box 2040, 3000 GD Rotterdam, The Netherlands.

E-mail address: f.leebeek@erasmusmc.nl (F.W.G. Leebeek).

INFECTION AND ENDOGENOUS HEPARINOIDS

Bacterial infections are an important and frequently occurring coexisting problem in cirrhotic patients that is related to the degree of liver dysfunction.² They are reported in up to 47% of hospitalized cirrhotic patients³ and result in increased mortality.⁴ Bacterial infections have been reported in 35% to 66% of cirrhotic patients with gastrointestinal bleeding,⁵ and infection is an independent risk factor for early rebleeding within 5 days of admission for variceal bleeding.^{6,7} Furthermore, spontaneous bacterial peritonitis commonly precedes variceal bleeding⁸ and recent evidence shows that prophylactic antibiotic therapy prevents early rebleeding.^{9,10} This evidence illustrates the pivotal role of bacterial infections in the cause of variceal bleeding in patients who have liver cirrhosis.¹¹

Endotoxemia is frequently found in cirrhotic patients,¹² originating from bacteria translocated from the bowel,¹¹ even in the absence of any signs of sepsis. Goulis and colleagues¹³ postulated the role of bacterial infections through subsequent release of endotoxins in the systemic circulation as critical for triggering variceal bleeding through two distinct pathways. First, endotoxins lead to an increase in portal pressure by contracting hepatic stellate cells through the induction of endothelin.¹⁴ Second, the release of nitric oxide (NO)^{15–17} and prostacyclin^{18,19} inhibits platelet aggregation.

Indeed, infection may lead to abnormalities in coagulation through multiple pathways. Sepsis can cause impairment of platelet aggregation, and production of cytokines in bacterial infections may lead to activation of clotting factors and fibrinolysis.¹¹ Here, the authors focus on the role of endogenous heparinoids. Heparinoids, both exogenous and endogenous, are cleared by the liver, and elevated levels have been reported in cirrhotic patients.²⁰ The influence of heparin-like substances is difficult to monitor in patients who have liver cirrhosis. Thromboelastography (TEG) is a quick and reliable method to assess clot formation and lysis and allows detection of heparin-like substances.²¹ Using TEG, 20 cirrhotic patients were shown to exhibit worsening TEG parameters the day before rebleeding.²² The same group demonstrated that bacterial infections significantly impair hemostasis in patients who have decompensated cirrhosis, also using TEG.²³ Montalto and colleagues²⁴ found a significant heparin activity using heparinase I–modified TEG in 28 of 30 cirrhotic patients, but none in those not infected, whereas other coagulation parameters were not altered. In a subsequent study, this heparin activity was found to be associated with anti–activated factor X concentrations in many patients.²⁵ Furthermore, the presence of endogenous heparinoids in cirrhotic patients who had acute variceal bleeding was demonstrated, which could contribute to failure to control acute bleeding and early rebleeding.²⁶ As a possible source for these endogenous heparinoids, it has been postulated that endotoxins and inflammation due to infection can release heparinoids from the endothelium and mast cells in a dose-dependent manner; in addition, endothelial cells are able to produce tissue-plasminogen activator, which induces fibrinolysis.²⁴

Heparin and heparan sulfate belong to the family of glycosaminoglycans, which are heteropolysaccharides, including hyaluronic acid, chondroitin, dermatome sulfate, and keratan sulfate. Recently, it has been shown that heparinase I–modified TEG detects the activity of not only heparan sulfate but also dermatan sulfate, which indicates that both of these glycosaminoglycans could be responsible for the endogenous heparinoid effect.²⁷ However, evidence suggests that heparan sulfate, which is specifically cleaved by heparinase III–modified TEG, is the most important heparinoid responsible for the heparin-like effect.²⁸

It can be concluded that the role of infection is well established in variceal bleeding in cirrhotic patients. Consequently, prophylactic antibiotics decrease the rate of bleeding. Therapeutic implications concerning the endogenous heparinoids in patients who have liver cirrhosis have not yet been identified.

RENAL FAILURE COAGULOPATHY IN CIRRHOSIS

Renal failure occurs frequently in patients who have liver cirrhosis.²⁹ Patients who have renal failure are at increased risk for bleeding complications.³⁰ Although the pathophysiology of this hemostatic dysfunction has not yet been fully elucidated, it appears to be multifactorial. Platelets play a pivotal role in the hemorrhagic tendencies in uremic patients.³⁰

Platelet dysfunction occurs as a result of intrinsic platelet abnormalities and impaired platelet–vessel wall interaction.^{31,32} Abnormalities of platelet alpha-granules with lower than normal content of ADP and serotonin^{33,34} and defective arachidonic acid metabolism leading to decreased platelet thromboxane A2 generation have been reported in uremic patients.³⁵ Furthermore, functional and biochemical alterations of the platelet cytoskeleton in uremia were found.³⁶ Uremic platelets have a defective interaction with vessel subendothelium,³⁷ which may, in part, result from intrinsic dysfunction of glycoprotein GpIIb-IIIa, a platelet membrane glycoprotein that plays a major role in platelet aggregation and adhesion through its interaction with fibrinogen and von Willebrand factor (vWF).^{33,38–40} Other causes of platelet dysfunction and impaired vessel wall interaction in uremia are discussed in more detail elsewhere in this issue.^{30,41,42}

The potential role of uremic toxins and the vessel wall in uremic bleeding has also been extensively investigated. NO is a potent modulator of vascular tone that inhibits platelet adhesion to the endothelium¹⁶ and platelet aggregation.⁴³ Studies in uremic patients have shown that platelet NO synthesis is increased and that uremic plasma stimulates NO production by cultured endothelial cells.⁴⁴ The increase in NO synthesis has been related to elevated levels of guanidinosuccinic acid, a uremic toxin that stimulates NO production in this setting.³⁰

Anemia is common in uremic patients and is an important clinical risk factor for bleeding complications: the decreased number of red cells may rheologically reduce physical platelet interactions with the vessel wall and metabolically reduce platelet function.⁴² Raising the hematocrit to 30% by red blood cell transfusions reduces the bleeding time in many patients, occasionally to a normal level.^{45,46} Elevation of hematocrit can also be achieved by administering recombinant human erythropoietin, which improves primary hemostasis through an increase of red cell mass but also through enhanced platelet aggregation and increased platelet adhesion to the endothelium, which is independent of the hematocrit rise.^{47–50}

Hemodialysis also has a favorable impact on bleeding complications in uremic patients but may only partially correct platelet dysfunction.^{51–54} In fact, the hemodialysis process itself may contribute to bleeding through the continuous platelet activation induced by the interaction between blood and artificial surfaces.⁵⁵

Platelet transfusion is not effective in managing bleeding complications because uremic plasma elicits changes in function of platelets from normal donors.⁴² Uremic plasma has been shown to inhibit platelet adhesion to inverted, de-endothelialized human umbilical cord artery segments, whereas uremic platelets adhere normally in the presence of normal plasma.⁵⁶ Therefore, rationale does not exist for platelet transfusion, which is sometimes used in interventions, such as dialysis line placement, to

eliminate temporarily the bleeding tendency in uremic patients. Instead, current treatment modalities for uremic bleeding include erythropoietin, desmopressin, and estrogens, which have reduced bleeding complications.^{42,57}

Although renal failure has classically been associated with a bleeding tendency, thrombotic events are also common among patients who have end-stage renal disease.⁵⁸ Various prothrombotic factors have been demonstrated in these patients. Elevated rates of thrombotic complications are thought to emerge as the bleeding tendency is better controlled.⁵⁹

ENDOTHELIAL FUNCTION IN CIRRHOSIS

In recent years, the role of endothelial function in vascular health and disease has been studied extensively. The endothelium not only serves as a barrier between blood and the vessel wall but also plays an important role in hemostasis, vessel tone regulation, vascular homeostasis, and inflammatory processes. In response to various mechanical and chemical stimuli, endothelial cells secrete a wide array of substances that mediate these functions.^{60–63} Endothelial dysfunction results in a loss of balance between prothrombotic and antithrombotic factors, vasoconstrictors and vasodilators, growth-promoting and growth-inhibiting factors, and proatherogenic and antiatherogenic factors,⁶² and is now recognized as an essential part of the pathogenesis of several conditions, such as coronary artery disease^{64,65} and microvascular complications in type 2 diabetes.⁶⁶

Portal hypertension is primarily caused by increased resistance to portal blood flow, which, in cirrhosis, is mainly determined by morphologic changes.⁶⁷ However, substantial evidence shows that this is aggravated by a dynamic component, in which endothelial dysfunction plays a central role. Endothelial dysfunction causes an imbalance between the vasodilator and vasoconstrictor forces, affecting the vascular tone of the circulation on two distinct anatomic levels: the arteries of the intrahepatic microcirculation and the arteries of the splanchnic circulation.

Sinusoidal endothelial cells (SECs) play a central role in mediating intrahepatic vascular resistance by producing and releasing vasoactive substances.⁶⁸ A cirrhotic liver cannot accommodate the increased portal blood flow caused by postprandial hyperemia, resulting in an abrupt increase in portal pressure.⁶⁹ Such repeated increases are considered to be an important factor in progressive dilatation of varices in cirrhosis.⁶⁷ In addition, endothelial dysfunction in the hepatic vascular bed is characterized by a defective vasodilatory response to acetylcholine and insufficient NO production by endothelial NO synthase (eNOS).^{70–72} Increased thromboxane A production in SECs has also been shown to contribute to increased intrahepatic resistance in cirrhosis.^{73,74} Thus, SEC dysfunction impairs the endothelium-dependent dilatation of the intrahepatic liver microcirculation, resulting in increased intrahepatic vascular resistance and portal hypertension.

SEC dysfunction is an early event in the pathogenesis of cirrhosis⁷⁵ and is considered the primary event that leads to portal hypertension and the subsequent arterial splanchnic and systemic vasodilatation.⁶⁸ In contrast to the hypoactive SECs, an increased production of NO is observed in the arteries of the splanchnic and systemic circulation in cirrhosis and other conditions that lead to portal hypertension.⁷⁶ This increase in NO leads to an increased endothelium-dependent dilatation and precedes the so-called “hyperdynamic circulatory syndrome.”^{76–78} Several complications of liver cirrhosis, such as variceal bleeding, ascites, hepatorenal syndrome, and hepatopulmonary syndrome, are closely related to the presence of these hemodynamic alterations.⁷⁷

Several clinical tests that evaluate endothelial function have been developed, mostly in relation to cardiovascular diseases.⁷⁹ Although clinical assessment of endothelial function tests in liver cirrhosis has received less attention, several promising markers of endothelial function in cirrhotic patients have been described. NO, its metabolites, and second messengers (cyclic GMP) are theoretically the clearest and most direct markers. Although assessment of vascular NO level is indicative of endothelial dysfunction in cirrhosis,⁶⁸ it is not yet widely used in clinical assessment of endothelial function. Interpretation of these measurements is often difficult and not always representative of endothelial NO production.⁸⁰ The procoagulant consequences of endothelial activation can be measured as a change in the balance of tissue-type plasminogen activator and plasminogen-activator inhibitor 1.⁸¹ A shift in this balance, related to the extent of cirrhosis, has been reported.^{82,83}

Furthermore, vWF is released into the circulation by activated endothelial cells and is easy to measure. Highly elevated levels of vWF in cirrhosis have been reported, which were strongly related to the severity of the disease.^{84,85} Moreover, vWF levels were significantly correlated with NO production, as evaluated by nitrite and nitrate levels.⁸⁶ Endothelial cell activation leads to increased expression of inflammatory cytokines and adhesion molecules. Serum levels of intercellular adhesion molecule-1 are increased in cirrhosis⁸⁷ and are reported to be of prognostic relevance in patients who have liver cirrhosis.⁸⁸ Finally, substantial evidence exists for strongly elevated endothelin-1 levels in cirrhosis,⁸⁹ which may also be considered as an index for endothelial function.⁶¹ To conclude, endothelial dysfunction testing appears promising for clinical research and should be evaluated in more detail for its clinical use.

Box 1

Mechanisms of superimposed conditions in liver cirrhosis leading to coagulopathic conditions

Bacterial infections/endotoxins

- Hemostatic imbalance
 - Reduced platelet aggregation
 - Activation clotting factors
 - Hyperfibrinolysis
 - Endogenous heparinoids
- Increased portal pressure (endothelin), predisposing to variceal bleeding

Renal failure

- Platelet abnormalities
- Impaired platelet–vessel wall interactions
- Anemia
- Abnormal NO production
- Others, such as drugs and comorbidity

Endothelial dysfunction

- Imbalance vasoconstrictors and vasodilators
- Intrahepatic vasoconstriction → increase of portal pressure
- Systemic vasodilatation → precedes hyperdynamic circulatory syndrome

SUMMARY

In this article, the authors discussed three superimposed coagulopathic conditions in patients who have liver cirrhosis, as summarized in **Box 1**. The pivotal role of infection in variceal bleeding is well established, and, among other things, it leads to abnormalities in coagulation. One of the pathways through which this occurs is shown to depend on endogenous heparinoids. Furthermore, renal failure may contribute to hemostatic imbalance in cirrhotic patients through so-called "uremic bleeding." Multifactorial platelet defects play a central role in the cause of uremic bleeding. Current treatment options include erythropoietin, desmopressin, and estrogens, which have been shown to reduce bleeding complications in renal failure. Finally, the authors discussed endothelial dysfunction, which is shown to play an important role in the development of portal hypertension in patients who have cirrhosis. Several promising markers of endothelial function in cirrhotic patients have recently become available and should be evaluated in more detail for their clinical use.

REFERENCES

1. Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. *J Hepatol* 2002;37(2):280–7.
2. Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. *Dig Liver Dis* 2001;33(1):41–8.
3. Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol* 1993;18(3):353–8.
4. Rimola A, Soto R, Bory F, et al. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. *Hepatology* 1984; 4(1):53–8.
5. Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999;29(6):1655–61.
6. Bernard B, Cadranet JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. *Gastroenterology* 1995; 108(6):1828–34.
7. Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1998;27(5):1207–12.
8. Bleichner G, Boulanger R, Squara P, et al. Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage. *Br J Surg* 1986;73(9): 724–6.
9. Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial. *Hepatology* 2004;39(3):746–53.
10. Jun CH, Park CH, Lee WS, et al. Antibiotic prophylaxis using third generation cephalosporins can reduce the risk of early rebleeding in the first acute gastroesophageal variceal hemorrhage: a prospective randomized study. *J Korean Med Sci* 2006;21(5):883–90.
11. Thalheimer U, Triantos CK, Samonakis DN, et al. Infection, coagulation, and variceal bleeding in cirrhosis. *Gut* 2005;54(4):556–63.
12. Lin RS, Lee FY, Lee SD, et al. Endotoxemia in patients with chronic liver diseases: relationship to severity of liver diseases, presence of esophageal varices, and hyperdynamic circulation. *J Hepatol* 1995;22(2):165–72.

13. Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* 1999;353(9147):139–42.
14. Pinzani M, Milani S, De Franco R, et al. Endothelin 1 is overexpressed in human cirrhotic liver and exerts multiple effects on activated hepatic stellate cells. *Gastroenterology* 1996;110(2):534–48.
15. Laffi G, Foschi M, Masini E, et al. Increased production of nitric oxide by neutrophils and monocytes from cirrhotic patients with ascites and hyperdynamic circulation. *Hepatology* 1995;22(6):1666–73.
16. Radomski MW, Palmer RM, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. *Lancet* 1987;2(8567):1057–8.
17. Riddell DR, Graham A, Owen JS. Apolipoprotein E inhibits platelet aggregation through the L-arginine:nitric oxide pathway. Implications for vascular disease. *J Biol Chem* 1997;272(1):89–95.
18. Gratton JP, Maurice MC, D'Orleans-Juste P. Characterization of endothelin receptors and endothelin-converting enzyme activity in the rabbit lung. *J Cardiovasc Pharmacol* 1995;26(Suppl 3):S88–90.
19. Vane JR, Botting RM. Pharmacodynamic profile of prostacyclin. *Am J Cardiol* 1995;75(3):3A–10A.
20. Teien AN. Heparin elimination in patients with liver cirrhosis. *Thromb Haemost* 1977;38(3):701–6.
21. Salooja N, Perry DJ. Thrombelastography. *Blood Coagul Fibrinolysis* 2001;12(5):327–37.
22. Chau TN, Chan YW, Patch D, et al. Thrombelastographic changes and early re-bleeding in cirrhotic patients with variceal bleeding. *Gut* 1998;43(2):267–71.
23. Papatheodoridis GV, Patch D, Webster GJ, et al. Infection and hemostasis in decompensated cirrhosis: a prospective study using thrombelastography. *Hepatology* 1999;29(4):1085–90.
24. Montalto P, Vlachogiannakos J, Cox DJ, et al. Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. *J Hepatol* 2002;37(4):463–70.
25. Zambruni A, Thalheimer U, Coppell J, et al. Endogenous heparin-like activity detected by anti-Xa assay in infected cirrhotic and non-cirrhotic patients. *Scand J Gastroenterol* 2004;39(9):830–6.
26. Thalheimer U, Triantos C, Samonakis D, et al. Endogenous heparinoids in acute variceal bleeding. *Gut* 2005;54(2):310–1.
27. Senzolo M, Coppell J, Cholongitas E, et al. The effects of glycosaminoglycans on coagulation: a thromboelastographic study. *Blood Coagul Fibrinolysis* 2007;18(3):227–36.
28. Senzolo M, Cholongitas E, Riddell A, et al. Heparinase I, II and III modified thromboelastography for the detection of different glycosaminoglycans' effect in cirrhotics with bacterial infection. *J Hepatol* 2006;44(Suppl 2):S72.
29. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *International Ascites Club. Hepatology* 1996;23(1):164–76.
30. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? *Blood* 1999;94(8):2569–74.
31. Livio M, Benigni A, Remuzzi G. Coagulation abnormalities in uremia. *Semin Nephrol* 1985;5(2):82–90.
32. Remuzzi G. Bleeding in renal failure. *Lancet* 1988;1(8596):1205–8.
33. Di Minno G, Cerbone A, Usberti M, et al. Platelet dysfunction in uremia. II. Correction by arachidonic acid of the impaired exposure of fibrinogen receptors by adenosine diphosphate or collagen. *J Lab Clin Med* 1986;108(3):246–52.

34. Eknoyan G, Brown CH 3rd. Biochemical abnormalities of platelets in renal failure. Evidence for decreased platelet serotonin, adenosine diphosphate and Mg-dependent adenosine triphosphatase. *Am J Nephrol* 1981;1(1):17–23.
35. Remuzzi G, Benigni A, Dodesini P, et al. Reduced platelet thromboxane formation in uremia. Evidence for a functional cyclooxygenase defect. *J Clin Invest* 1983; 71(3):762–8.
36. Escolar G, Diaz-Ricart M, Cases A, et al. Abnormal cytoskeletal assembly in platelets from uremic patients. *Am J Pathol* 1993;143(3):823–31.
37. Castillo R, Lozano T, Escolar G, et al. Defective platelet adhesion on vessel sub-endothelium in uremic patients. *Blood* 1986;68(2):337–42.
38. Benigni A, Boccardo P, Galbusera M, et al. Reversible activation defect of the platelet glycoprotein IIb-IIIa complex in patients with uremia. *Am J Kidney Dis* 1993;22(5):668–76.
39. Escolar G, Cases A, Bastida E, et al. Uremic platelets have a functional defect affecting the interaction of von Willebrand factor with glycoprotein IIb-IIIa. *Blood* 1990;76(7):1336–40.
40. Gawaz MP, Dobos G, Spath M, et al. Impaired function of platelet membrane glycoprotein IIb-IIIa in end-stage renal disease. *J Am Soc Nephrol* 1994;5(1):36–46.
41. Sohal AS, Gangji AS, Crowther MA, et al. Uremic bleeding: pathophysiology and clinical risk factors. *Thromb Res* 2006;118(3):417–22.
42. Weigert AL, Schafer AI. Uremic bleeding: pathogenesis and therapy. *Am J Med Sci* 1998;316(2):94–104.
43. Marietta M, Facchinetti F, Neri I, et al. L-arginine infusion decreases platelet aggregation through an intraplatelet nitric oxide release. *Thromb Res* 1997;88(2):229–35.
44. Noris M, Benigni A, Boccardo P, et al. Enhanced nitric oxide synthesis in uremia: implications for platelet dysfunction and dialysis hypotension. *Kidney Int* 1993; 44(2):445–50.
45. Fernandez F, Goudable C, Sie P, et al. Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. *Br J Haematol* 1985;59(1): 139–48.
46. Livio M, Gotti E, Marchesi D, et al. Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. *Lancet* 1982;2(8306):1013–5.
47. Cases A, Escolar G, Reverter JC, et al. Recombinant human erythropoietin treatment improves platelet function in uremic patients. *Kidney Int* 1992;42(3):668–72.
48. Fabris F, Cordiano I, Randi ML, et al. Effect of human recombinant erythropoietin on bleeding time, platelet number and function in children with end-stage renal disease maintained by haemodialysis. *Pediatr Nephrol* 1991;5(2):225–8.
49. Moia M, Mannucci PM, Vizzotto L, et al. Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. *Lancet* 1987; 2(8570):1227–9.
50. Van Geet C, Van Damme-Lombaerts R, Vanrusselt M, et al. Recombinant human erythropoietin increases blood pressure, platelet aggregability and platelet free calcium mobilisation in uraemic children: a possible link? *Thromb Haemost* 1990;64(1):7–10.
51. Di Minno G, Martinez J, McKean ML, et al. Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis. *Am J Med* 1985;79(5):552–9.
52. Rabiner SF. The effect of dialysis on platelet function of patients with renal failure. *Ann N Y Acad Sci* 1972;201:234–42.
53. Remuzzi G, Livio M, Marchiaro G, et al. Bleeding in renal failure: altered platelet function in chronic uraemia only partially corrected by haemodialysis. *Nephron* 1978;22(4–6):347–53.

54. Stewart JH, Castaldi PA. Uraemic bleeding: a reversible platelet defect corrected by dialysis. *Q J Med* 1967;36(143):409–23.
55. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. *Semin Thromb Hemost* 2004;30(5):579–89.
56. Zwaginga JJ, Ijsseldijk MJ, Beeser-Visser N, et al. High von Willebrand factor concentration compensates a relative adhesion defect in uremic blood. *Blood* 1990;75(7):1498–508.
57. Hedges SJ, Dehoney SB, Hooper JS, et al. Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007;3(3):138–53.
58. Casserly LF, Dember LM. Thrombosis in end-stage renal disease. *Semin Dial* 2003;16(3):245–56.
59. Escobar G, Diaz-Ricart M, Cases A. Uremic platelet dysfunction: past and present. *Curr Hematol Rep* 2005;4(5):359–67.
60. Caballero AE. Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. *Obes Res* 2003;11(11):1278–89.
61. Laffi G, Marra F. Complications of cirrhosis: is endothelium guilty? *J Hepatol* 1999;30(3):532–5.
62. Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. *Am J Med* 1998;105(1A):32S–9S.
63. Racanelli V, Rehermann B. The liver as an immunological organ. *Hepatology* 2006;43(2 Suppl 1):S54–62.
64. Mano T, Masuyama T, Yamamoto K, et al. Endothelial dysfunction in the early stage of atherosclerosis precedes appearance of intimal lesions assessable with intravascular ultrasound. *Am Heart J* 1996;131(2):231–8.
65. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340(2):115–26.
66. Tooke JE. Microvascular function in human diabetes. A physiological perspective. *Diabetes* 1995;44(7):721–6.
67. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. *J Hepatol* 2000;32(1 Suppl):141–56.
68. Iwakiri Y, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. *J Hepatol* 2007;46(5):927–34.
69. Bellis L, Berzigotti A, Abraldes JG, et al. Low doses of isosorbide mononitrate attenuate the postprandial increase in portal pressure in patients with cirrhosis. *Hepatology* 2003;37(2):378–84.
70. Gupta TK, Toruner M, Chung MK, et al. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *Hepatology* 1998;28(4):926–31.
71. Rockey DC, Chung JJ. Reduced nitric oxide production by endothelial cells in cirrhotic rat liver: endothelial dysfunction in portal hypertension. *Gastroenterology* 1998;114(2):344–51.
72. Sarela AI, Mihaimed FM, Batten JJ, et al. Hepatic and splanchnic nitric oxide activity in patients with cirrhosis. *Gut* 1999;44(5):749–53.
73. Graupera M, Garcia-Pagan JC, Pares M, et al. Cyclooxygenase-1 inhibition corrects endothelial dysfunction in cirrhotic rat livers. *J Hepatol* 2003;39(4):515–21.
74. Graupera M, March S, Engel P, et al. Sinusoidal endothelial COX-1-derived prostanooids modulate the hepatic vascular tone of cirrhotic rat livers. *Am J Physiol Gastrointest Liver Physiol* 2005;288(4):G763–70.
75. Braet F, Wisse E. Structural and functional aspects of liver sinusoidal endothelial cell fenestrae: a review. *Comp Hepatol* 2002;1(1):1.

76. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology* 2006;43(2 Suppl 1):S121–31.
77. Groszmann RJ, Abraldes JG. Portal hypertension: from bedside to bench. *J Clin Gastroenterol* 2005;39(4 Suppl 2):S125–30.
78. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. *Hepatology* 2002;35(2):478–91.
79. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 2007;115(10):1285–95.
80. Vapaatalo H, Mervaala E. Clinically important factors influencing endothelial function. *Med Sci Monit* 2001;7(5):1075–85.
81. Vaughan DE. PAI-1 and atherothrombosis. *J Thromb Haemost* 2005;3(8):1879–83.
82. Leebeek FW, Klufft C, Knot EA, et al. A shift in balance between profibrinolytic and antifibrinolytic factors causes enhanced fibrinolysis in cirrhosis. *Gastroenterology* 1991;101(5):1382–90.
83. Violi F, Ferro D, Quintarelli C, et al. Clotting abnormalities in chronic liver disease. *Dig Dis* 1992;10(3):162–72.
84. Ferro D, Quintarelli C, Lattuada A, et al. High plasma levels of von Willebrand factor as a marker of endothelial perturbation in cirrhosis: relationship to endotoxemia. *Hepatology* 1996;23(6):1377–83.
85. Lisman T, Bongers TN, Adelmeijer J, et al. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology* 2006;44(1):53–61.
86. Albornoz L, Alvarez D, Otaso JC, et al. Von Willebrand factor could be an index of endothelial dysfunction in patients with cirrhosis: relationship to degree of liver failure and nitric oxide levels. *J Hepatol* 1999;30(3):451–5.
87. Bruno CM, Sciacca C, Cilio D, et al. Circulating adhesion molecules in patients with virus-related chronic diseases of the liver. *World J Gastroenterol* 2005;11(29):4566–9.
88. Giron-Gonzalez JA, Martinez-Sierra C, Rodriguez-Ramos C, et al. Adhesion molecules as a prognostic marker of liver cirrhosis. *Scand J Gastroenterol* 2005;40(2):217–24.
89. Mallat A, Lotersztajn S. Multiple hepatic functions of endothelin-1: physiopathological relevance. *J Hepatol* 1996;25(3):405–13.