

Cardiac Operations in Cirrhotic Patients

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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 disappoint-

ing results and the surgical prognosis correlates with the severity of cirrhosis.⁵⁻⁸⁾ Because patients with cirrhosis have distinctive anatomical and physiological disorders⁹⁾ 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.

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Pathogenesis and Epidemiology

Cirrhosis is the end result of hepatocellular necrosis induced by diverse causes, such as hepatitis viruses, alcoholism, autoimmune disease, prolonged cholestasis, meta-

bolic 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 exists²⁷⁾ 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

	n	CPB use	Classification	Morbidity			Mortality		
				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-Turcotte⁴¹⁾ 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 classification⁴²⁾ 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 colleagues⁶⁾ 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 *Escheri-*

chia 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 cephalosporins 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 colleagues⁶⁾ 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 fentanyl anesthesia may be advanta-

geous 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 hyperammonemia.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 results⁵⁻⁷⁾ 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 definitive 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.

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