

Assessment of Hepatic Function, Operative Candidacy, and Medical Management after Liver Resection in the Patient with Underlying Liver Disease

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Abstract

Liver resection in patients with underlying liver disease remains a formidable challenge. It requires adequate patient selection, a precise surgical plan, and avoidance of additional ischemic insults during surgery. Precise estimation of the residual liver volume using computed tomography or magnetic resonance imaging and computer-assisted volumetry allows the calculation of residual to total liver volume (RLV/TLV) ratios. Although RLV/TLV ratios over 20 to 25% are considered sufficient in healthy livers, patients with cirrhosis may only tolerate resections that result in RLV/TLV ratios over 40% and higher. Conventional laboratory tests may not be able to sufficiently predict liver reserve after resection. Dynamic tests such as indocyanine green clearance have been used to assess residual liver function and assist in deciding about operability of patients with underlying liver disease undergoing extensive resections. Intraoperative management should focus on avoiding blood loss and ischemic injury to the liver. Low central venous pressure may reduce blood loss and is recommended if tolerated without impeding renal perfusion. Portal vein and hepatic artery occlusion during resection can reduce blood loss, but will cause ischemic insult to the liver that may jeopardize residual liver function and induce postoperative hepatic failure. When feasible, vascular occlusion should be avoided in patients with underlying liver disease. The postoperative recovery is usually fast if sufficient liver remains. However, vigilance is required to detect liver dysfunction and treat its complications.

Keywords

- ▶ hepatectomy
- ▶ liver function
- ▶ cirrhosis
- ▶ liver tumors
- ▶ dynamic liver tests
- ▶ liver injury

Preoperative Assessment

Evaluation of the Required Extent of Liver Resection

Most hepatic resections are performed as treatment for either primary liver tumors or metastasis secondary to extrahepatic tumors. These resections need to have a sufficient margin in order to be curative; therefore, the precise location of the tumor is necessary prior to surgery. It is further mandatory to estimate the remaining liver size to avoid insufficient functional reserve of the liver remnant

after resection. Estimation of the remaining liver function after resection can be complicated by baseline liver disease such as cirrhosis. Hepatic cirrhosis not only decreases the functional reserve of the remaining liver, but also renders it succintly sensitive to ischemic injury. Preoperative estimation of remaining liver size is the first step in creating a surgical plan for extensive hepatic resections of five or more segments in all patients with and without hepatic cirrhosis.

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Preoperative Assessment of Residual Hepatic Function

Estimation of Residual Liver Volume

Dual-phase computed tomography (CT) or magnetic resonance imaging (MRI) are the radiologic techniques of choice to assess tumor location and size. The aim is to evaluate if a curative resection is possible with an acceptable low risk of postoperative liver failure. Computer-assisted volumetry of the entire liver and the liver remnant after “virtual resection” allow the calculation of either the ratio of remnant liver volume to total liver volume (RLV/TLV ratio) or the ratio of remnant liver to body volume (RLV/BW ratio). Radiologic assessment of liver size is preferable over formulas that estimate liver size. There is good general correlation between estimated and measured liver size,¹ but in individual cases estimation of liver size may be erroneous depending on liver size.²

There is no consensus if RLV/BW or RLV/TLV ratios have a better ability to predict postoperative liver failure. Traditionally a RLV/TLV ratio above 20 to 25% is considered acceptable for tumor resections. The margin of safety needs to be much higher for living liver donation than for therapeutic liver resections. For living liver donation, conventionally RLV/BW ratios are used and a ratio > 0.6 is considered safe to avoid postoperative small for size syndrome.³ RLV/BW ratios are now also used for liver resections. Truant et al reported in 2004 that resections of more than 80% of the total liver volume did not increase the 3-month morbidity; however, patients who had less than 0.5% RLV/BW ratio had a significantly higher incidence of complications and mortality.⁴

This was a small retrospective study of only 31 patients; more recent studies have found a close correlation between RLV/BW and RLV/TLV ratios. Chun et al reported that a RLV/BW ratio of ≤ 0.4 or a RLV/TLV ratio of $\leq 20\%$ is a safe threshold to prevent postoperative liver failure in noncirrhotic patients.⁵

Patients whose disease is more extensive may benefit from preoperative chemoembolization or radiofrequency ablation to shrink the tumor(s), staged surgery for multilobar lesions, or preoperative portal vein embolization to increase the volume of the future liver remnant to achieve safe resection of otherwise unresectable tumors.⁶

Assessment of Operative Candidacy of Patients with Hepatic Cirrhosis

Hepatic cirrhosis renders the liver disproportionately sensitive to ischemic injury and even short episodes of ischemia-reperfusion may cause profound dysfunction of the remnant liver.

Hepatocellular carcinoma (HCC) is common with hepatic cirrhosis and is a frequent cause of mortality. Resection can improve survival and should be performed if it can be done safely, especially if the patient is not considered a transplant candidate. Staging of HCC should include the American Joint Committee on Cancer / International Union for Cancer Control definitions.

Large tumor size is not a contraindication for resection and the ability to perform a safe resection depends on the size of

the liver remnant and the ability to perform the resection without vascular occlusion techniques. There is no consensus of what are considered safe RLV/BW and RLV/TLV ratios; however, a RLV/TLV ratio < 40% is generally considered a very high risk for postoperative liver failure in cirrhotic patients.⁷ Patients with severe liver disease (Child C) are usually not considered candidates for liver resection at all. Patients with Child B cirrhosis will not tolerate major resections with a RLV/TLV ratio < 30%. The mortality of patients with Child A cirrhosis after liver resection has been reported to be 14% compared with 1% in patients without cirrhosis.⁸ Multiple studies have demonstrated that the Model of End-stage Liver Disease (MELD) score is a good predictor of postoperative complications such as acute liver failure and mortality after hepatic resections.^{9–11} These studies indicate that patients with a MELD score > 9 are at a substantial risk for postoperative complications and mortality and (extensive) resection should probably be avoided. Interestingly, the MELD score has not been useful in predicting morbidity or mortality risk after liver resection in patients without cirrhosis.¹²

Static laboratory tests may not be able to fully appreciate the ability of the liver to prevail despite reduction in size and ischemic injury associated with liver resections. As I will discuss later in this article, conventional laboratory tests are too insensitive to detect anything but severe restrictions in liver function. “Liver reserve” may be better assessed using dynamic liver function tests that are described in more detail below. Indocyanine green (ICG) clearance has been recognized as a useful test to assess the risk of liver resections for many years now. For example, Hummings et al. measured ICG clearance in 22 patients undergoing liver resection in 1992. Preoperative ICG clearance was the best predictor of mortality, better than any other liver laboratory test.¹³ Multiple newer studies also confirmed the utility of ICG clearance as a risk assessment tool.^{14–16} This has led to the development of an algorithm that includes total serum bilirubin levels as well as results from preoperative ICG clearance to aid in the decision about the extent of resection in patients with hepatic cirrhosis.¹⁴

Other dynamic function tests, for example, the monoethylglycineylidide (MEGX-) test¹⁷ or hippurate ratio,¹⁸ have also been tested as risk-stratification tools for hepatic resections with similar good results. We will describe these in more detail below.

Algorithms that include conventional and dynamic liver function tests can only guide decision making and are not intended to replace clinical decisions by experienced practitioners. Major resections even with total vascular occlusion are possible in patients with mild cirrhosis in the hands of experienced surgeons, hepatologists, and anesthesiologists.¹⁹

Evaluation of Liver Function

Conventional Liver Function Tests

Conventional liver function tests can be divided into tests that reflect liver function and those reflecting liver injury. Liver function can be further divided into metabolic and synthetic

function. Metabolic function comprises pathways that include enzymes of the cytochrome family (phase I) and glucuronidation pathways (phase II). Conventional liver function tests, such as the measurement of total bilirubin, reflect phase II metabolism. However, phase II metabolism is rather robust and insensitive to ischemic injury. Therefore, total bilirubin levels may overestimate the functional reserve of the liver and remain normal even when phase I metabolism is already substantially impaired. As a consequence, the early stages of liver dysfunction are often underdiagnosed when only phase II metabolism (e.g., total bilirubin) is taken into account.

The main synthetic functions that are commonly assessed with laboratory tests are protein synthesis and synthesis of coagulation factors. Impaired protein synthesis affects albumin concentrations and is therefore included in the Child-Turcotte score. However, albumin levels are rarely specific and sensitive enough to detect minor and intermediate compromised function. Fluid retention and protein loss with ascites may further decrease albumin levels; therefore, these may be not proportional to the decrease in synthetic function only.

Impaired synthesis of coagulation factors may result in an abnormal coagulation test, such as an increase of the international normalized ratio (INR). But liver disease affects not only the synthesis of procoagulant factors, but also anticoagulant factors such as protein C or protein S. The balance of pro- and anticoagulant factors may therefore be preserved (but much less stable) or tipped toward hypercoagulability even when the INR is substantially increased.

Transaminases reflect hepatic injury; they are intracellular and intramitochondrial enzymes that are released when cell death occurs. Transaminases may reflect the degree of injury,

but not necessarily impairment of function. Transaminases only increase with acute injury, but not with chronic disease; therefore, they are similar to troponin I in the presence of myocardial dysfunction. They are useful to detect acute organ injury, but not impairments of function.

These limitations of conventional liver function tests compromise their utility to assess hepatic reserve prior to liver resection. Conventional liver function becomes pathologic only late during disease progression. Therefore, patients usually do not tolerate any resections and prolonged hepatic ischemia when conventional tests are increased and other, more sensitive liver function tests may be better suited to evaluate preoperative hepatic reserve.

Dynamic Liver Function Tests

Dynamic liver function tests directly measure hepatic metabolism, usually of phase I oxidative pathways. These pathways are more sensitive to ischemia than phase II glucuronidation and will be abnormal even with mild forms of liver disease. Hence, these tests are more sensitive to detect even minor impairments of liver function. Dynamic liver function tests have the further advantage of assessing the metabolic reserve at the time of measurement, instead of relying on metabolites that may have accumulated and therefore allow a real-time assessment of function. **Fig. 1** depicts different static and dynamic liver function tests. This review will be limited to the most commonly studied tests, indocyanine green clearance, the monoethylglycinexylidide (MEGX) test, and sorbitol clearance.

Indocyanine Green Clearance

Indocyanine green (ICG) is a fluorescent dye that if given intravenously is eliminated through the bile within a few

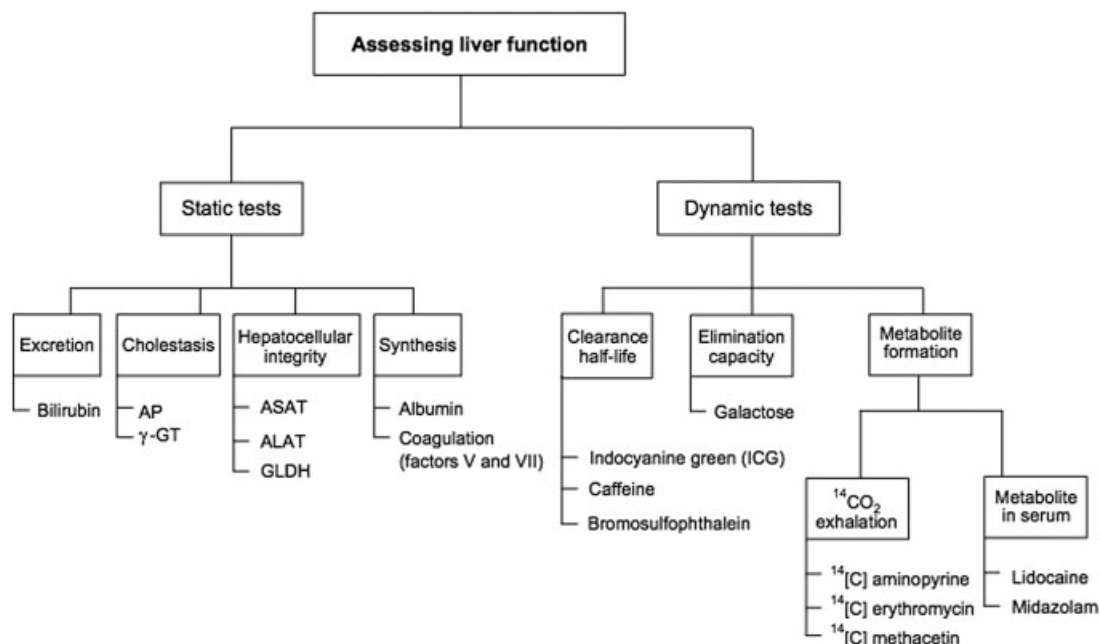


Fig. 1 Static and dynamic tests to assess liver function. AP, alkaline phosphatase; γ -GT, gamma-glutamyl transpeptidase; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; GLDH, glutamate dehydrogenase. (With permission from Sakka SG. Assessing liver function. *Curr Opin Crit Care* 2007;13(2):207–214.)

minutes in healthy subjects and does not undergo enterohepatic recirculation. Elimination (700 mL/min/m^2) is dependent on hepatocyte function, liver blood flow, and intact bile secretion and can be expressed by the percentage of ICG eliminated per minute (ICG plasma disappearance rate [ICG-PDR]). Normal ICG-PDR is over 18% / min and is usually measured over 15 minutes after injection of ICG. Indocyanine green absorbs infrared light at a frequency close to the absorption spectrum of deoxygenated blood; oxygen saturation measured by pulse oximetry decreases falsely for minutes after an intravenous bolus of ICG. A transcutaneous sensor similar to a conventional pulse oximeter, but with an infrared light source at the absorption spectrum of ICG (805 and 940 nm) may be used for noninvasive transcutaneous ICG clearance and has correlated very well with sequential plasma measurements of ICG.²⁰ Multiple studies confirmed the ability of ICG clearance to predict liver failure after hepatic resection. Hemming et al found that ICG-PDR was the best predictor of 30-day mortality after liver resection and an ICG-PDR.¹³

Furthermore, indocyanine green is a good predictor of graft loss or death within 30 days after liver transplantation.²¹ An ICG-PDR < 9.8% on day 7 predicted graft loss or death with a sensitivity of 75.0% and a specificity of 72.6%. As ICG-PDR depends on hepatic blood flow it has also been used to detect vascular complications during liver transplantation. Renn et al reported a case of portal vein and hepatic artery occlusion after liver transplantation that was only detected by a sudden decrease in ICG-PDR. Mandell et al²² describe a similar case in which a decrease of ICG-PDR led to the diagnosis of portal vein occlusion and allowed a rapid surgical correction and full recovery of graft function.

Indocyanine green plasma disappearance rate is also an excellent predictor of outcome and survival in intensive care unit (ICU) patients or patients with sepsis²³ an ICG-PDR < 8% is associated with a very high mortality. Surprisingly, ICG-PDR in this general ICU population was a better predictor of mortality than complex scoring systems such as the APACHE II (Acute Physiology and Chronic Health Evaluation II) or SAPS II (Simplified Acute Physiology Score II) scores.

Indocyanine green clearance is affected by biliary obstruction and can overestimate hepatic dysfunction when cholestasis is present. Indocyanine green has very few adverse effects, but should be avoided in patients with iodine allergies. It has been approved by the Food and Drug Administration to measure liver function, but the noninvasive, transcutaneous measurement of ICG clearance (LIMON, Pulsion Medical Systems AG, Feldkirchen, Germany) has not been approved.

Monoethylglycinexylidide (MEGX) Test

Lidocaine is an amide local anesthetic that has a high hepatic extraction ratio (0.53) and is then rapidly metabolized by the cytochrome P450 system through oxidative *N*-dealkylation. Its main metabolite is monoethylglycinexylidide (MEGX) can be easily measured in the plasma. Plasma MEGX levels can be determined before and then 15 and 30 minutes after a bolus injection of intravenous lidocaine. The rate of lidocaine

metabolism depends on hepatic blood flow and the activity of the cytochrome P-450 system, specifically the CYP 3A4 and CYP 1A2 isoenzymes.^{24,25} Erythromycin and ketoconazole inhibit the CYP 3A4 isoenzyme and can therefore affect the MEGX test adversely. Oxidative phase I metabolism by cytochrome P450 is more sensitive to ischemic insults than phase II glucuronidation and is therefore better suited to assess hepatic reserve. The MEGX is a good predictor of survival in patients with liver disease.^{26–28} Other studies have successfully used the MEGX test to assess cadaveric liver donor quality^{29,30} or posttransplant graft function.³¹

Similar to ICG clearance, MEGX measurements are also highly predictive of survival in general ICU populations. On day 4 after ICU admission, median MEGX levels were significantly lower in nonsurvivors than in survivors (23 $\mu\text{g/L}$ vs. 53 $\mu\text{g/L}$, $p < 0.01$).³² These results emphasize that hepatic dysfunction is much more common in critically ill patients and not readily detected with conventional liver function tests such as total bilirubin measurements. Despite this, MEGX testing is not routinely used in clinical practice.

Sorbitol Clearance

D-sorbitol is a nontoxic sugar with a very high hepatic extraction ratio (0.93) and is rapidly metabolized by the fructose pathway in the liver.³³ Because of the high hepatic extraction of D-sorbitol, its elimination correlates well with hepatic blood flow. In hepatic cirrhosis, total hepatic blood flow is not necessarily decreased, but the amount of effective blood flow, i.e., the fraction of total blood flow that gets in contact with hepatic sinusoids declines. A larger proportion of blood bypasses constricted sinusoids through trans- and extrahepatic shunts; therefore, it does not participate in the hepatic metabolism.³⁴

D-sorbitol elimination (and to some degree ICG clearance) is therefore likely a reflection of “functional” blood flow and not total hepatic blood flow. D-sorbitol has a higher extraction ratio than ICG (0.93 and 0.58, respectively) and is therefore less dependent on metabolic reserve of the liver and may more accurately estimate functional liver flow. There are few human studies of D-sorbitol elimination; more research is required to assess its clinical utility for liver resection and transplantation.

Preoperative Risk Assessment for Nonhepatic Disease

Cardiac and Coronary Disease

The most commonly used algorithm to aid in the decision about preoperative cardiac testing are the guidelines of the American College of Cardiology / American Heart Association on perioperative cardiovascular evaluation and care for noncardiac surgery (revised in 2007).³⁵ This algorithm considers any intraperitoneal surgery (which includes major hepatic resections) as intermediate risk surgery (only vascular surgery is considered high risk). Patients with poor (< 4 metabolic equivalents of task [METs]) or unknown functional capacity who have three or more clinical risk factors for cardiac events should undergo noninvasive testing for cardiac disease. Patients with 1 to 2 clinical risk factors can

undergo noninvasive testing for cardiac disease especially if this may change the perioperative management. Clinical risk factors include a history of ischemic heart disease, compensated or prior heart failure or cerebrovascular disease, diabetes mellitus, or renal insufficiency.

Patients with active cardiac conditions such as unstable coronary syndromes, decompensated heart failure (New York Heart Association [NYHA] functional class IV, worsening or new-onset heart failure), significant arrhythmias, or severe valvular disease should undergo testing prior to surgery in all cases except emergencies independent of ability to exercise.

The use of this algorithm may not be feasible when patients have rapidly growing or large tumors. Stress test, coronary angiography, and possible intervention either by percutaneous intervention or coronary bypass grafting may take too long and cause the tumor to be unresectable, hence taking away the patient's chance for cure. In these cases, surgery should proceed as long as the patient fully understands the increased risk for cardiac events and agrees with this plan.

Multiple other risk-assessment tools have been developed. The Revised Cardiac Risk Index³⁶ is probably the most widely used tool that is simple and easily applied with few questions. One point each is given for high-risk surgery (including intraperitoneal), a history of ischemic heart disease, congestive heart failure or cerebrovascular disease, preoperative treatment with insulin, or preoperative serum creatinine > 2.0 mg/dL.

The risk of major cardiac events increases with an increasing number of risk factors and is 0.4% for 0, 0.9% for 1, 6.6% for 2, and 11% for 3 or more points. This simple score has good predictive power, but has not been validated for patients undergoing hepatectomies.

Intraoperative Management

Anesthetic Management and Monitoring and Low Central Venous Pressure Technique

General endotracheal anesthesia is commonly required for hepatectomies.

(Radial) arterial catheters should be placed routinely to allow beat-to-beat blood pressure monitoring and facilitate frequent blood draws. Major (but not necessarily minor) resections will also require placement of a central venous catheter that allows monitoring of central venous pressure (CVP), large volume fluid administration, and central administration of vasoactive drugs.

Central venous pressure is not an adequate representation of volume status and responsiveness. Multiple studies starting with Shoemaker's study of intravascular volume and CVP 30 years ago³⁷ have demonstrated that there is no relationship between CVP and intravascular volume. Central venous pressure also does not predict which patients respond to a volume challenge favorably (i.e., with an increased blood pressure).³⁸

However, during liver resections CVP monitoring may be helpful. Central venous pressure correlates with hepatic vein pressure; therefore, intraparenchymal pressure will increase

with increased CVP. Many studies have demonstrated that low CVP (< 5 mm Hg) is associated with decreased blood loss³⁹⁻⁴¹ and perhaps even improved morbidity and mortality.⁴² These results have been criticized by some practitioners; two studies found no association between CVP and blood loss during living liver donation. Low CVP is not without risk; for example, low renal perfusion may exacerbate pre-existing renal insufficiency and cause acute kidney injury. This is particularly of concern if the patient has underlying hepatic cirrhosis and is dependent on a hyperdynamic state and high cardiac output to maintain (renal) perfusion pressure. Low CVP technique may furthermore affect beneficial hepatic artery flow and oxygen delivery to the liver.

In patients with no renal dysfunction and normal liver function, the low CVP technique is recommended. Reduction in blood loss and avoidance of blood transfusion facilitates resection and is likely going to improve outcome.⁴³ Adequate fluid resuscitation after the specimen was removed should avoid any adverse sequelae in most cases. Frequently, vasopressors are temporarily required to maintain perfusion pressure when using the low CVP technique.

Low CVP technique is not indicated if total hepatic occlusion is required. Occlusion of the suprahepatic inferior vena cava (IVC) substantially decreases cardiac preload, which is not tolerated if the patient is hypovolemic. Inferior vena cava clamping will require an adequate volume status in addition to vasopressor administration.

Surgical and Anesthetic Techniques to Preserve Liver Function

Frequently, major liver resections will require vascular occlusion to reduce blood loss and optimize the surgical field. Vascular inflow occlusion is often achieved by slinging an umbilical tape around the porta hepatis and then tightening it. This technique is called the Pringle maneuver and disrupts portal venous and hepatic arterial blood flow to the liver. The Pringle maneuver causes ischemic injury to the liver and can therefore only be applied for a limited time. This is particularly important if the liver has underlying disease such as hepatic cirrhosis. Cirrhotic livers are extraordinarily sensitive to ischemic injury. Application of the Pringle maneuver in cirrhotic patients causes significantly higher postoperative elevations of conventional liver function tests compared with noncirrhotic patients.⁴⁴ If possible, the Pringle maneuver should be avoided or its duration minimized in patients with hepatic cirrhosis.

Cholestatic livers are similarly sensitive to ischemic insults as cirrhotic livers. Reversible causes of cholestatic disease should be treated prior to major liver resections.⁴⁵ Stenting and drainage of extrahepatic biliary obstructions and then delay of surgery until resolution of cholestasis can greatly reduce the risk of postoperative liver failure.⁴⁶

Earlier studies in animals⁴⁷ and humans^{48,49} using ischemic preconditioning to ameliorate hepatic injury had been quite promising. For example, Clavien et al randomized 100 patients to 10 minutes of hepatic ischemia followed by 10 minutes reperfusion or no ischemic preconditioning. All patients then underwent major hepatic resection with at

least 30-minute ischemic time. The authors found that patients who had undergone ischemic preconditioning had lower postoperative transaminase levels. This beneficial effect was particularly noticeable in young patients. However, a more recent meta-analysis found a similar decrease in transaminase levels, but no improvement of mortality, liver function, or other morbidity between the groups.⁵⁰ These results were lately confirmed for patients undergoing liver resection with total vascular exclusion (TVE). Jeon et al found no difference in outcome or laboratory markers in patients who received ischemic preconditioning when undergoing major liver resection with TVE compared with patients without ischemic preconditioning.⁵¹ Due to this absence of convincing evidence, we cannot recommend the routine use of ischemic preconditioning.

Selective vascular inflow occlusion may be used by occluding only the right or left branches of the portal vein and hepatic artery. This technique will require a more complex dissection of the porta hepatis, but results in decreased injury to the remaining lobe of the liver and may be a very suitable technique to avoid ischemic injury in patients with preexisting liver dysfunction and cirrhosis.

Total vascular exclusion comprises temporary occlusion of the porta hepatis (e.g., using the Pringle maneuver) and clamping of the IVC both above and below the liver. This results in substantial reduction of right ventricular preload and is usually not tolerated when a low CVP technique is used. Fluid loading prior to IVC clamping is mandatory; additional vasopressors are often required to maintain blood pressure. This is particularly true in patients with underlying liver disease who need a hyperdynamic circulation to compensate for low systemic vascular resistance. Close communication about the surgical plan between the anesthesiologist and surgeon is essential to avoid potentially catastrophic events.

Postoperative Management

Routine Postoperative Management

The perioperative mortality for patients undergoing hepatic resections has vastly improved over the last few decades, and now is 5% or less in high volume centers. The most important factors affecting perioperative mortality are blood loss, the amount of liver resected, and the functional reserve of the remaining liver.⁵² Consideration to these factors during the surgery is essential to guide postoperative management and to achieve favorable outcomes.

In the absence of underlying hepatic dysfunction or significant comorbidities, patients undergoing simple partial hepatectomy may be safely managed in a stepdown unit during the first postoperative day. Because patients with baseline hepatic dysfunction are at increased risk of complications in the immediate postoperative period, we recommend ICU-level care, invasive blood pressure monitoring, and a urinary catheter to measure urine output. Continuous blood pressure monitoring with a radial arterial line is standard, and routine use of a femoral arterial line is usually not required unless an extensive hepatic resection with total vascular exclusion is

expected. Total vascular occlusion, including clamping of the vena cava, causes profound hypotension requiring high-dose vasopressors. This may dampen the tracing of the radial artery catheter; in this situation, a femoral arterial line will continue to provide reliable arterial blood pressure data.

Central line access is usually recommended for major resections to allow rapid administration of fluid, blood, and vasoactive drugs if necessary.

Most patients will not require postoperative ventilatory support; if the patient arrives intubated in the ICU, extubation can proceed rapidly as long as there are no major complications. Large fluid and transfusion requirements, bleeding, and hemodynamic instability may preclude extubation. The patients may require longer ventilatory support if the development of liver failure due to a small liver remnant is suspected. Liver failure will result in decreased lactate metabolism and metabolic acidosis that will require the patient to hyperventilate to maintain a normal pH. It will be safer to support the patient with a ventilator during this time to avoid exhaustion until the metabolic acidosis is resolving.

Fluids and Electrolytes

Patients with cirrhosis have high circulating blood volume requirements and after large abdominal surgery are susceptible to fluid shifts, reaccumulation of ascites, and episodes of hypotension. Colloid fluid administration is effective for bolus resuscitation to rapidly restore intravascular volume. Hypotension refractory to fluid administration should be treated with vasopressors (norepinephrine ± vasopressin) and the cause for hypotension needs to be swiftly investigated. Hypovolemia due to underresuscitation or bleeding are common and may be exaggerated with underlying cirrhotic vasodilation.

An understanding of the intraoperative events, estimated blood loss, and total fluid volume given including blood products will help guide the initial management. Close observation should be paid to achieve adequate end organ perfusion with a goal urine output of > 0.5 mL/kg/h.

Acute kidney injury is common after major hepatic resection with a reported incidence of up to 15%.⁵³ In patients with hepatic cirrhosis, acute kidney injury is often confounded by prerenal azotemia and hepatorenal syndrome (HRS). Hepatorenal syndrome occurs with advanced cirrhosis and results from peripheral and splanchnic vasodilation, leading to decreased renal perfusion, increased sodium reabsorption, and total body volume overload. Inadequate resuscitation and infection predispose to HRS; albumin and vasopressors administration and antibiotics may facilitate clinical improvement.⁵⁴

Drains placed in the abdomen should be observed for signs of hemorrhage or bile leak. The character of the fluid draining should be corroborated with the patient's clinical picture, keeping in mind that drains may have shifted or clogged. The absence of significant drainage does not rule out the presence of bleeding or bile leak. Bile leaks are common and may occur in up to 20% of hepatectomies.

As fluid shifts between vascular compartments, occasionally the judicious use of diuretics can help prevent volume

overload beyond postoperative day 2; though care should be taken to assess the patient's complete clinical picture. Overdiuresis and low circulating intravascular volume can have profound consequences as mentioned above.

Diligent replacement of electrolytes is prudent because nearly all posthepatectomy patients will have some degree of electrolyte abnormalities in the postoperative period. Hypophosphatemia occurs frequently and aggressive repletion is appropriate to prevent deficient energy metabolism manifesting as cardiac or respiratory dysfunction.⁵⁵

Postoperative Hepatic Function

The risk of postoperative hepatic dysfunction in patients with normal underlying liver parenchyma is low as long as sufficient hepatic volume remains. After major resections vigilance and close postoperative monitoring of liver function is essential to identify patients at risk for liver failure. Initial laboratory studies should include a complete blood count, basic metabolic panel, INR, partial thromboplastin time (PTT), hepatic function tests, and lactate level. The INR and lactate levels should be measured frequently; these are the fastest and most sensitive and specific of conventional laboratory markers. Transaminases will initially increase from intraoperative hepatic manipulation, and total serum bilirubin levels may require days to increase. Decreasing arterial lactate levels will help assess adequate hepatic function. Additional signs that the liver is sufficiently functioning include increased blood glucose levels from hepatic gluconeogenesis.

For patients undergoing hepatic artery or portal vein reconstruction, an abdominal Doppler should be obtained to ensure adequate flow and normal velocities. Portal vein thrombosis may present as large volume ascites, encephalopathy, and liver failure and needs to be addressed rapidly. Venous thromboembolism prophylaxis should be weighed against the risk of bleeding. Liver dysfunction is associated with a decrease in pro- and anticoagulant factors and thrombin formation may be normal or even increased even in the presence of increased coagulation parameters.⁵⁶ Low-molecular-weight heparin or unfractionated heparin should be administered if there is no risk of significant bleeding.⁵⁷

Posthepatectomy liver failure (PHLF) has been defined by a 2011 international consensus as the presence of elevated INR and hyperbilirubinemia on postoperative day 5. It is further subdivided into three clinical grades: (1) biological liver failure requiring no change in management, (2) deviation from regular course requiring no invasive therapy, and (3) invasive treatment required. To date, no studies have shown improved survival when treating PHLF, and the only definitive treatment remains orthotopic liver transplantation. Supportive care focuses on identifying and treating the underlying etiology. Institution of antibiotic therapy, identification of vascular compromise or biliary leak, and appropriate nutritional supplementation (30% more in stressed states) are essential elements of management. Encephalopathy should be treated, for example, with lactulose, and mannitol can be utilized to reduce

intracranial hypertension. Clinically significant coagulopathy from thrombocytopenia or elevated INR resulting in bleeding will require administration of clotting factors and blood products. However, we caution against administering clotting factors only to treat elevated laboratory tests in the absence of clinical significant bleeding or prior to invasive procedures.⁵⁸

The Patient with Liver Disease Undergoing Nonhepatic Surgery

Determination of which patients are at risk of liver dysfunction after surgery is not clearly defined. Of note, the available literature of surgical risk in patients with cirrhosis is limited to retrospective investigations. Furthermore, these studies typically involve patients with only mild hepatic dysfunction, limiting their applicability to those most at risk. Clearly, elective surgery is less common for patients who simply will not survive without urgent liver transplantation. However, in those less-acute patients with liver disease, efforts to clearly define operative candidacy have been challenging.

The Child-Turcotte-Pugh (CTP) class can be quickly calculated at the bedside and is the metric often used in the clinical studies, correlating well with mortality. The CTP scoring system is based on the patient's serum bilirubin, albumin, prothrombin time, as well as the severity of ascites and encephalopathy.⁵⁹ The CTP class is often criticized based on the subjective nature for two of its parameters (ascites and encephalopathy) and its broad variation of hepatic function within each class, especially within class B. Nonetheless, mortality rates are predictable following general surgery (CTP-A 10%, CTP-B 30%, CTP-C 76–82%).⁵⁹ The CTP-B or CTP-C patients are not candidates for elective major surgery. The CTP-A patients with significant portal hypertension characterized by thrombocytopenia (i.e., platelets < 100,000), esophageal varices, or elevated portal pressures by invasive monitoring are rarely candidates for elective major surgery, and definitely not candidates for major liver resections.

The model for end-stage liver disease (MELD) was first developed to determine survival after transjugular intrahepatic portocaval shunt (TIPS) procedures. However, in 2002 MELD was identified as a reliable index that could predict short-term mortality rates of liver transplantation candidates.⁶⁰ The MELD score is calculated based on serum bilirubin, serum creatinine, and international normalized ratio. The MELD is more objective than the CTP score and is a good predictor of 30-day mortality in patients with cirrhosis undergoing nontransplant surgery.⁶¹ The postoperative mortality rate in nontransplant patients rises in a linear fashion 1% for each increase in MELD point below 20 and 2% for MELDs above 20.⁶¹ Furthermore, several authors have demonstrated that MELD scores above 14 predict a poor outcome after intraabdominal surgery.^{62–64} Some have also demonstrated that a MELD > 14 is comparable to CTP class C and that MELD scores can correctly predict poor outcomes better than the CTP score (77 vs. 23%).⁶⁴

Summary

Patients with underlying liver disease undergoing hepatic resection face substantial risk of postoperative liver failure. Precise assessment of preoperative liver function and reserve, the extent of resection, and other comorbidities is essential to be able to decide if the patient is a candidate for surgery. The extent of resection can be evaluated using computed tomography or magnetic resonance imaging scans and computer simulations that allow virtual resection prior to surgery.

Comorbidities such as cardiac disease should be assessed according to standard guidelines for non-cardiac surgery such as the American Society of Anesthesiologists / American Heart Association guidelines. Conventional liver function tests are frequently too insensitive to assess liver reserve. Dynamic liver function tests such as ICG clearance may be better suited to detect patients with limited hepatic reserve who may not tolerate major resections. Intraoperative management should aim to reduce further injury to the diseased liver by avoiding hepatic ischemia, volume overload or bleeding. Algorithms may help assess the risk of major resections in patients with underlying liver disease. However, in complex cases, the decision about operability should be made by a team of experienced surgeons, hepatologists, and anesthesiologists.

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