Chapter 73
Anesthesia and the Hepatobiliary System

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Key Points

• All volatile anesthetics decrease hepatic blood flow, but desflurane and sevoflurane have the least significant effect on total hepatic blood flow and hepatic oxygen delivery, whereas halothane induces the most profound reductions in hepatic blood flow.

• Advanced liver disease may impair the elimination, prolong the half-life, and potentiate the clinical effects of several drugs, including morphine, meperidine, alfentanil, vecuronium, rocuronium, mivacurium, benzodiazepines, and dexamethasone. These drugs should be used cautiously in patients with cirrhosis or end-stage liver disease from any cause, and their dosage and administration should be adjusted accordingly.

• Abnormal liver enzyme test results may be seen in up to 4% of normal individuals and up to 36% of psychiatric patients, although the prevalence of clinically significant hepatic dysfunction in these individuals is less than 1%, thus suggesting that further costly preoperative testing is unnecessary in asymptomatic patients.

• Patients with asymptomatic elevations in serum transaminase levels (less than two times normal values) may undergo surgery with minimal impact on perioperative outcome.

• Retrospective data suggest that patients with acute hepatitis from any cause are at increased risk for hepatic failure and death after elective surgery. Thus, elective surgery should be delayed in these individuals until resolution of acute hepatocellular dysfunction can be confirmed.

• Asymptomatic patients with any form of chronic hepatitis should be carefully assessed before elective surgery, and meticulous care should be taken to maintain hepatic perfusion in the perioperative period and to avoid any hepatotoxic drugs or significant hypotension that could precipitate liver failure or hepatic encephalopathy.

• Based on large retrospective studies, patients with cirrhosis who are undergoing abdominal surgery, especially those in Child-Turcotte-Pugh (CTP) class C, appear to have an increased risk of perioperative death. Elective surgery in these individuals should be avoided, if possible, in favor of less invasive procedures.

• Postoperative jaundice may occur as a result of intraoperative hepatobiliary injury, anesthetic-induced hepatotoxicity, severe hepatic hypoperfusion (e.g., cardiogenic or hypovolemic shock), and a variety of medications.

• Patients with the most advanced forms of liver disease (e.g., CTP class B or C cirrhosis) should receive management designed to maximize hepatic perfusion and hepatic oxygen delivery and to prevent and treat the complications of hepatic encephalopathy, cerebral edema, coagulopathy, hemorrhage, and portal hypertension.

The liver is the largest organ in the body, and it plays a critical role in the homeostasis of many physiologic systems, including nutrient and drug metabolism, synthesis of plasma proteins and critical hemostatic factors, and detoxification and elimination of many endogenous and exogenous substances.1 Acute or chronic liver dysfunction can impair the response to anesthesia and surgery in several critical ways, whereas certain anesthetics and hemodynamic disturbances can induce unique and serious alterations in postoperative hepatic function.

This chapter reviews the anesthetic implications of acute and chronic liver disease, the impact of anesthetics
on hepatic function, evaluation of perioperative changes in liver function test results and hepatobiliary function, and periprocedural considerations for some selected surgical procedures involving the liver and gallbladder.

**EFFECT OF ANESTHETICS ON HEPATIC FUNCTION**

This section focuses on the impact of volatile and intravenous anesthetics on liver blood flow and hepatic function. Halothane hepatitis and related volatile anesthetic–induced hepatotoxicity are discussed in Chapter 26.

**VOLATILE ANESTHETICS**

Volatile anesthetics variably influence blood flow to the liver, whereas intravenous anesthetics and opioids probably have a less significant impact. However, many potential confounding variables can influence hepatic blood flow and liver function, including the animal species studied, the subject’s age, intravascular volume status, the type of mechanical ventilation used, body position at the time of physiologic measurements, simultaneous surgical procedures, changes in arterial blood pressure, concomitant use of vasoressors and local anesthetics, and alterations in hemoglobin and arterial oxygen concentrations. Yet reasonably firm conclusions can be reached regarding the impact and probable clinical significance of anesthetic drugs on hepatic function in normal and cirrhotic patients.

The impact of volatile anesthetics on hepatic blood flow (including hepatic arterial and portal venous blood flow), oxygen delivery, and hepatic oxygen supply-to-demand ratios has been determined for all the major volatile anesthetics, primarily in rat and pig experimental models. Human studies also support the findings of these early experimental investigations.2,3 Many measurement techniques have been used to assess hepatic and portal venous blood flow, although plasma clearance of indo-cyanine green is most commonly used to assess hepatic blood flow. Transesophageal echocardiography can also evaluate hepatic vein flow, but it is only an indirect measurement of hepatic perfusion and oxygenation (see also Chapter 46). A novel technique involving pulsed Doppler probes implanted in animals and in humans undergoing cholecystectomy has allowed accurate measurement of hepatic arterial and portal vein blood flow.4 Most anesthetics decrease portal blood flow (PBF) because of decreased cardiac output; however, hepatic arterial blood flow (HABF) may increase, although often not sufficiently to restore total hepatic blood flow (THBF) to normal values.5 THBF is equal to the sum of PBF and HABF. Mean arterial blood pressure (MAP) and cardiac output decrease with all volatile anesthetics, but a more pronounced reduction in PBF, HABF, and THBF occurs with halothane and enfurane than with isoflurane and sevoflurane (Fig. 73-1).2,4,6-10 These changes generally apply across a range of minimum alveolar concentrations (MACs). Volatile anesthetics also alter portal venous and hepatic arterial vascular resistance to variable degrees; these changes, in conjunction with decreases in cardiac output, MAP, and mesenteric sympathetic tone, modify the hepatic vascular supply.11

Although all volatile anesthetics decrease MAP and PBF, halothane has a more consistently dramatic impact on HABF. Halothane causes vasoconstriction in the hepatic arterial vascular bed, as reflected by an increase in hepatic arterial resistance.4,12 In vivo videomicroscopy after halothane exposure in rats demonstrated reduced sinusoidal blood flow as a result of decreased sinusoidal diameter, thus providing direct evidence of vasoconstriction at the microvascular level.12 In contrast, isoflurane increased flow velocity in hepatic sinusoids and in this way preserved microvascular blood flow more than halothane or enfurane.12 Benumof and colleagues demonstrated markedly reduced HABF after halothane administration in two patients during hepatic arteriography; hepatic blood flow returned to normal 20 minutes after discontinuation of halothane anesthesia.13

Halothane also reduces hepatic oxygen delivery and hepatic venous oxygen saturation (Fig. 73-2).14 These changes are related to decreased MAP and more dramatic reductions in cardiac output with halothane than with any other volatile anesthetics.5 Gelman and associates demonstrated that during surgical stress in pigs, fentanyl or isoflurane anesthesia, which decreases MAP by less than 30%, provided adequate oxygen supply, whereas halothane anesthesia, which decreases arterial blood pressure more than 30%, provided inadequate hepatic oxygen supply.9 This finding also applies to episodes of hepatic ischemia, in which fentanyl or isoflurane provided better protection than halothane or enfurane. In addition to vascular changes, hepatic function, as measured by serum transaminase levels, also suggests an unfavorable impact of halothane versus isoflurane.3

Volatile anesthetic–induced alterations in hepatic blood flow are, in part, mediated by an autoregulatory...
mechanism that maintains constant THBF. This physiologic adaptation is termed the hepatic arterial buffer response (HABR), which matches reductions in PBF with increases in HABF to maintain total blood flow to the liver constant in the presence of profound hypovolemia, indirect effects of major abdominal surgery, or severe hemorrhage. Halothane disrupts this compensatory response, whereas sevoflurane and isoflurane maintain HABR. Sevoflurane further suppresses hepatic arterial vasoconstriction and thus maintains HABF more effectively than does halothane. Sevoflurane is also consistently equivalent or superior to isoflurane in maintaining HABF, hepatic oxygen delivery, and oxygen delivery-to-consumption ratios. In addition, laboratory studies demonstrated insignificant changes in conventional liver function test results after exposure to isoflurane or desflurane, with the most favorable profiles with desflurane and sevoflurane as compared with other volatile anesthetics.

The encouraging results obtained with sevoflurane versus older volatile anesthetics are further supported by the observation that compound A produced by prolonged, low-flow sevoflurane anesthesia does not adversely affect hepatic function in adult surgical patients as determined by liver function testing or measurement of arterial ketone body ratios, a putative measure of hepatocyte function. In a large clinical study of sevoflurane, Bito and co-workers noted mild postoperative increases in bilirubin and transaminase values in 100 surgical patients receiving low- and high-flow sevoflurane or isoflurane anesthesia, but no evidence of clinical hepatotoxicity. Routine liver function test results are often mildly increased after surgery and anesthesia with volatile anesthetics, although the specific contribution of the anesthetic itself is debatable.

Administration of either sevoflurane or desflurane to human volunteers not undergoing surgery produced no significant abnormalities in liver function test results, thus suggesting that other perioperative surgical factors may induce mild, transient alterations in plasma transaminase levels. In fact, early human investigations found steep decreases in estimated hepatic blood flow immediately after the induction of anesthesia correlated with the decreases in arterial blood pressure. 

Hepatic blood flow rapidly returned to normal soon after the start of surgery, a finding suggesting global reductions in cardiac output and blood pressure as mechanisms responsible for the reduced hepatic blood flow, rather than a sustained adverse influence of specific volatile or intravenous anesthetics on hepatic blood flow. In experimental and human ischemia-reperfusion injury studies, sevoflurane had favorable effects on hepatic function through an ischemic-preconditioning effect. These data are consistent with the favorable cardiac ischemic-preconditioning effect of sevoflurane.

Desflurane had effects similar to those of isoflurane on hepatic blood flow and function when assessed in animal and human investigations. In chronically instrumented dogs, Merin and associates demonstrated slight but significant decreases in THBF at 1.75 MAC as a result of decreased PBF, but no significant differences between desflurane and isoflurane in any measure of hepatic blood flow over a range of MAC values. Armbruster and co-workers observed decreased THBF at 1 MAC desflurane in pigs, but only at levels of hypotension unlikely to be encountered clinically and without alterations in liver function test results. Other canine data suggested better preservation of THBF with desflurane than with halothane or isoflurane (Fig. 73-3). Subsequent studies in human volunteers examining hepatic function rather than hepatic blood flow failed to demonstrate any hepatotoxic effects of desflurane.

In contrast to healthy volunteers and surgical patients, substantially less information is available describing the impact of anesthetics on hepatic function in patients with advanced liver disease. Desflurane and isoflurane may not change perioperative liver function test results in adult surgical patients with chronic liver disease. Experimental models of hepatic injury showed lesser increases in hepatic enzymes and no evidence of microscopic hepatocyte injury with sevoflurane compared with halothane-treated rats. Isoflurane was more efficient at preserving hepatic blood flow in cirrhotic animals than is ketamine or halothane, although other studies showed no difference in hepatic function in cirrhotic rats exposed to fentanyl, halothane, enflurane, or isoflurane. However, halothane decreases both hepatic blood flow and hepatic function and should not be given to patients with advanced liver disease. Given the current availability of other volatile anesthetics and the overall marked decreased use of halothane, this issue is primarily of historical interest. Moreover, as a consequence of the hepatotoxic potential of halothane, halothane should not be used in healthy adults or in any patient with significant hepatic dysfunction.

In this regard, other anesthetics devoid of hepatotoxicity are available. Xenon, an inert gas first described as...
having anesthetic properties in 1951, has been considered to be an ideal inhaled anesthetic because it is nonexplosive and nonflammable, exhibits low toxicity, has no known teratogenic effects, and has rapid induction and recovery profiles resulting from its extremely low blood-gas coefficient of 0.115, the lowest of all known anesthetics. Its hemodynamic profile is similar to that of propofol anesthesia in humans, and it caused less hypotension and had no effect on left ventricular function when compared with isoflurane in human studies. Although animal investigations suggested a substantial increase in cerebral perfusion with xenon when compared with intravenous anesthetics, xenon has no effect on other regional organ perfusion, including liver perfusion. It does not alter HABF, and given the absent effect on cardiac output, it should, in theory, have no impact on THBF (unlike all other volatile anesthetics). It also does not alter liver function tests. In an experimental model, Reinelt and colleagues noted higher hepatic venous oxygen content levels in pigs exposed to 73% to 78% xenon versus intravenous anesthesia with pentobarbital and buprenorphine. These observations were believed to be secondary to a possible reduction of plasma catecholamine levels and subsequent reduced hepatic metabolism and increased hepatic venous oxygen content. Xenon may therefore prove to be an ideal anesthetic with regard to hepatic perfusion. Larger clinical trials in patients with both normal and abnormal hepatic function are necessary before definitive conclusions can be reached relative to its safety in patients with acute and chronic liver disease.

In summary, the influence of volatile anesthetics on hepatic blood flow and function is complex and is related not only to features unique to the anesthetic itself but also to other patient-related variables such as the severity of underlying liver dysfunction, the presence of advanced age, and the impact of surgical stress and intraabdominal surgical manipulation. However, sevoflurane, desflurane, and isoflurane have been consistently shown to preserve hepatic blood flow and function better than halothane or enflurane.

**INTRAVENTOUS ANESTHETICS**

When compared with volatile anesthetics, less information is available regarding the impact of intravenous anesthetics on hepatic function (see also Chapters 31 to 33). Early investigations suggested that etomidate and thiopental decreased hepatic blood flow, either from increased hepatic arterial vascular resistance or from reduced cardiac output and blood pressure, whereas ketamine has little impact on hepatic blood flow, even in large doses. With the use of sensitive radiolabeled microsphere determinations of organ blood flow in animals, propofol was found to increase THBF in both the hepatic arterial and portal venous circulations, thus suggesting a significant splanchnic vasodilator effect of this drug. THBF was maintained in some animal models even with significant reductions in MAP, whereas other animal models showed decreased mean hepatic blood flow despite increased MAP, a finding attributed to species-specific effects of propofol. Limited human data suggest a more favorable splanchnic and hepatic oxygen delivery balance with propofol than with halothane. Meierhenrich and colleagues demonstrated increased hepatic blood flow with propofol in humans by using transesophageal echocardiographic Doppler-derived measurements of hepatic blood flow, a technique considered more accurate than hepatic clearance of indicator dyes. Studies using indicator dyes in humans and animals suggested decreased hepatic blood flow with propofol, whereas other animal investigations using techniques not involving dye showed improved hepatic blood flow under propofol anesthesia. Overall, an antioxidant effect may occur with propofol in patients undergoing liver surgery and orthotopic liver transplantation (see also Chapter 74), although the ultimate effect of this drug on ischemia-reperfusion injury may be modest, at best, in these patient populations. In summary, based on limited clinical and experimental data, it appears that intravenous anesthetics have only a modest impact on hepatic blood flow and no meaningful adverse influence on postoperative liver function when blood pressure and cardiac output are adequately maintained.

**CENTRAL NEURAXIAL ANESTHESIA**

The effect of spinal or epidural anesthesia on liver blood flow and hepatic function is not clearly an anesthetic drug–induced alteration in hepatic function (see Chapter 56). Kennedy and colleagues showed that hepatic blood flow decreased during high spinal and epidural anesthesia and appeared to mirror simultaneous reductions in MAP. Other animal data suggested reduced PBF and unchanged HABF with high epidural blockade, thus causing a decrease in THBF. This finding was confirmed in humans undergoing thoracic epidural anesthesia in which echocardiography confirmed reductions in hepatic venous blood flow.
may be reversed and hepatic blood flow maintained with the administration of vasopressors (e.g., dopamine or ephedrine) to restore PBF or fluid administration to maintain normal arterial blood pressure, although vasopressors may actually further reduce hepatic blood flow. Presumably, hypotension-induced reductions in hepatic blood flow are secondary to decreased splanchnic blood flow and thus reduced PBF. The impact of absorbed local anesthetic, with or without epinephrine, on cardiac output or splanchnic vascular resistance is unknown.

**EFFECT OF HEPATIC DYSFUNCTION AND HEPATOBILIARY DISEASE ON ANESTHETIC DRUG PHARMACOKINETICS**

Liver disease may have a significant impact on drug metabolism and pharmacokinetics as a result of alterations in protein binding, reduced levels of serum albumin and other drug-binding proteins, altered volume of distribution because of ascites and increased total-body water compartments, and reduced metabolism secondary to abnormal hepatocyte function (see Chapters 24 and 74). In addition, sedatives and opioids may have exaggerated effects in patients with advanced liver disease and may either induce or worsen hepatic encephalopathy. The impact of long-term alcohol ingestion on hepatic enzyme induction may also influence the ultimate effect of drugs in patients with cirrhosis.

The impact of liver disease on drug disposition depends not only on the elimination pathways for a given drug but also on the severity of the underlying hepatic dysfunction. The efficiency of drug removal by the liver is determined by several factors, including hepatic blood flow, hepatic enzyme activity and efficiency, the extent of plasma protein binding, cholestasis-induced alterations in the enterohepatic circulation and metabolism of enteral drugs, and the presence of portosystemic shunts that exclude certain drugs from elimination by the diseased liver. In addition, the influence of liver disease on drug elimination differs for enteral and parenteral drugs. In general, severe liver disease predictably alters the metabolism of drugs with large extraction ratios, such as lidocaine and meperidine, in which clearance primarily depends on hepatic blood flow or portosystemic shunting. Conversely, the metabolism of low-extraction drugs, such as the benzodiazepines, is influenced mainly by protein binding, in which unbound drug is available for elimination, and by intrinsic hepatic clearance and metabolism, which are reduced in accordance with the severity of hepatocellular dysfunction. However, an increased free fraction of a drug because of reduced levels of plasma proteins may counter the impact of reduced hepatic metabolism and lead to modest changes in the ultimate effect of the drug. Finally, greater free fractions of available drug as a result of reduced protein binding may lead to greater drug deposition in tissues (and a potentially increased volume of distribution), which in conjunction with reduced hepatic metabolism may increase drug half-life. It is thus evident that drug pharmacokinetics in the presence of advanced liver disease is complex. The impact on different classes of drugs is discussed separately.

**OPIOIDS**

The significantly reduced metabolism of morphine in patients with advanced cirrhosis leads to a prolonged elimination half-life, markedly increased bioavailability of orally administered morphine, decreased plasma protein binding, and potentially exaggerated sedative and respiratory-depressant effects (see also Chapter 31). Although extrahepatic metabolism may contribute to morphine clearance in patients with cirrhosis, the administration interval should be increased 1.5- to 2-fold in these patients and the oral dose of the drug reduced because of increased bioavailability. Similar changes occur with meperidine, in which a 50% reduction in clearance and a doubling of the half-life have been observed. In addition, clearance of normeperidine is reduced, and patients with severe liver disease may experience neurotoxicity from accumulation of normeperidine.

In contrast to these drugs, fentanyl is a highly lipid-soluble synthetic opioid that has a short duration of action after a single intravenous bolus dose because of rapid redistribution into storage sites. With repeated administration or continuous infusions, accumulation may occur and lead to prolonged effects. Because fentanyl is almost completely metabolized in the liver, its elimination should be predictably prolonged in patients with advanced liver disease. However, fentanyl elimination is not appreciably altered in patients with cirrhosis. Whether the limited extent of liver disease in the study patients affected the pharmacokinetic data or whether continuous infusions or repeated doses in cirrhotic patients produce more exaggerated and pronounced effects is unknown.

Sufentanil, a more potent but similar synthetic lipophilic opioid, is also extensively metabolized by the liver and is highly protein bound. Single-dose pharmacokinetics is not significantly altered in patients with cirrhosis, although the impact of continuous infusions and reduced protein binding is as ill-defined for sufentanil as for fentanyl. Alfentanil, a short-acting opioid less potent than fentanyl, is also exclusively metabolized by the liver and is highly protein bound. However, unlike with fentanyl or sufentanil, the half-life of alfentanil is almost doubled in patients with cirrhosis, and higher free fractions of the drug are observed; these higher free fractions can potentially lead to a prolonged duration of action and enhanced effects. Remifentanil is a synthetic opioid with an ester linkage that allows for rapid hydrolysis by blood and tissue esterases; such hydrolysis leads to high clearance, rapid elimination, and recovery that is almost independent of the dose or duration of infusions. Predictably, the clearance and elimination of remifentanil are indeed unaltered in patients with severe liver disease or in those undergoing liver transplantation.

**SEDATIVE-HYPNOTIC DRUGS**

Thiopental has a small hepatic extraction ratio, and therefore its metabolism and clearance should be adversely affected in patients with liver disease (see also Chapter 32). However, the elimination half-life of thiopental is unchanged in cirrhotic patients, possibly
NEUROMUSCULAR BLOCKING DRUGS

In contrast to opioids and intravenous anesthetics, more comprehensive information is available regarding the impact of cirrhosis on the pharmacokinetics and pharmacodynamics of neuromuscular blocking drugs (see also Chapter 34). Vecuronium is a steroidal muscle relaxant that undergoes hepatic elimination. This drug has decreased clearance, a prolonged elimination half-life, and prolonged neuromuscular blockade in patients with cirrhosis (Fig. 73-3). The impact of alcoholic liver disease is less definite, with clearance and elimination half-lives typically unchanged. Rocuronium also undergoes hepatic metabolism and elimination. Hepatic dysfunction can increase the volume of distribution of rocuronium, thus prolonging its elimination half-life, as well as producing a longer clinical recovery profile and return of normal twitch tension. Gao and associates observed a 24% decrease in rocuronium infusion requirement in 17 patients during the anhepatic phase of liver transplantation. Although the initial clinical recovery of neuromuscular function is not affected by liver disease, larger initial doses or repeated administration will typically prolong the effect of rocuronium in the presence of significant hepatic dysfunction.

The increased volume of distribution for some drugs observed in cirrhotic patients can also prolong the elimination half-life of pancuronium. Muscle relaxants that undergo organ-independent elimination, such as atracurium (nonspecific ester hydrolysis) and cisatracurium (Hofmann elimination), have elimination half-lives and clinical durations of action similar to those observed in normal patients and in patients with end-stage liver disease. The unique elimination of mivacurium by plasma cholinesterase is, however, altered by cirrhosis. Mivacurium is associated with significantly longer recovery of twitch tension and has a longer elimination half-life (18 versus 34 minutes in normal versus cirrhotic patients, respectively) and a longer residence time in patients with hepatic failure than in normal patients, a finding closely correlated to reduced plasma cholinesterase activity in cirrhotic patients. This reduced activity is related to reduced clearance by plasma cholinesterase of the two active isomers of mivacurium, cis-trans and trans-trans. Infusion rates of mivacurium should be adjusted accordingly in patients with advanced liver disease. The impact of liver disease on mivacurium’s pharmacokinetics is likely of historical interest, as the drug is no longer available in the United States. The changes observed with mivacurium are predictably expected with succinylcholine if decreased plasma cholinesterase levels are present because of advanced liver disease. Lowered cholinesterase levels have been observed in these individuals, and they may prolong the effect of succinylcholine.

Sugammadex “reverses” neuromuscular blockade from steroidal neuromuscular blocking drugs (vecuronium and rocuronium) by a mechanism completely different from that of neostigmine. Sugammadex encapsulates rocuronium, so it cannot cause neuromuscular blockade. The sugammadex-rocuronium complex is then transported through perfusion mainly to the kidney for excretion. Sugammadex is excreted unchanged in the urine.

In summary, cirrhosis and other forms of advanced liver disease predictably reduce the elimination of vecuronium, rocuronium, and mivacurium and prolong the duration...
HEPATOBILIARY COMPLICATIONS

RISK FACTORS FOR POSTOPERATIVE HEPATOBILIARY COMPLICATIONS

The anesthesia literature is replete with detailed descriptions of preoperative assessment of cardiac and renal risk for noncardiac surgery. Because preoperative risk factors for the development of postoperative hepatic dysfunction or failure after nonhepatic surgery have not been clearly elucidated, anesthesiologists have based decisions regarding the care of patients with preoperative hepatic dysfunction on data derived in the 1960s and 1970s. Unfortunately, prospective studies addressing these issues in the current era of newer anesthetic and surgical techniques are lacking. Assessment of risk factors for postoperative hepatic insufficiency requires consideration of the following: (1) asymptomatic elevations in preoperative liver enzyme test results; (2) acute hepatitis (viral, drug, toxin), steatosis, chronic hepatitis, and cirrhosis; and (3) the types of surgical procedures that potentially predispose to postoperative liver dysfunction.

ASYMPTOMATIC PREOPERATIVE LIVER ENZYME TEST ABNORMALITIES

Unnecessary laboratory test screening may reveal abnormally elevated liver enzyme test results in otherwise healthy patients. Abnormalities in standard liver enzyme tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, occur in 0.1% to 4% of the general population, as well as in as many as 36% of psychiatric patients, in whom alcohol and illicit drug abuse is prominent. However, the overall prevalence of clinically significant hepatic dysfunction in asymptomatic patients is less than 1%. A retrospective analysis of 91 noncirrhotic patients with serum liver enzyme levels greater than 1.5 times normal who were undergoing surgery reported no development of hepatic failure or postoperative complications related to hepatic dysfunction. Of these patients, 34 had hepatology consultations resulting in additional laboratory and ultrasonographic testing that failed to influence either the management or outcome of their cases. Thus, pursuing more extensive evaluation with costly tests such as ultrasonography, radionuclide imaging, or liver biopsy is rarely indicated.

In general, the most appropriate initial approach to a surgical patient with abnormal liver enzyme test results consists of a detailed history and physical examination. Symptoms of fatigue, anorexia, nausea, vomiting, biliary colic, pruritus, fever, or dark-colored urine warrant further evaluation because these findings may suggest clinically active hepatobiliary disease and thus potentially preclude elective surgery. If, however, the patient is asymptomatic, the significance of abnormal enzyme test results can be questioned. The patient should be further asked about a history of associated diseases such as chronic hepatitis, a family history of Wilson disease, hemochromatosis, α1-antitrypsin deficiency, diabetes mellitus, hyperthyroidism or hypothyroidism, and previous transfusion history. All medications, including vitamins and herbal or other homeopathic remedies, should be reviewed for potential hepatotoxic side effects. The patient should be further questioned regarding alcohol or other illicit drug use, the presence of tattoos, sexual promiscuity, and consumption of raw seafood because they are potential risk factors for infectious hepatitis.

Physical examination may reveal findings consistent with active liver disease, such as icterus, palmar erythema, spider angiomata, gynecomastia, hepatosplenomegaly, ascites, or peripheral edema. Although these findings invariably suggest a diagnosis of cirrhosis, it is reasonable to repeat the test if a complete history and physical examination fail to suggest a cause of the biochemical abnormality. Minor increases in liver enzyme test results are defined as less than twice the normal value, and, given a negative history and physical examination, they do not warrant additional testing before anesthesia and surgery. Assessment of larger increases in liver enzyme test results requires an analysis of the specific abnormality.

AST and ALT are sensitive indicators of hepatocyte integrity. AST is present in hepatocyte cytoplasm and mitochondria, but it is also ubiquitous in cardiac and skeletal muscle; in kidney, brain, pancreas, and lung tissue; and in red and white blood cells. AST is therefore a less specific index of cellular injury than is ALT, which is...
primarily found in the cytoplasm of hepatocytes. Both enzymes are released when the hepatic cell membrane is injured, although a correlation appears to exist between the degree of injury and serum aminotransferase levels. The AST/ALT ratio may also be helpful in distinguishing between alcohol-induced hepatitis and viral hepatitis. Alcohol tends to damage hepatocyte mitochondria preferentially, thereby causing an elevation in AST usually greater than twice the ALT. In addition, ALT activity is diminished in patients with alcohol-induced liver disease because these individuals tend to have deficiencies of pyridoxal 5-phosphate, a vitamin necessary for ALT function. In contrast, a decrease in the AST/ALT ratio is more consistent with a diagnosis of viral hepatitis. Aminotransferases also increase in choledocholithiasis, cholangitis, and ischemic hepatitis. Ischemic hepatitis may not uncommonly produce levels greater than 10,000 International Units/L.

Similar to AST, alkaline phosphatase is present in many tissues, including bone, intestine, kidney, and placenta, as well as in leukocytes. The enzyme catalyzes the hydrolysis of orthophosphate from ester substrates at an alkaline pH. In hepatocytes, alkaline phosphatase is synthesized by biliary epithelial cells and is released in relation to the degree of bile duct obstruction. Measuring serum \( \gamma \)-glutamyltransferase (GGT), an enzyme found predominantly in hepatocytes and biliary epithelial cells, may aid in distinguishing between hepatic and bone causes of increased alkaline phosphatase. Although GGT is a very sensitive indicator of the presence or absence of hepatobiliary disease, by itself it lacks specificity because it is also increased in patients with myocardial infarction, renal disease, diabetes mellitus, and chronic obstructive pulmonary disease. If both alkaline phosphatase and GGT levels are elevated, the abnormality probably reflects hepatobiliary disease. Increased levels of alkaline phosphatase and GGT usually occur in extrahepatic bile duct obstruction and intrahepatic cholestasis from infiltrative diseases such as sarcoidosis, from mass lesions such as primary or metastatic carcinoma, or from drug-induced cholestasis.

Although liver enzyme elevation is an indication of active disease, synthetic hepatic function is best measured by serum bilirubin, albumin, and the prothrombin time. The bilirubin concentration in plasma varies in accordance with its production and inversely with hepatic clearance. Hepatic microsomal enzymes convert unconjugated bilirubin to the more water-soluble form, thereby permitting excretion in bile and preventing central nervous system toxicity. Total bilirubin levels represent both conjugated (direct bilirubin) and unconjugated (indirect bilirubin) forms. Unconjugated hyperbilirubinemia suggests hemolysis or an inherited disorder of bilirubin metabolism such as Gilbert syndrome. If more than 50% of the total serum bilirubin is conjugated, cholestasis or hepatocellular dysfunction is implied. Albumin is synthesized solely in the liver and, in healthy adults, has a half-life of approximately 21 days. The normal level of 3.5 g/dL usually decreases in long-standing and severe liver disease but is also influenced by overall nutritional status.

Finally, hepatobiliary dysfunction can cause an abnormal prothrombin time by impairing synthesis of the essential clotting factors II (prothrombin), VII, IX, and X. Hepatic synthesis of these factors depends on vitamin K, a fat-soluble vitamin found in certain foods and produced by intestinal bacteria, so abnormalities in prothrombin activity (as expressed by the international normalized ratio [INR]) may also occur in patients with malnutrition or malabsorption syndromes. The plasma half-time of these vitamin K–dependent factors is very short (<24 hours), and hence the INR responds rapidly to changes in synthetic function. This rapid response makes this test a more sensitive index of hepatic function than serum albumin.

Although no prospective, randomized, controlled studies have been designed to assess the perioperative risk of anesthesia or surgery in asymptomatic patients with elevated liver enzyme test results, a suggested approach to these patients is outlined in Figure 73-5.

**ACUTE HEPATITIS**

The diverse roles of the liver in drug metabolism, hemostasis, and coagulation function, in association with surgery and anesthesia-related alterations in hepatic perfusion, make it an organ extremely susceptible to clinically important hepatocellular injury induced by viruses or by alcohol or other drugs. Consensus opinion, based largely on data derived from older, predominantly retrospective studies, is that acute hepatitis, whether viral, alcohol induced, or drug induced, is a risk for the development of hepatic failure or death after elective surgery. In 1982, Powell-Jackson and co-workers described 36 patients who underwent exploratory laparotomy for either suspected extrahepatic biliary tract obstruction or intraabdominal malignancy, all of whom were ultimately found to have viral or alcoholic hepatitis, cirrhosis, or Budd-Chiari syndrome. Of these patients, 61% suffered significant morbidity, including postoperative liver failure, and 31% died within 1 month of surgery. One hundred percent of patients with histologically proven hepatitis died. Greenwood and associates also reported high mortality rates in patients with alcoholic hepatitis who were undergoing open liver biopsy. Bell and colleagues, however, noted that survival rates were not influenced by the presence of biopsy-proven hepatitis in 164 patients with alcoholic cirrhosis who required emergency portocaval shunts for esophageal variceal bleeding.

In the current era of advanced diagnostic testing and imaging in which nonoperative management of extrahepatic biliary tract obstruction can be performed with endoscopic retrograde cholangiopancreatography (ERCP), invasive procedures such as open liver biopsy or exploratory laparotomy can be avoided. The preponderance of earlier information on perioperative morbidity and mortality indicates that elective surgery should be delayed in patients with acute hepatitis of any origin until resolution of hepatocellular dysfunction can be confirmed. The influence of the type of surgery on patients with hepatitis is described later.

**STEATOSIS AND STEATOHEPATITIS**

Patients with chronic, asymptomatic increases in serum aminotransferase levels are often found by liver biopsy to
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Asymptomatic Patient with Abnormal Liver Test Results

![Diagram of liver test results](image)

**Figure 73-5. Approach to asymptomatic patients with abnormal liver test results who are presenting for surgery.** 
*ALT*, Alanine aminotransferase; *AST*, aspartate aminotransferase; *ETOH*, ethanol; *GGT*, γ-glutamyltransferase; *HX*, history; *INR*, international normalized ratio; *NL*, normal; *R/O*, rule out.

have steatosis (fatty liver) or steatohepatitis.¹²¹ Hultcrantz and co-workers studied 149 asymptomatic patients with at least a 6-month history of elevated aminotransferase levels that were found incidentally during routine laboratory screening.¹²² Liver biopsy confirmed the diagnosis of steatosis in 64% of these patients, most of whom were obese or diabetic or had a history of excessive alcohol use. In a subsequent study, Hay and colleagues demonstrated a 21% incidence of steatohepatitis in a similar patient population.¹²³ Both studies concluded that chronic hepatitis or cirrhosis cannot be differentiated from steatosis or steatohepatitis based solely on clinical laboratory or noninvasive radiologic or ultrasonographic criteria. In a retrospective analysis of 135 patients who underwent hepatic resection, Behms noted an increased incidence of postoperative liver failure and mortality when histopathologic examination revealed hepatocytes with greater than 30% fatty infiltration.¹²³ Brolin and associates noted a 6% incidence of biopsy-proven nonalcoholic steatohepatitis and subclinical cirrhosis in patients undergoing gastric bypass surgery; postoperative mortality was higher in affected patients than in those with normal hepatic histologic features.¹²⁴ Despite recommendations to the contrary,¹²⁵ steatosis and steatohepatitis should probably be considered significant risk factors for postoperative complications, especially after abdominal procedures. For this reason, patients with asymptomatic, chronic (>6 months) elevations in hepatic enzyme levels should be thoroughly evaluated before elective surgery.

**CHRONIC HEPATITIS**

The extent of anesthetic or surgical risk imposed by chronic forms of hepatitis primarily relates to the severity of associated hepatic synthetic dysfunction. Runyon retrospectively studied 20 asymptomatic patients who had chronic hepatitis B or C and were undergoing general or spinal anesthesia for a total of 34 surgical procedures, most of which were at operative sites distant from the liver.¹²⁶ Liver enzyme test results did not worsen postoperatively, nor did any patient experience postoperative liver failure or death. Higashi and colleagues assessed the postoperative outcomes of 119 patients with chronic hepatitis who were undergoing liver resection for primary hepatocellular
carcinoma (HCC). Patients with the most impaired liver enzyme test results had a higher incidence of hepatic failure, recurrent HCC, and death. Abnormal liver enzyme test results in an otherwise healthy patient reflect either a subclinical acute process such as viral or toxin-mediated hepatitis or a chronic disorder such as chronic hepatitis.

Asymptomatic patients with any form of chronic hepatitis should be screened before elective surgery for evidence of hepatic dysfunction, with the INR being the most sensitive indicator of the severity of hepatocellular dysfunction. When surgery cannot be avoided, hepatic perfusion should be maintained, and factors that could precipitate liver failure, hepatic encephalopathy, or both, should be avoided (see later).

## CIRRHOSIS AS A PERIOPERATIVE RISK FACTOR

Cirrhosis is a syndrome of end-stage liver disease pathologically characterized by severe fibrosis and nodular regeneration of the liver parenchyma (see also Chapter 74). Alcohol abuse remains the most common cause of cirrhosis. Other causes include chronic hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson disease, and idiopathic cirrhosis. The Child-Turcotte-Pugh (CTP) and the Model for End-Stage Liver Disease (MELD) scoring systems are the most frequently used tools to predict perioperative risk in cirrhotic patients undergoing abdominal surgery, exclusive of portosystemic shunt procedures (Table 73-1). The CTP scoring system assigns points based on levels of serum albumin and bilirubin, the INR, the degree of ascites, and the presence and grade of encephalopathy and stratifies risk in order of severity as class A, B, or C. Several studies have used this system to predict perioperative outcome in cirrhotic patients undergoing a variety of surgical procedures. Originally used to predict mortality following transjugular intrahepatic portosystemic shunt (TIPS) procedures, the MELD (see later) scoring system uses serum bilirubin, creatinine, and INR in a calculation that predicts survival in patients with end-stage liver disease: $MELD = 3.78 \times (\text{serum bilirubin} \text{mg/dL}) + 11.2 \times (\text{INR}) + 9.57 \times (\text{serum creatinine} \text{mg/dL}) + 6.43$. A score of 40 or more is equated with a predicted mortality rate higher than 70%, whereas a score lower than 9 predicts less than a 2% mortality rate.

Garrison and co-workers retrospectively evaluated outcomes in 100 patients with histologically proven cirrhosis who were undergoing surgery predominantly for biliary tract procedures (cholecystectomy, choledochotomy), as well as for gastroduodenal repair, colon and small bowel resection, and open liver biopsy. An overall operative mortality rate of 30% and an additional perioperative morbidity rate of 30% were noted, with sepsis-mediated multiorgan system failure the major cause of death (87%). When stratified to CTP classes A, B, or C, mortality was 10%, 31%, and 76%, respectively. Excluding the CTP classification, the authors also performed a multivariate analysis of other perioperative variables and concluded that preoperative prolongation of the prothrombin time, decreased serum albumin, and a total leukocyte count greater than 10,000/cm$^3$ predicted increased mortality. Finally, operative mortality was considerably higher in patients requiring urgent versus elective surgery (57% versus 10%). More than a decade later, Mansour and associates retrospectively analyzed 92 cirrhotic patients who were undergoing abdominal procedures and described nearly identical results, with mortality rates of 10%, 30%, and 82% in patients with CTP classes A, B, and C, respectively. Other retrospective studies have also shown increased perioperative risk during major abdominal surgery, especially under emergency circumstances and in CTP class C cirrhotic patients.

Rice and colleagues, however, described the lack of predictability of the CTP classification in patients with chronic liver failure who were undergoing not only abdominal surgery but also coronary bypass grafting, orthopedic procedures, and other peripheral surgical procedures. In this retrospective analysis of 40 patients, perioperative prolongation of the INR and clinical evidence of encephalopathy were the only variables most closely associated with increased mortality (10 and 35 times that of normal individuals, respectively).

Ziser and co-workers, in the largest of all these retrospective studies, established an 11.6% 30-day mortality rate in 773 patients with cirrhosis who were undergoing a variety of surgical procedures involving local, regional, or general anesthesia. Multivariate analysis identified male gender, CTP class C, ascites, azotemia, perioperative infection, higher American Society of Anesthesiologists (ASA) physical classification, a diagnosis of cryptogenic cirrhosis, and surgery of the respiratory system as risk factors independently associated with mortality. Further analysis identified additional risk factors for perioperative complications (Fig. 73-6). Teh and associates retrospectively reported the utility of the MELD score in predicting mortality of cirrhotic patients undergoing nonhepatic surgery. Comparing 777 cirrhotic patients undergoing major surgery with 303 cirrhotic patients undergoing minor procedures, the authors showed that MELD score, age, and ASA classification could quantify risk of mortality in cirrhotic patients, independent of the procedure.

### TABLE 73-1 MODIFIED CHILD-TURCOTTE-PUGH SCORING SYSTEM

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Modified CTP Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>A</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)†</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
</tbody>
</table>

*Class A = 5 to 6 points, B = 7 to 9 points, and C = 10 to 15 points.
†For cholestatic diseases (e.g., primarily biliary cirrhosis), the bilirubin level is disproportionate to the impairment in hepatic function, and an allowance should be made. For these conditions, assign 1 point for a bilirubin level less than 4 mg/dL, 2 points for a bilirubin level of 4 to 10 mg/dL, and 3 points for a bilirubin level greater than 10 mg/dL.
The effect of pneumoperitoneum on hepatic blood flow remains controversial. However, Meierhenrich and colleagues, using transesophageal echocardiography, noted an increase in hepatic perfusion with carbon dioxide insufflation in healthy patients undergoing laparoscopic hernia repair.\(^{149}\)

In addition to surgery of the biliary tract, stomach, and colon, hepatic resection for HCC is a known risk factor for the development of liver failure in patients with preoperative hepatic dysfunction. Most patients with HCC have liver dysfunction associated with either chronic hepatitis or cirrhosis.\(^{128,150}\) The diminished functional hepatic reserve of these patients may decrease the amount of tissue that can be resected without compromising viable parenchyma and causing liver failure, the most common cause of death after this surgical procedure. Wu and co-workers retrospectively analyzed cirrhotic patients undergoing hepatic resection for HCC based on their degree of hepatic dysfunction.\(^{151}\) By limiting the amount of tissue resection in patients with significant hepatic dysfunction (i.e., poorer CTP class), the authors noted 5-year survival rates comparable to those in patients with less severe forms of cirrhosis who underwent more extensive resections. Perioperative hemorrhage is a common occurrence in cirrhotic patients undergoing resection for HCC because of contributing factors such as portal hypertension, coagulation abnormalities, and highly vascular adhesions in patients with previous abdominal surgery. Preoperative evaluation of patients with HCC by indocyanine green 15-minute retention,\(^ {151,152}\) or by direct measurement of the hepatic venous pressure gradient,\(^ {153}\) can be beneficial in predicting postoperative outcomes in cirrhotic patients undergoing hepatic resection for HCC.

Cardiothoracic surgery is associated with a high mortality rate in patients with preexisting liver disease.\(^ {138,154,155}\) Hepatic dysfunction is often exacerbated by cardiopulmonary bypass (CPB), although the precise mechanism of this dysfunction has not been clearly elucidated. In a canine model of hypothermic nonpulsatile CPB, Koizumi and colleagues noted a decrease in PBF and HABF without a concomitant change in hepatic oxygen metabolism.\(^ {158}\) Normothermic CPB was associated with a similar decline in PBF, but HABF was maintained. Increasing the dose of fentanyl from 10 to 50 \(\mu g/\text{kg/hr}\) significantly suppressed HABF and impaired hepatic oxygen metabolism in both normothermic and hypothermic CPB, thus suggesting the possibility of fentanyl-mediated peripheral venous pooling and subsequent lowering of cardiac output. Okano and co-workers assessed hepatosplanchnic oxygenation in 25 patients with no history of hepatic dysfunction who were undergoing elective coronary artery bypass grafting with either normothermic (\(>35^\circ\) C) or hypothermic (\(<32^\circ\) C) CPB.\(^ {156}\) Hepatic venous desaturation and functional impairment of hepatic sinusoidal endothelial cells occurred in both groups, but hepatocellular dysfunction was not observed.

In addition to the possible effects of hepatic artery and portal venous perfusion, other potential determinants of hepatic dysfunction after CPB include hypotension, low cardiac output syndrome, hypoxemia, microembolism or macroembolism, cytokine and oxygen free radical formation, and the influence of vasoactive and anesthetic drugs.
Small retrospective studies showed 11% to 30% mortality rates in CTP class A and B patients undergoing non-emergency cardiac surgery. Although more deaths occurred in the CTP class B group, significant morbidity, particularly in the form of postoperative hemorrhage and infection, was seen in the CTP class A patients. Noncardiac, thoracic surgery has also been suggested as a risk factor for postoperative mortality in patients with cirrhosis, although the basis for this association remains speculative.

Finally, patients with cirrhosis have an increased risk of developing both inguinal and umbilical hernias possibly related to an increase in intraabdominal pressure related to ascites. Successful surgical repair of an umbilical hernia under general anesthesia and of an inguinal hernia under local anesthesia have been described for all CTP classifications.

**POSTOPERATIVE JAUNDICE**

Postoperative jaundice occurs as a result of overproduction and underexcretion of bilirubin, direct hepatocellular injury, or extrahepatic obstruction. Most causes of postoperative jaundice manifest within 3 weeks of surgery and can be classified as either mild (<4 mg/dL) or severe (>4 mg/dL). Box 73-1 lists the most common causes of postoperative jaundice based on the nature of the pathophysiology. Jaundice secondary to hemolysis, the liver’s capacity to conjugate bilirubin (normal rate of production, 250 to 300 mg/day) has been exceeded. Hemolysis-induced anemia is therefore associated with unconjugated (indirect) hyperbilirubinemia and, in the perioperative period, can usually be attributed to either drug-induced or mechanically induced erythrocyte destruction. The primary mechanisms by which certain drugs cause hemolysis and subsequent jaundice are as follows: (1) the drug adsorption type, whereby an antibody (immunoglobulin G) reacts with a drug bound to the red blood cell membrane; (2) the neoantigen type (so-called innocent bystander), whereby the drug combines with the erythrocyte membrane and an antibody reacts with the newly formed antigenic site to activate the complement cascade; and (3) the autoimmune type, caused by an autoantibody (IgG) to erythrocytes. Medications commonly used perioperatively and associated with one or more forms of hemolytic anemia are listed in Box 73-2.

The degree of associated jaundice is related to the rate of hemolysis and excess production of bilirubin, with the neoantigen mechanism most likely to cause acute anemia, hemoglobinuria, and renal failure. The diagnosis is made by the laboratory constellation of anemia, indirect hyperbilirubinemia, positive direct antiglobulin test, low serum haptoglobin, and a peripheral blood smear noteworthy for fragmented erythrocytes and reticulocytosis. Mechanical destruction of erythrocytes can also occur from surgically implanted prosthetic heart valves or from intrinsically diseased valves.

Multiple blood transfusions can increase levels of unconjugated bilirubin because approximately 10% of stored whole blood undergoes hemolysis within 24 hours of transfusion (see also Chapter 61). Each 0.5-L unit of blood stored in citrate-phosphate-dextrose-adrenaline (CPDA-1) yields 7.5 g of hemoglobin, which is then converted to approximately 250 mg of bilirubin. Multiple units of blood may therefore overwhelm the liver’s ability to conjugate and excrete bilirubin. Finally, reabsorption of extravasated blood, as occurs with retroperitoneal or intraabdominal hematomas, may increase the bilirubin load and cause postoperative jaundice. This cause is not uncommon after major trauma or repair of ruptured aortic aneurysms.

Hepatocellular injury can cause postoperative jaundice (as previously discussed) by drug-induced, ischemic, or virally mediated mechanisms. In addition to potential anesthetic-induced hepatotoxicity, some commonly prescribed drugs can cause hepatocellular injury that mimics either hepatitis or cholestasis based on liver test abnormalities (Tables 73-2 and 73-3). With the exception of acetaminophen, which can directly cause hepatocyte necrosis, drug-induced hepatotoxicity is primarily the result of either idiosyncratic reactions or alterations in bile flow resulting in cholestasis.

Postoperative jaundice may also result from hepatic hypoperfusion. Cardiogenic and noncardiogenic shock can decrease HABF and PBF and cause hepatocellular...
necrosis. Marked elevations in aminotransferase levels are common, with hyperbilirubinemia usually a late finding. In addition to hemodynamic alterations in hepatic blood flow, sepsis or the systemic inflammatory response syndrome is associated with cholestasis and jaundice, presumably because of the effects of circulating endotoxins or other inflammatory mediators on bile formation and flow. Finally, viral hepatitis should be eliminated as the cause of postoperative jaundice because viral exposure may have occurred before surgery.

### TABLE 73-2 DRUG-INDUCED HEPATOTOXICITY

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<thead>
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<th>Agent</th>
<th>Hepatocellular Cytotoxicity</th>
<th>Cholestasis</th>
<th>Steatosis</th>
</tr>
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<tbody>
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<td>✓</td>
<td></td>
<td></td>
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<td>Alcohol&lt;sup&gt;205&lt;/sup&gt;</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Allopurinol&lt;sup&gt;206&lt;/sup&gt;</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Amiodarone&lt;sup&gt;207&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid&lt;sup&gt;208&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Aspirin&lt;sup&gt;209&lt;/sup&gt;</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Azathioprine&lt;sup&gt;208&lt;/sup&gt;</td>
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<td>✓</td>
<td></td>
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<tr>
<td>Bleomycin&lt;sup&gt;210&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Bosentan&lt;sup&gt;211&lt;/sup&gt;</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers&lt;sup&gt;208&lt;/sup&gt;</td>
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<td>✓</td>
<td></td>
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<td>Captopril&lt;sup&gt;212&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Chlorpromazine&lt;sup&gt;213&lt;/sup&gt;</td>
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<td>Danazol&lt;sup&gt;215&lt;/sup&gt;</td>
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<td>NSAIDs&lt;sup&gt;226-228&lt;/sup&gt;</td>
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<tr>
<td>Steroids, anabolic&lt;sup&gt;232&lt;/sup&gt;</td>
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<td>Steroids, oral contraceptives&lt;sup&gt;193&lt;/sup&gt;</td>
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<tr>
<td>Sulfonamides&lt;sup&gt;228&lt;/sup&gt;</td>
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<td>Tacrine&lt;sup&gt;233&lt;/sup&gt;</td>
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<td>✓</td>
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<td></td>
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<tr>
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<td>✓</td>
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<td>Tolcapone&lt;sup&gt;235&lt;/sup&gt;</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>Trazodone&lt;sup&gt;216&lt;/sup&gt;</td>
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<tr>
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<td></td>
<td>✓</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>Zafirlukast&lt;sup&gt;239&lt;/sup&gt;</td>
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</tr>
</tbody>
</table>

FeSO₄, Ferrous sulfate; IV, intravenous; NSAIDs, nonsteroidal antiinflammatory drugs.
Obstruction of the common bile duct by a gallstone, stricture, or tumor can result in failure to excrete conjugated bilirubin (obstructive jaundice) with significant perioperative morbidity and mortality. Factors associated with a poor outcome after surgery in patients with obstructive jaundice include extrahepatic obstruction as a result of malignancy, malnutrition, hypoalbuminemia, low hematocrit (<30%), azotemia, and the level and duration of hyperbilirubinemia.166,167 Dixon and colleagues cited an overall mortality rate of 9.1% in a retrospective analysis of 373 patients requiring surgery for obstructive jaundice, but a 60% mortality rate for patients with anemia, malignancy, and marked hyperbilirubinemia (>11 mg/dL).168 Of paramount significance is the association of acute renal failure with obstructive jaundice.169,170 The incidence of postoperative acute renal failure is approximately 8% to 10% and correlates directly with the degree of hyperbilirubinemia, with mortality rates as high as 70% to 80% reported. Neither bilirubin nor bile acids themselves are directly nephrotoxic, but experimental evidence suggests a negative chronotropic, vasodilatory, and diuretic effect of bile salts that results in systemic and thus renal hypoperfusion. The changes appear to be related to enhanced absorption of endotoxin from the gastrointestinal tract because of low intestinal levels and high serum levels of bile acids. This process stimulates the release of inflammatory mediators, in particular endothelin, a potent renal vasoconstrictor that leads to a further decline in renal perfusion.171,172 Other experimental data have implicated endotoxemia-induced nitric oxide release as a further mediator of renal hypoperfusion.173 Clinicians rely on the limitations of urine output as a method of monitoring renal perfusion. It is more reliable to monitor effective blood volume and cardiac function with either a central venous or pulmonary artery catheter or to perform transesophageal echocardiography, with the goal of maintaining renal perfusion by augmenting cardiac output.114 No data have documented the clinical benefit of mannitol, furosemide, or dopamine in perioperative renal protection,111,174 and the potential benefit of endothelin receptor blockers has yet to be thoroughly assessed in clinical studies.171

### TABLE 73-3  HERBAL PRODUCTS AND HEPATOTOXICITY

<table>
<thead>
<tr>
<th>Herbal</th>
<th>Hepatocellular</th>
<th>Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh240</td>
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<td>✓</td>
</tr>
<tr>
<td>Celandine241</td>
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<td></td>
</tr>
<tr>
<td>Chaparral242</td>
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<td></td>
</tr>
<tr>
<td>Comfrey243</td>
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<td></td>
</tr>
<tr>
<td>Echinacea244</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germander245</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jin bu huan (levotetra-hydropalmitine)246</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Kava247</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Margosa oil208</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Mu huang248</td>
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<td></td>
</tr>
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<td>Sassafras208</td>
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<tr>
<td>Yerba208</td>
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</table>

**PERIOPERATIVE MANAGEMENT OF PATIENTS WITH ASYMPTOMATIC OR CHRONIC LIVER DYSFUNCTION**

The goal of perioperative management of patients with asymptomatic elevations in aminotransaminase, alkaline phosphatase, or bilirubin levels or in patients with preexisting chronic liver disease is prevention of acute liver failure or further hepatic deterioration. Acute liver failure, defined by encephalopathy in the setting of acute liver injury (e.g., viral hepatitis, toxin ingestion, idiosyncratic drug reaction, sepsis, or shock), is further categorized into hyperacute, acute, or subacute forms based on the time interval between the onset of jaundice and encephalopathy (0 to 7 days, 8 to 28 days, or >28 days, respectively).175 Patients with the hyperacute form of acute liver failure tend to have a more favorable survival rate (35%), whereas those with the acute and subacute forms have poorer prognoses, with mortality rates of 93% and 86%, respectively.176 Perioperative risks should be identified, and therapy should be directed to minimize hepatotoxicity and maximize hepatic oxygen delivery. For example, drugs such as acetaminophen or combined drugs such as acetaminophen with hydrocodeine probably should not be administered to patients with asymptomatic increases of liver enzyme test results or chronic liver dysfunction. In patients with cholelithiasis and biliary tract obstruction, the use of opiates should be limited preoperatively because these drugs can cause spasm of the choledochoduodenal sphincter (sphincter of Oddi) and a subsequent increase in intrabiliary tract pressure.176,177 These effects appear to be more pronounced for fentanyl, morphine, and meperidine and less severe for opiate agonist-antagonists.176,177 Intraoperatively, opiates may be used with the recognition that the possible development of sphincter of Oddi spasm can be treated directly with naloxone or by relaxing smooth muscle tone with either glucagon or nitroglycerin177,178 (which induces release of nitric oxide179,180).

Remifentanil has an effect similar to that of other opiates on the sphincter of Oddi. Fragen and colleagues studied remifentanil given to six healthy adult volunteers who underwent radionuclide imaging of the gallbladder before and after remifentanil infusion.181 The recovery time for dye to appear in the duodenum after discontinuation of the infusion was significantly greater than in the control phase of the study. The authors noted, however, that this delay in recovery of gallbladder function was shorter than in studies using morphine or meperidine. Finally, no data support the benefit or detriment of regional versus general anesthesia, nor do data suggest particular anesthetic agents that should be administered or avoided in patients with preexisting hepatic dysfunction, with the exception of halothane, as previously discussed.

Patients with more advanced liver disease (e.g., CTP class B or C cirrhosis) require an anesthetic plan designed to maximize hepatic oxygen delivery and prevent and treat the complications of encephalopathy, cerebral edema, coagulopathy, hemorrhage, and portal hypertension. Hepatic encephalopathy commonly occurs in patients with chronic liver disease because of the following: accumulation of circulating neurotoxins such as...
unmetabolized ammonia, gut-derived false neurotransmitters, γ-aminobutyric acid (GABA), and endogenous GABA receptor agonists; altered neurotransmission by the excitatory neurotransmitter glutamate; or altered cerebral energy homeostasis. Clinically, hepatic encephalopathy is manifested by neuropsychiatric abnormalities ranging from subtle personality changes and cognitive dysfunction to more advanced depression of consciousness, delirium, and coma. Clinical signs include abnormalities in psychometric testing and apraxia, as well as the more severe findings of asterixis, hyperreflexia, and decerebration. When hepatic encephalopathy occurs with acute liver failure, it often has a rapid onset and is invariably complicated by cerebral edema. Cerebral edema develops as a result of the osmotic effect of accumulated glutamine that produces astrocyte cell swelling or as a result of cerebral vasodilation caused by loss of autoregulation, or because of both mechanisms. These patients invariably require urgent liver transplantation.

Many factors may precipitate hepatic encephalopathy in patients with chronic liver disease. Potassium levels should be monitored, and hypokalemia should be treated to decrease the effect of decreased potassium levels on renal production of ammonia. Arterial pH should be maintained near normal because systemic alkalemia is also noted to increase the diffusion of ammonia across the blood-brain barrier, a process that can potentially worsen the degree of encephalopathy. Effective circulatory blood volume should be maintained, and anemia should be corrected to maintain hepatic oxygenation and promote the metabolism of circulating toxins. Benzodiazepines should be used judiciously because they may activate the central GABA-benzodiazepine receptor ligand and worsen hepatic encephalopathy. All psychoactive drugs have potentially deleterious effects on hepatic encephalopathy by further suppressing a vulnerable central nervous system. Moreover, propofol can be used as an anesthetic for cirrhotic patients undergoing endoscopic procedures. Compared with benzodiazepines and opioids, propofol appears to have a greater safety profile; it allows for a more rapid and predictable awakening, it does not precipitate hepatic encephalopathy, and it is associated with few side effects, as well as having no effects on liver function tests. Hepatic encephalopathy is also a recognized complication of the TIPS procedure.

When patients remain obtunded or comatose after anesthesia and surgery, therapy is often directed toward decreasing ammonia production. Lactulose is administered either by nasogastric tube or by enema to create an osmotic, cathartic effect and to lower intestinal pH, thereby decreasing the survival of ammonia-producing bacteria. Flumazenil, a specific antagonist of central benzodiazepine receptors, can improve the level of consciousness in selected cirrhotic patients with severe hepatic encephalopathy.

Perioperative hemorrhage in patients with significant liver dysfunction may occur because of bleeding diatheses or the complications of portal hypertension, or both. Synthetic hepatic function, as measured by the INR, is useful to assess the severity of the coagulopathy and to gauge therapy, including the subcutaneous administration of vitamin K, transfusion of fresh frozen plasma, use of recombinant factor VII or other factors, and plasmapheresis. In patients with acute liver failure, plasmapheresis may have potential benefit because it promotes rapid correction of coagulopathy while minimizing the chances of excessive intravascular volume, but this approach has not been validated.

Hemorrhage may also occur as a result of gastrointestinal bleeding from rupture of esophageal or gastric varices as a complication of portal hypertension. Intraoperatively, it is advisable to avoid the placement of a transesophageal echocardiography probe, to avoid initiation of bleeding in patients with esophageal varices. Pharmacologic therapy for acute esophageal variceal bleeding includes use of the combination of vasopressin and nitroglycerin, somatostatin, or octreotide, a synthetic analogue of somatostatin. Portal hypertension may also lead to the development of ascites. Ascites occurs in patients with advanced liver disease secondary to renal retention of sodium and water and localization of this excess fluid in the peritoneal cavity because of portal hypertension. In addition to the general measures of sodium and water restriction and diuretic therapy, therapeutic paracentesis may be indicated if a patient presents for surgery with tense ascites. Relief of tense ascites may improve pulmonary gas exchange and reduce the risk of gastric aspiration. Care should be taken, however, to prevent circulatory collapse by the concomitant administration of intravenous colloid solutions because intravascular volume re-equilibration occurs 6 to 8 hours after the removal of a larger volume of ascitic fluid. Finally, patients with end-stage liver disease are at risk for the development of either hepatorenal or hepatopulmonary syndrome. Hepatorenal syndrome is a state of functional renal failure characterized by azotemia, hyperosmolar urine, and urinary sodium excretion less than 10 mEq/L. Although the pathogenesis of this syndrome has not been clearly elucidated, there appears to be a decrease in renal perfusion pressure related to systemic vasodilation in combination with a loss of renal autoregulation because of increased sympathetic activity. The diagnosis of hepatorenal syndrome in patients with end-stage liver disease usually signals the need for orthotopic liver transplantation. In the event that transplantation is not possible, management is supportive and consists of the use of intravenous volume challenges and large-volume paracentesis to relieve tense ascites.

Hepatopulmonary syndrome, which is defined by the triad of end-stage liver disease, increased alveolar-arterial gradient, and intrapulmonary vascular dilation, is characterized by the clinical features of digital clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia, in addition to the other clinical characteristics of portal hypertension. Orthodeoxia, defined as arterial oxygen desaturation that is more pronounced in the upright position and relieved by recumbency, is a common phenomenon of hepatopulmonary syndrome. The pathogenesis of hepatopulmonary syndrome is considered to be primarily related to intrapulmonary vascular dilation, which is diagnosed by contrast-enhanced echocardiography, perfusion lung scanning, or pulmonary arteriography. Current pharmacologic therapy for this disorder is limited; however, orthotopic liver transplantation may lead to a reversal of these pulmonary changes.
ANESTHETIC CONSIDERATIONS FOR PROCEDURES INVOLVING THE LIVER AND BILIARY SYSTEM

TRANSGUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PROCEDURE

TIPS is a percutaneously created intrahepatic connection of the portal and systemic circulations. This procedure is typically used in patients with end-stage liver disease to decrease portal pressure and attenuate the complications related to portal hypertension, such as variceal bleeding or refractory ascites. Diversion of PBF into the hepatic vein is achieved by placement of an expandable intraparenchymal tract (Fig. 73-7).

Although most patients can undergo TIPS placement with sedation, some clinicians prefer to use general anesthesia in selected patients because of the prolonged nature of the procedure, the potential respiratory-depressant effects of sedatives in cirrhotic patients with underlying pulmonary dysfunction as a result of ascites and/or hypoxemia from the hepatopulmonary syndrome, and concern regarding possible gastric aspiration. Regardless of the anesthesia technique chosen, appropriate intravascular volume resuscitation is often necessary before the procedure, especially in patients who have had variceal bleeding. In addition, patients with cirrhosis who are undergoing a TIPS procedure frequently have severe coagulopathy that requires preprocedural procoagulant therapy.

Several complications can occur during placement of TIPS that may require intervention by the anesthesiologist. Pneumothorax or neck vessel injury can occur during vessel puncture. These complications may be reduced by ultrasonographic guidance during jugular vein puncture. Additionally, cardiac dysrhythmias can be mechanically induced during intracardiac catheter passage. Finally, acute, life-threatening hemorrhage caused by hepatic artery puncture in conjunction with a hepatic capsular tear or by extraportal portal venous puncture can occur. Hemodynamic status can deteriorate, with the development of pulmonary edema and congestive heart failure, in patients with borderline cardiac reserve.

HEPATIC RESECTION

Preoperative considerations (as previously described) before hepatic resection involve risk assessment primarily using CTP and MELD scores (see also Chapter 74). Surgical procedures should be limited to patients with CTP class A and significantly compensated CPT B status. MELD scores higher than 10 pose significant risk of postoperative liver failure in cirrhotic patients with HCC. Severe thrombocytopenia or large varices represent major perioperative risk factors and should preclude surgery. Significant anemia and coagulopathy, if present, should be corrected preoperatively. Decisions regarding the choice and doses of anesthetics should account for any baseline hepatic parenchymal dysfunction, as well as the potential postoperative dysfunction resulting from resection of a major portion of the liver parenchyma. No data show hepatotoxicity with either sevoflurane or desflurane, and thus both drugs are safe to administer, provided hepatic hypoperfusion is avoided. Indeed, hepatic preconditioning with sevoflurane has been shown to decrease postoperative complications in patients undergoing hepatic resection.

Although the risk of significant intraoperative blood loss is well known and the need for appropriate monitoring and sufficient vascular access to permit rapid transfusion is widely accepted, overall fluid management during major hepatic resection is controversial. At some centers, fluid and blood administration is used liberally, beginning early in the course of resection, with the goal of increasing intravascular volume as a buffer against sudden blood loss. Other centers favor maintenance of low central venous pressure during resection to minimize blood loss from hepatic venous radicals, major hepatic veins, or the vena cava. These sites typically contribute to most bleeding during hepatic resection. Notably, reduction of intrahepatic venous pressure can also be achieved by using a modest degree of the Trendelenburg position, an approach that potentially maintains or even increases cardiac preload and cardiac output, as well as reducing the risk of air embolism from disrupted hepatic veins. In patients without preexisting renal dysfunction, the latter approach does not appear to have a significant impact on postoperative renal function.

Although basic postoperative management concerns are similar to those of other major abdominal procedures, several aspects of care are notable. Intravenous fluids should be supplemented with either sodium or potassium phosphate, which is often needed to prevent severe hypophosphatemia and to facilitate liver regeneration. Decreased clearance of hepatically metabolized drugs is important in selecting and titrating methods of postoperative analgesia.

Figure 73-7. Transjugular intrahepatic portosystemic shunt (TIPS) procedure. A stent (or stents) is passed through the internal jugular vein over a wire into the hepatic vein (A); dilated esophageal varices (EV) are apparent. The wire and stent or stents are then advanced into the portal vein (B), after which blood can pass through the portal vein into the hepatic vein and bypass and decompress dilated esophageal veins (C). (Reproduced with permission from University of Michigan Health System: <www.med.umich.edu/1libr/topics/liver09.htm/>
HEPATIC CRYOTHERAPY

Hepatic cryotherapy involves the application of material at subzero temperature by multilumen probes positioned intraoperatively under sonographic guidance. This procedure is used to treat nonresectable malignant hepatic tumors. Preanesthetic considerations for hepatic cryotherapy are similar to those for hepatic resection. Heat conservation measures should be instituted during the procedure, with continual monitoring of core temperature. Intraoperative bleeding is rarely significant enough to cause hemodynamic instability. Postoperative pulmonary, renal, and coagulation problems may manifest as sequelae of the “cryoshock syndrome,” even after a procedure with unequivocal intraoperative stability.203

Acknowledgment

The authors gratefully acknowledge the assistance of Kelly Lewis, PharmD, in the preparation of Tables 73-2 and 73-3.

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