The patient with cirrhosis who presents for non-hepatic surgery

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Introduction

There is significant risk involved in subjecting patients with liver cirrhosis to surgery. Advanced liver disease is associated with systemic dysfunction affecting the cardiovascular, respiratory, renal, gastrointestinal, immunological, haematological, coagulation, endocrine and central nervous systems. Perioperative risk stratification can be very challenging. This is aggravated by the fact that cirrhosis is often indolent and asymptomatic until patients present with complications of the disease.

The word ‘cirrhosis’ is derived from the Greek word kirrhos, meaning tawny, with reference to the tawny yellow hepatic nodules associated with this entity. This phrase was coined in 1819 by Rene Laënnec, famous for his invention of the stethoscope.1 Cirrhosis is defined histologically as a diffuse process in which the normal anatomical lobules are replaced by architecturally abnormal nodules separated by fibrous tissue.2

Organ system involvement

Cardiovascular system. The concept of ‘cirrhotic cardiomyopathy’

Patients with liver cirrhosis have a ‘hyperdynamic’ circulation due to a fall in the systemic vascular resistance. This is offset by an increase in the cardiac output. Patients may appear to have adequate cardiac reserve at rest. However, when subjected to physiological or pharmacological stress they may decompensate. The concept of the ‘cirrhotic cardiomyopathy’ is defined by the presence of one or more of the following:

- Increased cardiac output, but blunted inotropic response to stress.
- Diastolic dysfunction.
- No overt left ventricular failure at rest.
- Electrophysiological abnormalities (chronotropic incompetence and prolonged QT interval).3

Rhythm disturbances in patients with cirrhosis have also been described. These include atrial flutter/fibrillation, as well as ectopic beats.4

Respiratory system involvement

Several unique respiratory pathologies may be associated with cirrhosis and portal hypertension. These include the hepatopulmonary syndrome, portopulmonary hypertension and hepatic hydrothorax. In addition, other factors contributing to respiratory compromise may include pre-existing COPD, tense ascites and muscle wasting.

The hepatopulmonary syndrome

This condition is defined by the triad of widened A-a gradient (more than 20 mmHg) while breathing room air, portal hypertension and the presence of intrapulmonary vascular dilatation.5 This condition is the result of dilatation of the precapillary and capillary vessels leading to ventilation-perfusion mismatch. In addition, there is impairment of hypoxic pulmonary vasoconstriction. The combination of the aforementioned factors leads to the classic manifestations of orthodeoxia and platypnoea (a drop in arterial oxygenation with dyspnoea when an upright posture is adopted).6 Currently, there is no pharmacological treatment for the hepatopulmonary syndrome. Liver transplantation is the only viable option. Five-year survival for patients with the hepatopulmonary syndrome without liver transplantation is 23%.7

Portopulmonary hypertension (PPHTN)

The cause of PPHTN has not yet been clearly elucidated. Of interest is that the development of PPHTN has no correlation with the severity
of the liver disease. Proposed mechanisms include increased levels of endothelin-1 (a potent pulmonary vasoconstrictor). Other vasoactive molecules may shunt past the liver directly to the lungs. These include angiotensin 1, thromboxane B2 and prostaglandin F\(_2\alpha\). Assessment of right ventricular function is essential in patients in the preoperative period who have evidence of PPHTN. Pharmacological treatment options include prostenoids (epoprostenol), endothelin receptor blockers (bosentan) and phosphodiesterase-5 inhibitors (sildenafil).

**Hepatic hydrothorax**

Hepatic hydrothorax is defined as the presence of ascitic fluid in the pleural space in the absence of underlying primary cardiorespiratory pathology. The proposed mechanism is the movement of ascitic fluid through very small defects in the diaphragm into the pleural space. Right-sided disease predominates. Management of hepatic hydrothorax can be challenging as the condition is typically recalcitrant. Failure of medical therapy may require transjugular intrahepatic portosystemic shunting (TIPS) or video-assisted thoracoscopic (VATS) repair of diaphragmatic defects.

**Renal involvement and the hepatorenal syndrome (HRS)**

Renal dysfunction in patients with cirrhosis is often multifactorial (intravascular volume depletion, shock, sepsis, concomitant use of nephrotoxic drugs). However, they can uniquely develop the hepatorenal syndrome, a diagnosis largely made by exclusion.

**Table I: Diagnostic criteria HRS**

| Grade | Criteria |
|-------|----------|
| 0     | Minimal encephalopathy, lack of detectable changes in personality. No asterixis. |
| 1     | Trivial lack of awareness, shortened attention span, sleep disturbance, slowing ability to do mental tasks. Asterixis may be present. |
| 2     | Lethargy, apathy, disorientation to time. Amnesia of recent events. Slurred speech. Asterixis present. |
| 3     | Somnolence, confusion, disorientation to place, clonus, nystagmus, positive Babinski sign. Asterixis usually absent. |
| 4     | Coma, lack of verbal, eye and oral response to stimuli. |

Splanchnic vasodilatation leads to a decrease in blood pressure and circulating blood volume. This results in activation of the renin-angiotensin system and sympathetic stimulation, which in turn gives rise to renal vasoconstriction and a reduced GFR. There are two types of HRS.

**Type I HRS.** This is a rapidly progressive form characterised by a doubling in serum creatinine to a level above 221 \(\mu\)mol/L in less than two weeks and is often triggered by a septic insult (typically spontaneous bacterial peritonitis).

**Type II HRS.** This typically has a slower progression, characterised by refractory ascites and sodium retention.

The prognosis of type I HRS is particularly poor with an average median survival time of approximately three months. Liver transplantation is the treatment of choice for both type I and type II HRS. Pharmacotherapy includes the vasoconstrictor terlipressin (1 mg 4-6 h IVI) in combination with albumin (1 g/kg/day). Preoperative evaluation of electrolyte and renal function is essential. A serum sodium level of < 126 mEq/L is a strong independent predictor of mortality.

**Hepatic encephalopathy**

This phenomenon, the pathophysiology of which is complex and partly understood, is a potentially life-threatening complication of liver failure.

**Table II: The West Haven criteria for altered mental status in hepatic encephalopathy**

| Grade | Criteria |
|-------|----------|
| 0     | Minimal encephalopathy, lack of detectable changes in personality. No asterixis. |
| 1     | Trivial lack of awareness, shortened attention span, sleep disturbance, slowing ability to do mental tasks. Asterixis may be present. |
| 2     | Lethargy, apathy, disorientation to time. Amnesia of recent events. Slurred speech. Asterixis present. |
| 3     | Somnolence, confusion, disorientation to place, clonus, nystagmus, positive Babinski sign. Asterixis usually absent. |
| 4     | Coma, lack of verbal, eye and oral response to stimuli. |

The proposed pathophysiology of hepatic encephalopathy lies in altered metabolism of ammonia, neurotransmitters (glutamate, glutamine and serotonin) and other intermediary metabolites (lactate and pyruvate). Endogenous benzodiazepine-like substances working on GABA receptors may also play a role. Precipitating/aggravating factors should be avoided during the perioperative period. These include gastrointestinal bleeding, excess dietary protein, hyponatraemia, hypokalaemia, hypoxia, sepsis and benzodiazepines. Serum ammonia levels should be investigated in patients with suspected hepatic encephalopathy. Therapy with lactulose, which reduces intestinal ammonia production,
and enteral antibiotics (rifamixin/neomycin) have in some studies been shown to improve outcome.\textsuperscript{15}

**Effects of liver disease on haemostasis**

Traditionally, coagulopathy from liver disease has been a major contributor to perioperative complications. However, recent evidence has shown that a significant number of patients develop venous thrombosis due to a net rebalance of procoagulant/anticoagulant systems.\textsuperscript{16} Both the primary and secondary haemostatic pathways are affected in a number of ways:

- **Clotting factors.** The liver is the site of synthesis of all coagulation factors, although some, including F VIII are also synthesised at extrahepatic sites.
- **Alterations in the fibrinolytic system.** Impaired synthesis of thrombin activatable fibrinolysis inhibitor (TAFI) and \(\alpha_2\)-antiplasmin. Reduced clearance of tissue plasminogen activator.
- **Platelet abnormalities**
  - Thrombocytopenia from reduced megakaryopoiesis and splenic sequestration.
  - Thrombocytopathy from defective platelet activation, renal impairment and sepsis.

Status of the coagulation system will impact on the suitability of neuraxial techniques in patients with cirrhosis. Global coagulation assays such as the thromboelastograph (TEG) may better reflect the dynamic effects of the procoagulant, anticoagulant, platelet and fibrinolytic pathways.\textsuperscript{17} Preoperative platelet count and INR should routinely be obtained.

**Perioperative risk stratification in patients with liver cirrhosis**

It is estimated that up to 10% of patients with advanced liver disease will undergo surgery in the last two years of their lives. Two risk stratification scores have been designed to assess perioperative risk in patients with chronic liver disease – the Child Pugh Turcotte classification and the Model of End-Stage liver disease (MELD) score.

Two studies, separated by 13 years, showed almost identical results with respect to perioperative mortality in patients undergoing abdominal surgery: 10% for class A, 30% for class B, 76-82% for class C.\textsuperscript{18, 19}

The MELD score formula incorporates s-creatinine, bilirubin and INR. A study by Teh and colleagues\textsuperscript{20} showed an almost linear increase relative risk of death in patients with a MELD score > 8. Cardiac surgery, emergency surgery and open abdominal surgery had particularly poor outcomes.

**Specific anaesthetic considerations**

Careful evaluation of the aforementioned systems with relevant special investigations needs to be obtained. It should be noted that transaminase levels (AST, ALT) are often normal or only moderately raised even in patients with significant cirrhosis.\textsuperscript{21} Preparation should include correcting coagulopathy, addressing encephalopathy, preventing sepsis and optimising renal function.\textsuperscript{22} The decreased baseline hepatic perfusion makes the cirrhotic liver more susceptible to hypoxic and hypotensive episodes in the perioperative period. Anaesthetic agents may reduce hepatic blood flow by 30-50%. Halothane should be avoided as it has the most deleterious effect on splanchic blood flow. Desflurane, sevoflurane and isoflurane are the preferred volatile agents.

Cirrhosis can lead to significant pharmacokinetic and pharmacodynamic disturbances. This is often aggravated by concomitant renal dysfunction. Reduced albumin and \(\alpha_2\)-acid glycoprotein synthesis may lead to an increase in the unbound fraction of drugs. Water-soluble drugs will have an increased volume of distribution (Vd) in patients with ascites, possibly necessitating a larger loading dose. Alteration in blood-brain-barrier permeability and increased GABA-ergic tone may explain the increased sensitivity to opioid analgesics, anxiolytics and sedatives.\textsuperscript{23}

Propofol is a suitable induction agent, provided the blood pressure is maintained. Atracurium and cisatracurium are the muscle relaxants of choice because neither the liver nor kidney is required for their elimination. Due to their increased Vd, larger

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**Table III:** The Child Pugh Turcotte classification (CPT)

|                      | 1 point | 2 points | 3 points               |
|----------------------|---------|----------|------------------------|
| Encephalopathy       | Absent  | Medically controlled (I-II) | Poorly controlled (III – IV) |
| Ascites              | Absent  | Medically controlled       | Poorly controlled           |
| Bilirubin (mg/L)     | < 20    | 20 - 30 | > 30                   |
| Albumin (g/L)        | > 35    | 28 - 35 | < 28                   |
| INR                  | < 1.7   | 1.7 – 2.2 | > 2.2                |

CPT class A (5-6 points), CPT class B (7-9 points), CPT class C (10 -15 points).
doses may be required. The pharmacokinetic disposition of remifentanil, fentanyl and sufentanil appear to be relatively unchanged.

**Monitoring and fluid administration**

Tight control of blood pressure is mandatory, so invasive monitoring is required for most procedures. The use of cardiac output monitors is appropriate for major surgery, or for patients with significant cardiac decompensation. TEE has the advantage of real-time dynamic evaluation of cardiac function, as well as assessing response to fluid administration. Traditionally, pulmonary artery catheters with thermodilution technique have been used to determine the cardiac output. The use of uncalibrated pulse contour analysis such as the Vigileo™ system may be inaccurate. A recent study showed that in cirrhotic patients with hyperdynamic circulation, the Vigileo™ system showed a degree of error and unreliability higher than that considered acceptable for clinical purposes.

Management of intraoperative fluid status can be challenging. There is a tendency for expansion of the extravascular compartment. Colloid solutions, in particular albumin, may be more effective in these patients. There is evidence that albumin may negate the haemodynamic disturbances associated with large volume paracentesis, as well as having a role in the management of the HRS as alluded to earlier.

**Conclusion**

Patients with liver cirrhosis pose significant challenges to the anaesthetist. The morbidity and mortality of this condition bears testimony to the seriousness of this disease. Careful evaluation of all the organ systems that may be affected needs to be conducted. Protection of the compromised liver during the perioperative period is essential.

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