Review

Cardiac Operations in Cirrhotic Patients

Nobuhiko Hayashida, MD, and Shigeaki Aoyagi, MD

It is well recognized that morbidity and mortality rates after cardiac operations with cardiopulmonary bypass in patients with cirrhosis are significantly higher than those in the general cardiac surgical population. Several contributing factors peculiar to cirrhosis, such as compromised nutritional status, increased susceptibility to infections, and impaired coagulopathy, may be responsible for the poor prognosis. It is empirically agreed that cardiac operations using cardiopulmonary bypass are contraindicated in patients with advanced cirrhosis. However, the population of cirrhotic patients who are referred for cardiac operations is still small and definitive indications for surgical interventions remain unknown. Moreover, cirrhotic patients have many distinctive anatomical and physiological features that influence postoperative course considerably. In this article, we reviewed the literature with special reference to its clinical features and clinical outcomes after cardiac surgery that would help cardiac surgeons to decide therapeutic modality. Further understanding of the unique condition, careful patient selection and intensive postoperative care are required to improve the clinical outcome in cirrhotic patients undergoing cardiopulmonary bypass. Recent developments in minimally invasive procedures, such as off-pump coronary artery bypass grafting, however, may enable us to treat patients with advanced cirrhosis safely. (Ann Thorac Cardiovasc Surg 2004; 10: 140–7)

Key words: comorbidity, cirrhosis, morbidity and mortality, indication

Introduction

As surgical techniques and postoperative patient care improve, the number of patients with advanced age and significant preoperative comorbidities who are referred for major surgery is increasing.[1] Among the coexistent disorders, cirrhosis is still a challenging clinical problem in surgical patients.[2-4] Because of the compromised health status in cirrhotic patients, their postoperative clinical results are unsatisfactory.[2-4] Particularly in the cardiac surgical field, postoperative morbidity and mortality rates remain significantly high in such patients.[5-8] It is generally agreed that several factors peculiar to cirrhosis rather than cardiac disorders are responsible for the disappointing results and the surgical prognosis correlates with the severity of cirrhosis.[5-8] Because patients with cirrhosis have distinctive anatomical and physiological disorders[9] that influence their perioperative course substantially, further understanding of the features may modulate the current surgical results. Moreover, because the population of cardiac surgical patients with this comorbidity is small and few reports have explored clinical results,[5-8] definitive recommendations and indications for cardiac surgery are still unknown. Accordingly, accumulation of cases and detailed evaluation of clinical results in cardiac surgical field are mandatory for the decision of therapeutic strategies and for the improvement of clinical results in cirrhotic patients.

From Department of Surgery, Kurume University School of Medicine, Fukuoka, Japan

Received January 19, 2004; accepted for publication April 19, 2004.
Address reprint requests to Nobuhiko Hayashida, MD: Department of Surgery, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan.

Pathogenesis and Epidemiology

Cirrhosis is the end result of hepatocellular necrosis induced by diverse causes, such as hepatitis viruses, alcoholism, autoimmune disease, prolonged cholestasis, metabolic disorders, and cardiogenic congestion and ischemia.[9] Inflammatory process initiated by hepatocellular necrosis stimulates the deposition of collagen around hepatocytes and in sinusoidal membranes, with resulting profound alteration in hepatocyte function and hepatic blood flow. The altered hepatic architecture and perisinusoidal fibrosis cause increased hepatic vascular resistance, resulting in portal hypertension and its associated complications of variceal hemorrhage, encephalopathy, ascites, and hypersplenism. Fully developed cirrhosis is progressive and irreversible with currently available therapy. Although racial and ethnic differences exist, chronic hepatitis B and C viral infection and alcoholism are the most common causes of cirrhosis worldwide.[9-13] Several epidemiologic studies have shown that approximately 4 million persons in the United States and probably more than 170 million persons worldwide (3%) are infected with hepatitis C virus.[14-16] Various studies have suggested that 3% to 20% of chronically infected patients develop cirrhosis.[11,17] Especially in the Asian countries, cirrhosis and hepatocellular carcinoma caused by hepatitis viruses are highly prevalent.[18-20]

The expansion of alcohol consumption and the liberalization of drinking norms during the post-World-War II eras have had a profound impact on medical and health interpretations of the role of alcohol use in liver disease.[21,22] It is widely believed that alcohol abuse and hepatitis C virus infection frequently coexist and they act synergistically to promote the development and progression of liver damage.[10,23] Moreover, recent studies have shown that the incidence of nonalcoholic fatty liver disease is increasing because of the inexorable rise in the prevalence of obesity and diabetes mellitus.[24-26] The prevalence of the disease has been estimated to be 24% of the entire U.S. population.[24] The disorder in some patients leads to progressive hepatic fibrosis and eventually cirrhosis.[24-26] Advanced liver disease, therefore, is still a major health problem worldwide.

Congestive heart failure due to myocardial infarction, cardiomyopathy, rheumatic heart disease, congenital heart disease with left to right shunt, or constrictive pericarditis increases hepatic venous pressure and decreases hepatic blood flow, with resulting congestive liver fibrosis and cirrhosis.[27] Multiple medications for cardiac disorders and blood transfusion during prior cardiac surgery may also compromise liver function. Accordingly, a close association between cardiac and hepatic disorders exists[27] and we often encounter patients with liver dysfunction in the cardiac surgical field. The frequency of end-stage liver disease, i.e., cirrhosis in patients who are referred for cardiac surgery, however, is considerably low because of their compromised health status and decreased life expectancy. In a recent study, the incidence of cirrhotic patient who underwent cardiac operations was reported to be 0.27%.[28]

Evaluation of Patients with Cirrhosis

Key aspects of the evaluation of cirrhotic patients in the surgical setting are the following: (1) estimation of hepatic functional reserve, (2) identification of coexisting anatomical and physiological disorders associated with portal hypertension. It is well known that cirrhosis is often accompanied by anemia, leukopenia, and thrombocytopenia secondary due to poor nutritional status, bleeding from varices, and hypersplenism.[9] Impaired coagulopathy manifested by a prolonged prothrombin time is also seen in cirrhotic patients because many of the coagulation factors are synthesized by the liver and because primary fibrinolysis is prominent.[9] Lower serum levels of cholinesterase, a hepatocyte secretion enzyme, represent impaired hepatic protein synthesis.[29] Hypoalbuminemia and low albumin to globulin ratio also are reliable indices of malnutritional status and reduced hepatic functional reserve.[9,30] Bilirubinemia of greater than 3.0 mg/dL is indicative of hepatic decompensation and the levels correlate with the mortality in patients with cardiac failure requiring left ventricular assist device.[9,31] Serum levels of hyaluronate, procollagen III N-terminal propeptide and type IV collagen are sensitive markers of hepatic fibrosis.[30,32,33] Because of the presence of portosystemic collaterals, ammoniemia, a cause of hepatic encephalopathy, is often observed in cirrhotic patients.[9]

An indocyanine green (ICG) clearance test, that reflects the hepatic uptake clearance, is useful for assessing hepatic functional reserve.[34,35] The decrease in ICG clearance has been shown to be a prognostic index of survival in cirrhotic patients and to predict poor clinical outcomes after hepatic resection and cardiac surgery.[36-38] Scintigraphy of ^{99m}Tc diethylenetriamine pentaacetic acid-galactosyl human serum albumin, an analog ligand to asialoglycoprotein receptors, also provides invaluable information with regard to functioning hepatocyte mass.[39,40]

Percutaneous liver biopsy is a useful technique for establishing the diagnosis and cause of cirrhosis, and for assessing its severity. However, because of recent advances in diagnostic technologies, such as laboratory tests above-mentioned and imaging tools, and because of bleed-

Table 1. Summary of postoperative clinical results in cirrhotic patients

				Morbidity			Mortality		
	n	CPB use	Classification	Class A	Class B	Class C	Class A	Class B	Class C
Klemperer et al.[5]	13	Yes	Child	25%	100%	–	0%	80%	–
Bizouarn et al.[6]	12	Yes	Child-Pugh	50%	100%	–	0%	50%	–
Kaplan et al.[7]	8	Yes	Child	100%	100%	–	0%	50%	–
Kaplan et al.[7]	2	No	Child	100%	–	–	0%	–	–
Hayashida et al.[8]	15	Yes	Child-Pugh	40%	100%	100%	0%	50%	100%
Hayashida et al.[8]	3	No	Child-Pugh	–	33%	–	–	0%	–

CPB, cardiopulmonary bypass.

ing complication, liver biopsy may not be imperative in clinical practice. Imaging tools, such as ultrasound, computed tomography and magnetic resonance imaging, are useful diagnostic techniques of portal hypertension, morphological changes of the liver and spleen, and ascites. Endoscopic diagnosis of esophagogastric varices should also be entertained because bleeding from varices is the single most life-threatening complication of portal hypertension, responsible for approximately one third of all deaths in patients with cirrhosis.[9]

The grading of severity of cirrhosis is made according to the criteria of Child-Turcotte[41] or Child-Pugh.[42] The criteria have been employed to assess long term prognosis in cirrhotic patients and to predict operative outcome.[7,42,43] The Child-Pugh classification[42] is based upon the following five factors graded from 1 to 3; presence of encephalopathy, severity of ascites, total bilirubin level, albumin level and prothrombin time. Patient's cirrhotic status is classified into three groups according to the sum of the score (class A, from 5 to 6; class B, from 7 to 9; class C, from 10 to 15). Because these variables are readily available in our clinical practice with minimal invasiveness, this classification has received wide acceptance as a method of assessing hepatic functional status and surgical risk. In patients undergoing noncardiac surgical interventions, the operative mortality rates for classes A, B, and C have been shown to be in the range of 0% to 5%, 10% to 15%, and greater than 25%, respectively.[9]

Clinical Outcomes after Cardiovascular Surgery

Mortality after cardiovascular surgery

Clinical outcomes after cardiac operations in cirrhotic patients reported in the recent literature[5,6,8] are summarized in Table 1. The consensus of opinion among these clinical studies is that patients with mild cirrhosis (Child class A cirrhosis) tolerated cardiac operations satisfactorily. Patients with more advanced cirrhosis (Child class B or C cirrhosis), however, had a significantly higher mortality rate (50-100%) after cardiopulmonary bypass. Moreover, Bizouarn and colleagues[6] have demonstrated that the health status remained compromised even well after the operation because of persistent hepatic dysfunction. Accordingly, it is generally agreed that elective cardiac operations using cardiopulmonary bypass are contraindicated in patients with moderate to severe cirrhosis. Even in cases of emergency, a decision of therapeutic strategy should be made carefully on the basis of the individual life expectancy considering cardiac and hepatic disorders. In contrast, Kaplan et al.[7] have shown that cardiac surgery on a beating heart or cardiac surgery with short duration of cardiopulmonary bypass may be performed with good results in patients with cirrhosis. The results are in agreement with our recent published data,[8] in which three patients with Child class B cirrhosis underwent off-pump coronary artery bypass grafting (CABG). It has been well documented that the use of cardiopulmonary bypass triggers the production and release of numerous vasoactive substances and cytotoxic chemicals that affect coagulopathy, vascular resistance, vascular permeability, fluid balance, and major organ function.[44,45] Other contributing factors, such as hypothermia, hemodilution and hypoperfusion during cardiopulmonary bypass, also may be responsible for the morbidity and mortality after operation.[46] The avoidance of cardiopulmonary bypass use, therefore, may theoretically improve postoperative clinical outcome by preventing its adverse side effects. Several recent case reports in which surgical revascularization was performed without cardiopulmonary bypass in cirrhotic patients also have shown encouraging results.[47,48] Although the technique is not indicated in all patients requiring cardiac surgical interventions, off-pump CABG can be an alternative therapeutic strategy for patients with moderate to severe cirrhosis requiring surgical revascularization. However, the reported number of cirrhotic patients who underwent this procedure is still substantially small and the long-term result remains unknown. Further investigations, therefore, are required for the universal application of this technique in advanced cirrhosis. If the use of cardiopulmonary bypass is deemed unavoidable, the duration should be minimized by means of the most simple and expeditious surgical procedure.

Postoperative complications and management

Although the mortality rates after cardiac operations are relatively low in patients with mild cirrhosis, the incidence of postoperative major complications is strikingly high.[5-8] The operative morbidity rates for Child classes A, B, and C cirrhosis have been shown to be 25% to 50%, 100%, and 100%, respectively.[5-8] Common characteristics of postoperative complications in cirrhosis included infections, excessive mediastinal bleeding, gastrointestinal disorders, hepatic and renal failure, and fluid retention characterized by ascites, pericardial effusion, and pleural effusion. It seems probable that the majority of these complications are attributable to the clinical and pathophysiologic features of cirrhosis rather than impaired cardiac function.

The incidence of severe infections, such as mediastinitis and septicemia, has been reported to be 25% to 33%.[5-8] Although the cause of the increased susceptibility to infections is not evident at present, alteration of immune function, poor nutritional status and the higher incidence of reexploration for bleeding in cirrhosis may account for the results. Several epidemiologic studies have shown that infection remains a leading cause of death among hospitalized cirrhotic patients.[49-52] The higher prevalence of infections is accounted for by decreased reticuloendothelial function and impairment of several components of cell-mediated and humoral immunity.[53] Urinary tract infections, spontaneous bacterial peritonitis, respiratory tract infections, and bacteremia are the most frequent bacterial infectious complications seen in these patients and the prevalence increases with advancing clinical stage of cirrhosis.[49-53] It has been demonstrated that between 20% and 50% of cirrhotic patients develop these infections during hospitalization and most bacterial infections are hospital-acquired.[49-53] Logistic regression analysis in a recent prospective study has identified admission for gastrointestinal bleeding and a low serum albumin as independent risk factors for development of bacterial infections.[50] As prophylactic treatment in cirrhotic patients against bacterial infections, selective intestinal decontamination with norfloxacin has been used. Its efficacy in reducing the risk of gram-negative Escherichia coli and streptococci, which are the most common types of infecting organism, have been reported.[51,54,55] In cirrhotic patients developing bacterial infections, third-generation cephalospolins are currently advocated because of their high level of intrinsic activity against the pathogens as well as their safe use at high doses.[51,56] However, the emergence of pathogens resistant to those regimens and severe hospital-acquired staphylococcal infections, especially by methicillin-resistant Staphylococcus aureus, has recently been observed in cirrhotic patients undergoing prophylaxis.[51,54-57] In addition to the markedly high prevalence of infections in cirrhosis per se, cardiac surgical patients are subject to profound surgical invasiveness, endotoxemia and impairment in immune function, especially when cardiopulmonary bypass is used.[58-60] Once major infectious complications develop after cardiac procedures in cirrhotic patients, the mortality rate is miserably high. Therefore, meticulous perioperative management of infections by means of screening the carriage of pathogens, early diagnosis, and administration of antibiotics and immune globulins, are mandatory for the prevention of the disastrous complication. Our protocol of prophylactic treatment for cirrhotic patient is as follows. Cefazolin sodium hydrates (1,000 mg) is given intravenously before skin incision, in the cardiopulmonary bypass priming solution and every 6 hours in the first 24 hours after surgery. Its administration (twice a day) is continued at least for five days after surgery. Polyethylene glycol treated human normal immunoglobulin (2,500 mg) is also given twice a day for three days.

Hemorrhagic complication is a major concern in cirrhotic patients undergoing surgical interventions because complicated coagulopathy due to thrombocytopenia, platelet dysfunction, reduced coagulation factors, and fibrinolysis is frequently observed.[9,61,62] The condition may be further aggravated by the hematological derangement inherent with cardiopulmonary bypass.[63-65] Hypothermia and hemodilution during cardiopulmonary bypass may also influence the coagulopathy. Excessive mediastinal bleeding requiring reexploration occurred in up to 31% of cirrhotic patients undergoing cardiac surgical procedures.[5-8] Chest tube drainage and transfusion requirements in those patients are reported to be three times higher than those in the standard cardiac surgical population.[5,7] Bizouarn and colleagues[6] have shown that the use of high-dose aprotinin provided beneficial effects on hemostasis even in such patients. In the report, however, late cardiac tamponade probably due to minor mediastinal bleeding after surgery occurred in 17% of their patients. Therefore, meticulous surgical hemostasis and optimization of coagulopathy by means of administration of pharmacological agents, such as vitamin K, tranexamic acid, and antifibrinolytics, are essential for the reduction of blood loss and transfusion requirements. Bleeding from esophagogastric varices is also a major postoperative complication in cirrhotic patients. Variceal hemorrhage occurred in approximately 10% to 20% of cardiac surgical patients.[5-8] It appears that the incidence of this complication increases with the advance of cirrhotic status. Preoperative evaluation with endoscopy and eradication of varices by endoscopic sclerotherapy if present are necessary, especially in patients with a history of variceal hemorrhage or with moderate to severe cirrhosis.

Further deterioration of liver function that is already compromised in cirrhosis after cardiac surgery is of great concern. In patients with normal preoperative liver function, 1% to 3% of patients undergoing cardiac surgical procedures developed liver dysfunction, defined as the presence of jaundice or the elevation in alanine aminotransferase levels.[66,67] Postoperative liver dysfunction was associated with higher morbidity and mortality.[66,67] Although the pathogenesis is multifactorial, liver cell damage due to decreased hepatic blood flow during cardiopulmonary bypass seems to be fundamental.[46,67] Hepatic hemodynamics are characterized by a dual supply of blood from the hepatic artery and the portal vein. The portal vein contributes two thirds of the total hepatic blood flow, while hepatic arterial perfusion accounts for over one half of the liver's oxygen supply.[9] As hepatic portal perfusion decreases as a result of increased portal venous resistance, hepatic arterial flow increases by its autoregulatory or buffer response.[9] Therefore, the hepatic artery plays an important role in hepatic blood supply in cirrhosis. An experimental study, that evaluated hepatic circulation and oxygen metabolism during cardiopulmonary bypass, has demonstrated that total hepatic blood flow and oxygen delivery decreased during cardiopulmonary bypass and the decreases were more marked with a larger dose of fentanyl.[68] Hepatic arterial blood flow, however, did not change during normothermic cardiopulmonary bypass with a lower dose of fentanyl, whereas it decreased significantly during hypothermic cardiopulmonary bypass.[68] Accordingly, normothermic cardiopulmonary bypass with a lower dose of fenatnyl anesthesia may be advantageous in cirrhotic patients in terms of preserving hepatic arterial blood flow. In a recent experimental study,[69] liver function was better preserved by higher hematocrit (25%) during cardiopulmonary bypass compared to lower hematocrit (15%). Avoidance of low hematocrit during cardiopulmonary bypass may also be a useful adjunct in cirrhosis.

Cirrhotic patients have significant abnormalities in their fluid balance, as manifested by the development of ascites, pleural effusion, and peripheral edema.[70-72] As severity of cirrhosis advances, the abnormality in volume regulation becomes refractory to medical treatment. In that situation, renal function becomes progressively impaired, with resulting acute renal failure, so-called hepatorenal syndrome.[70] A markedly activated renin-angiotensin-aldosterone system and sympathetic system, and a blunted responsiveness to atrial natriuretic factor are well documented in such patients and the imbalances in these neurohormonal factors are believed to play a pathogenic role in the complication.[71-74] It is well recognized that cardiopulmonary bypass stimulates the production and release of vasoactive substances, such as sympathetic amines, renin, angiotensin, aldosterone, and vasopressin.[44] Biological activity of endogenous atrial natriuretic peptides may also decrease after cardiopulmonary bypass.[75] Because all these responses lead to sodium and water retention, the edematous status may further worsen after cardiac surgery. The incidence of postoperative fluid retention, characterized by ascites, pericardial effusion, and pleural effusion are considerably high and the management is troublesome in most cases.[6,8] In our clinical practice, the medical treatment of the abnormalities is based on a low-sodium diet, and administration of aldosterone antagonists and loop diuretics. Patients who are refractory to these conventional therapies, however, may require different therapeutic modalities, such as paracentesis and hemodialysis, particularly when renal dysfunction develops. Recently, natriuretic effects of synthetic urodilatin, an atrial natriuretic peptide, have been proven even in cirrhotic patients with ascites.[76] Perioperative use of the regimen may improve clinical outcome after cardiac operations.

Perioperative ammonia concentration also should be controlled meticulously because patients with portal hypertension are particularly prone to develop hyperammoniemia.[77] We control its level by eliminating protein from the diet, removing nitrogen from the gastrointestinal tract by cathartics and enemas, and administering intestinal antibiotics.

Table 2. Recommended cardiac surgical approaches in cirrhotic patients

	Cardiac operations under CPB	Cardiac operations without CPB
Child-Pugh class A	Acceptable	Acceptable
Child-Pugh class B	Contraindicated*	Acceptable
Child-Pugh class C	Contraindicated	Unknown

* Cardiac operations are contraindicated unless a clear need that transcends the poor prognosis after cardiopulmonary bypass exists. CPB, cardiopulmonary bypass.

Recommended Cardiac Surgical Approaches in Cirrhotic Patients

On the basis of our experience of 18 patients,[8)] together with the previous clinical results[5-7)] in cirrhotic patients, our recommendations and indications for cardiac operations are summarized in Table 2. Although postoperative morbidity rates are high, all patients with mild cirrhosis (Child-Pugh class A) can be candidates for cardiac surgery irrespective of the use of cardiopulmonary bypass. In patients with more advanced cirrhosis (Child-Pugh classes B and C), however, postoperative mortality is unacceptably high and this patient subgroup may not be suitable for elective cardiac operations with cardiopulmonary bypass. Especially in the emergency cases, a clear need for an operation that transcends the poor prognosis after cardiopulmonary bypass must exist. Although defintive studies involving more patients are required, recent developments in minimally invasive procedures, such as off-pump CABG, may enable us to treat patients with advanced cirrhosis safely.

Acknowledgments

This work was supported in part by the Grant-in-Aid for Encouragement of Young Scientists, Japan Society for the Promotion of Science (grant A-14770696) and Grant-in-Aid for Scientific research (grant C-15591505 and grant C-14571290), Japan.

References

1. Edwards FH, Clark RE, Schwartz M. Coronary artery bypass grafting: the Society of Thoracic Surgeons National Database experience. *Ann Thorac Surg* 1994; **57**: 12–9.
2. Leonetti JP, Aranha GV, Wilkinson WA, Stanley M, Greenlee HB. Umbilical herniorrhaphy in cirrhotic patients. *Arch Surg* 1984; **119**: 442–5.
3. Doberneck RC, Sterling WA, Allison DC. Morbidity and mortality after operation in nonbleeding cirrhotic patients. *Am J Surg* 1983; **146**: 306–9.
4. Aranha GV, Sontag SJ, Greenlee HB. Cholecystectomy in cirrhotic patients: a formidable operation. *Am J Surg* 1982; **143**: 55–60.
5. Klemperer JD, Ko W, Krieger KH, et al. Cardiac operations in patients with cirrhosis. *Ann Thorac Surg* 1998; **65**: 85–7.
6. Bizouarn P, Ausseur A, Desseigne P, et al. Early and late outcome after elective cardiac surgery in patients with cirrhosis. *Ann Thorac Surg* 1999; **67**: 1334–8.
7. Kaplan M, Cimen S, Kut MS, Demirtas MM. Cardiac operations for patients with chronic liver disease. *Heart Surg Forum* 2002; **5**: 60–5.
8. Hayashida N, Shoujima T, Teshima H, et al. Clinical outcome after cardiac operations in patients with cirrhosis. *Ann Thorac Surg* 2004; **77**: 500–5.
9. Rikkers LF. Surgical complications of cirrhosis and portal hypertension. In: Sabiston DC, Lyerly HK eds.; Textbook of Surgery. Philadelphia: W.B. Saunders Company, 1997; pp 1088–103.
10. Bhattacharya R, Shuhart MC. Hepatitis C and alcohol: interactions, outcomes and implications. *J Clin Gastroenterol* 2003; **36**: 242–52.
11. Dore GJ, Freemen AJ, Law M, Kaldor JM. Is severe liver disease a common outcome for people with chronic hepatitis C? *J Gastroenterol Hepatol* 2002; **17**: 423–30.
12. Douds AC, Cox MA, Iqbal TH, Cooper BT. Ethnic differences in cirrhosis of the liver in a British city: alcoholic cirrhosis in South Asian men. *Alcohol Alcohol* 2003; **38**: 148–50.
13. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999; **229**: 790–9.
14. Feng X. Hepatitis C infection: a review. *Lippincotts Prim Care Pract* 1999; **3**: 345–53.
15. Ramadori G, Meier V. Hepatitis C virus infection: 10 years after the discovery of the virus. *Eur J Gastroenterol Hepatol* 2001; **13**: 465–71.
16. Boyer N, Marcellin P. Pathogenesis, diagnosis and management of hepatitis C. *J Hepatol* 2000; **32**: 98–112.
17. Seeff LB, Hoofnagle JH. Appendix: The National Institutes of Health Consensus Development Conference Management of Hepatitis C 2002. *Clin Liver Dis* 2003; **7**: 261–87.
18. McCaughan GW. Asian perspectives on viral hepatitis: hepatitis C virus infection. *J Gastroenterol Hepatol* 2000; **15** (Suppl): G90–3.

19. Merican I, Guan R, Amarapuka D, et al. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol* 2000; **15**: 1356–61.
20. Pokorski RJ. Long-term morbidity and mortality risk in Japanese insurance applicants with chronic hepatitis C virus infection. *J Insur Med* 2001; **33**: 12–36.
21. Kerr WC, Fillmore KM, Marvy P. Beverage-specific alcohol consumption and cirrhosis mortality in a group of English-speaking beer-drinking countries. *Addiction* 2000; **95**: 339–46.
22. Herd D. Ideology, history and changing models of liver cirrhosis epidemiology. *Br J Addict* 1992; **87**: 1113–26.
23. Regev A, Jeffers LJ. Hepatitis C and alcohol. *Alcohol Clin Exp Res* 1999; **23**: 1543–51.
24. Agrawal S, Bonkovsky HL. Management of nonalcoholic steatohepatitis: an analytic review. *J Clin Gastroenterol* 2002; **35**: 253–61.
25. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathologic severity. *Gastroenterology* 1999; **116**: 1413–9.
26. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994; **107**: 1103–9.
27. Naschitz JE, Slobodin G, Lewis RJ, Zuckerman E, Yesshurun D. Heart diseases affecting the liver and liver diseases affecting the heart. *Am Heart J* 2000; **140**: 111–20.
28. Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. *Ann Thorac Surg* 2000; **69**: 823–8.
29. Hirata N, Sawa Y, Matsuda H. Predictive value of preoperative serum cholinesterase concentration in patients with liver dysfunction undergoing cardiac surgery. *J Card Surg* 1999; **14**: 172–7.
30. Luo JC, Hwang SJ, Chang FY, et al. Simple blood tests can predict compensated liver cirrhosis in patients with chronic hepatitis C. *Hepatogastroenterology* 2002; **49**: 478–81.
31. Reinhartz O, Farrar DJ, Hershon JH, Avery GJ Jr, Haeusslein EA, Hill JD. Importance of preoperative liver function as a predictor of survival in patients supported with Thoratec ventricular assist devices as a bridge to transplantation. *J Thorac Cardiovasc Surg* 1998; **116**: 633–40.
32. Olga OZ, Nikolai DY. Invasive and non-invasive monitoring of hepatitis C virus-induced liver fibrosis: alternatives or compliments? *Curr Pharm Biotechnol* 2003; **4**: 195–209.
33. Oh S, Afdhal NH. Hepatic fibrosis: are any of the serum markers useful? *Curr Gastroenterol Rep* 2001; **3**: 12–8.
34. Gadano A, Hadengue A, Vachiery F, et al. Relationship between hepatic blood flow, liver tests, haemodynamic values and clinical characteristics in patients with chronic liver disease. *J Gastroenterol Hepatol* 1997; **12**: 167–71.
35. Kawasaki S, Sugiyama T, Iga T, et al. Pharmacokinetic study on the hepatic uptake of indocyanine green in cirrhotic patients. *Am J Gastroenterol* 1985; **80**: 801–6.
36. Watanabe Y, Kumon K. Assessment by pulse dye-densitometry indocyanine green (ICG) clearance test of hepatic function of patients before cardiac surgery: its value as a predictor of serious postoperative liver dysfunction. *J Cardiothorac Vasc Anesth* 1999; **13**: 299–303.
37. Okamoto E, Kyo A, Yamanaka N, Tanaka N, Kuwata K. Prediction of the safe limits of hepatectomy by combined volumetric and functional measurements in patients with impaired hepatic function. *Surgery* 1984; **95**: 586–92.
38. Hemming AW, Scudamore CH, Shackleton CR, Pudek M, Erb SR. Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. *Am J Surg* 1992; **163**: 515–8.
39. Sugahara K, Togashi H, Takahashi K, et al. Separate analysis of asialoglycoprotein receptors in the right and left hepatic lobes using Tc-GSA SPECT. *Hepatology* 2003; **38**: 1401–9.
40. Onodera Y, Takahashi K, Togashi T, Sugai Y, Tamaki N, Miyasaka K. Clinical assessment of hepatic functional reserve using ^{99m}Tc DTPA galactosyl human serum albumin SPECT to prognosticate chronic hepatic diseases–validation of the use of SPECT and a new indicator. *Ann Nucl Med* 2003; **17**: 181–8.
41. Boyer TD. Portal hypertension and its complications: bleeding esophageal varices, ascites, and spontaneous bacterial peritonitis. In: Zakim D, Boyer TD eds.; Hepatology: A Textbook of Liver Disease. Philadelphia: W.B. Saunders Company, 1982; pp 464–99.
42. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646–9.
43. Merkel C, Bolognesi M, Finucci GF, et al. Indocyanine green intrinsic hepatic clearance as a prognostic index of survival in patients with cirrhosis. *J Hepatol* 1989; **9**: 16–22.
44. Downing SW, Edmunds LH Jr. Release of vasoactive substances during cardiopulmonary bypass. *Ann Thorac Surg* 1992; **54**: 1236–43.
45. Casey LC. Role of cytokines in the pathogenesis of cardiopulmonary-induced multisystem organ failure. *Ann Thorac Surg* 1993; **56**: S92–6.
46. Okano N, Miyoshi S, Owada R, et al. Impairment of hepatosplanchnic oxygenation and increase of serum hyaluronate during normothermic and mild hypothermic cardiopulmonary bypass. *Anesth Analg* 2002; **95**: 278–86.
47. Sakakibara Y, Imazuru T, Watanabe K, et al. Repeat coronary artery bypass in a patient with liver cirrhosis. *Thorac Cardiovasc Surg* 1998; **46**: 99–100.
48. Guadino M, Santarelli P, Bruno P, Piancone FL, Possati G. Palliative coronary artery surgery in patients with severe noncardiac diseases. *Am J Cardiol* 1997; **80**:

1351–2.
49. Navasa M, Fernandez J, Rodes J. Bacterial infections in liver cirrhosis. *Ital J Gastroenterol Hepatol* 1999; **31**: 616–25.
50. Deschenes M, Villeneuve JP. Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis. *Am J Gastroenterol* 1999; **94**: 2193–7.
51. Navasa M, Rimola A, Rodes J. Bacterial infections in liver disease. *Semin Liver Dis* 1997; **17**: 323–33.
52. Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol* 1993; **18**: 353–8.
53. Wyke RJ. Bacterial infections complicating liver disease. *Baillieres Clin Gastroenterol* 1989; **3**: 187–210.
54. Campillo B, Dupeyron C, Richardet JP, Mangeney N, Leluan G. Epidemiology of severe hospital-acquired infections in patients with liver cirrhosis: effect of long-term administration of norfloxacin. *Clin Infect Dis* 1998; **26**: 1066–70.
55. Ortiz J, Vila MC, Soriano G, et al. Infections caused by Escherichia coli resistant to norfloxacin in hospitalized cirrhotic patients. *Hepatology* 1999; **29**: 1064–9.
56. Westphal JF, Jehl F, Vetter D. Pharmacological, toxicologic, and microbiological considerations in the choice of initial antibiotic therapy for serious infections in patients with cirrhosis of the liver. *Clin Infect Dis* 1994; **18**: 324–35.
57. Campillo B, Dupeyron C, Richardet JP. Epidemiology of hospital-acquired infections in cirrhotic patients: effect of carriage of methicillin-resistant Staphylococcus aureus and influence of previous antibiotic therapy and norfloxacin prophylaxis. *Epidemiol Infect* 2001; **127**: 443–50.
58. Aydin NB, Gercekoglu H, Aksu B, et al. Endotoxemia in coronary artery bypass surgery: a comparison of the off-pump technique and conventional cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2003; **125**: 843–8.
59. Riddington DW, Venkatesh B, Biovin CM, et al. Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass. *JAMA* 1996; **275**: 1007–12.
60. Taggart DP, Sundaram S, McCartney C, et al. Endotoxemia, complement, and white blood cell activation in cardiac surgery: a randomized trial of laxatives and pulsatile perfusion. *Ann Thorac Surg* 1994; **57**: 376–82.
61. Humphries JE. Transfusion therapy in acquired coagulopathies. *Hematol Oncol Clin North Am* 1994; **8**: 1181–1201.
62. Joist JH. Hemostatic abnormalities in liver disease. In: Colman RW, Hirsh J, Marder VJ eds.; Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia: J.B. Lippincott, 1994; p 906.
63. Khuri SF, Wolfe JA, Josa M, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss. *J Thorac Cardiovasc Surg* 1992; **104**: 94–107.
64. Yau TM, Carson S, Weisel RD, et al. The effect of warm heart surgery on postoperative bleeding. *J Thorac Cardiovasc Surg* 1992; **103**: 1155–63.
65. Mazer CD, Hornstein A, Freedman J. Platelet activation in warm and cold heart surgery. *Ann Thorac Surg* 1995; **59**: 1481–6.
66. Raman JS, Kochi K, Morimatsu H, Buxton B, Bellomo R. Severe ischemic early liver injury after cardiac surgery. *Ann Thorac Surg* 2002; **74**: 1601–6.
67. Michalopoulos A, Alivizatos P, Geroulanos S. Hepatic dysfunction following cardiac surgery: determinants and consequences. *Hepatogastroenterology* 1997; **44**: 779–83.
68. Koizumi M, Matsumoto N, Ueda K. Influences of cardiopulmonary bypass and fentanyl anesthesia on hepatic circulation and oxygen metabolism in beagles. *Anesth Analg* 1998; **86**: 1177–82.
69. Nollert G, Sperling J, Sakamoto T, Jaeger BR, Jonas RA. Higher hematocrit improves liver blood flow and metabolism during cardiopulmonary bypass in piglets. *Thorac Cardiovasc Surg* 2001; **49**: 226–30.
70. Gentilini P, LaVilla G, Romanelli RG, Foschi M, Laffi G. Pathogenesis and treatment of ascites in hepatic cirrhosis. *Cardiology* 1994; **84**: 68–79.
71. Martin PY, Schrier RW. Pathogenesis of water and sodium retention in cirrhosis. *Kidney Int Suppl* 1997; **59**: S43–9.
72. Gines P, Fernandez-Esparrach G, Arroyo V, Rodes J. Pathogenesis of ascites in cirrhosis. *Semin Liver Dis* 1997; **17**: 175–89.
73. Morali GA, Floras JS, Legault L, Tobe S, Skorecki KL, Blendis LM. Muscle sympathetic nerve activity and renal responsiveness to atrial natriuretic factor during the development of hepatic ascites. *Am J Med* 1991; **91**: 383–92.
74. Laffi G, Marra F, Pinzani M, et al. Effects of repeated atrial natriuretic peptide bolus injections in cirrhotic patients with refractory ascites. *Liver* 1989; **9**: 315–21.
75. Hayashida N, Chihara S, Kashikie H, et al. Biological activity of endogenous atrial natriuretic peptide during cardiopulmonary bypass. *Artif Organs* 2000; **24**: 833–8.
76. Carstens J, Greisen J, Jensen KT, Vilstrup H, Pedersen EB. Renal effects of a urodilatin infusion in patients with liver cirrhosis, with and without ascites. *J Am Soc Nephrol* 1998; **9**: 1489–98.
77. Teshima H, Hayashida N, Akashi H, Aoyagi S. Surgical treatment of a descending aortic aneurysm in a patient with noncirrhotic portal hypertension and a portal systemic shunt. *Circ J* 2002; **66**: 1176–7.