Liver Disease and Anesthesia

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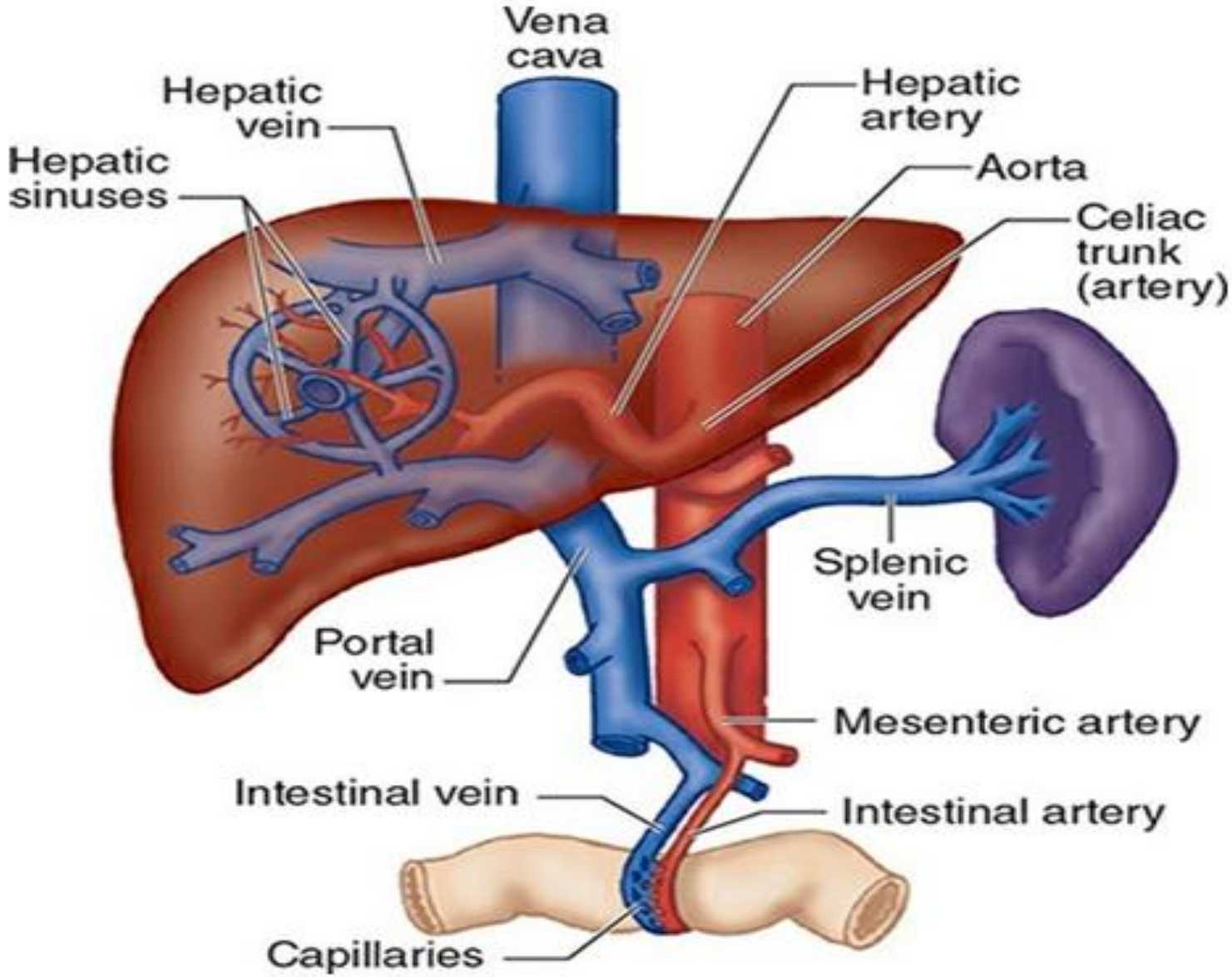
- The liver is a **large, complex organ with multiple functions**.
- Patients with liver failure present **a significant challenge to the anesthetist**.
- A good understanding of normal liver physiology, causes of liver dysfunction, and its multi-system impact on patient function are very important in managing these patients.
- The liver is the heaviest and largest organ in the body, weighing approximately 1500 g in adults.
- It is separated **by the falciform ligament** into right and left anatomic lobes.
- The liver is made up of 50,000 to 100,000 discrete anatomic units called **lobules**.
- Hepatic arterial flow is dependent **on metabolic demand (autoregulation)**, whereas **flow through the portal vein is dependent on blood flow to the gastrointestinal tract and the spleen**


Vena cava
Hepatic vein
Hepatic sinuses
Hepatic artery
Aorta
Celiac trunk (artery)
Splenic vein
Portal vein
Mesenteric artery
Intestinal vein
Intestinal artery
Capillaries

Hepatic function:

- **Metabolic:** metabolism of carbohydrate, lipid, amino acid, ammonia formation, interconversion of sugars and metabolism of drugs
- **Regulation of blood glucose**
- **Synthesis of protein and clotting factors**
- **Secretory**: secretion of bile in the intestine, and conjugation of bilirubin.
- **Detoxification**: detoxification of drugs, steroids, thyroid hormones, and endogenous metabolites.
- **Storage**: storage of glycogen, B12, iron, and vitamin A

Hepatic blood flow

- 20% of cardiac output

Hepatic artery

- 30% of hepatic blood flow
- 90% of oxygen deliver

Portal vein

- 70% of hepatic blood flow
- 10% of oxygen deliver

Anesthetics can alter hepatic perfusion by altering blood flow through either the hepatic artery, portal vein, or both

Serum Bilirubin

- The normal total bilirubin concentration, composed of conjugated (direct), water soluble, and unconjugated (indirect) lipid-soluble forms, is less than 1.5 mg/dL (<25 mmol/L) and reflects the balance between bilirubin production and excretion.
- Jaundice is usually clinically **obvious when total bilirubin exceeds 3 mg/dL.**
- A predominantly **conjugated hyperbilirubinemia** may reflect hepatocellular dysfunction, congenital or acquired intrahepatic cholestasis, or extrahepatic biliary obstruction
- **unconjugated** may be seen with hemolysis or with congenital or acquired defects in bilirubin conjugation.
- **Unconjugated bilirubin** is neurotoxic, and high levels may produce encephalopathy

Serum Aminotransferases (Transaminases)

- These enzymes are released into the circulation as a result of **hepatocellular injury or death**.

- **Two types:**
  - **aspartate aminotransferase (AST), also known as serum glutamic-oxaloacetic transaminase (SGOT)**
  - **alanine aminotransferase (ALT), also known as serum glutamic pyruvic-transferase (SGPT).**

Serum Alkaline Phosphatase

Serum Albumin

- The normal serum albumin concentration is **3.5 to 5.5 g/dL.**

- Because its **half-life is approximately 2 to 3 weeks**, albumin concentration may initially be normal with acute liver disease.

- Albumin values **less than 2.5 g/dL** are generally **indicative of chronic liver disease, acute stress, or severe malnutrition**.

Blood Ammonia

- Significant elevations of blood ammonia levels usually reflect disruption of hepatic urea synthesis.
- **Normal levels are 47 to 65 mmol**/L (**80–110 mg/dL**).
- Marked elevations usually reflect **severe hepatocellular damage and may cause encephalopathy**.

Prothrombin Time (PT)

- normally ranges **between 11 and 14 s**, measures the activity of fibrinogen,prothrombin, and factors V, VII, and X.
- The relatively **short half-life of factor VII (4–6 h)** makes the PT useful in evaluating the hepatic synthetic function of patients with acute or or chronic liver disease
- Prolongations of the PT **greater than 3 to 4 s** from the control are considered significant and usually correspond to an INR greater than 1.5.

Liver function test

- The most commonly performed liver tests are neither sensitive nor specific.
- No one laboratory test evaluates overall hepatic function Many “liver function” tests, such as serum transaminase measurements, reflect hepatocellular integrity more than hepatic function.
- Liver tests that do assess hepatic synthetic function include **serum albumin, prothrombin time (PT) or international normalized ratio (INR), serum cholesterol**, and **plasma pseudocholinesterase.**

- Moreover, because of the liver's large functional reserve, substantial cirrhosis may be present with few or no laboratory abnormalities evident.

- Liver abnormalities can often be divided into **either parenchymal disorders or obstructive disorders** based on laboratory tests.
- Obstructive disorders **primarily affect the biliary excretion of substances**, whereas **parenchymal disorders result in generalized hepatocellular dysfunction**
- LFTs measure the concentrations of various proteins and enzymes in the blood that are either produced by liver cells or released when liver cells are damaged.
- divided to Tests of liver function, of cell injury, of biliary obstruction

Prothrombin time (PT)

- Is a measure of the extrinsic pathway of coagulation, it measures factors I, II, V, VII and X.
- **Prolongation** can reflect **deficiencies of vitamin K** relating to impaired absorption from poor quality bile production or abnormalities in factor VII synthesis, both relating to liver dysfunction.

Albumin

- is synthesized in the liver; low serum albumin may reflect liver dysfunction.
- Hypo-albuminemia also occurs in malnutrition, nephrotic syndrome, malabsorptive states and late pregnancy.

Tests of cell injury

- Alanine Amino Transferase (ALT) and Aspartate Amino Transferase (AST) These tests are used to detect liver cell damage, however there is no correlation between levels and degree of damage.
- Elevated ALT and AST out of proportion with the enzymes indicative of biliary obstruction, suggests an intra-hepatic problem.

Tests of biliary obstruction

- Bilirubin is elevated by any of the following:
  - hemolysis,
  - biliary stricture,
  - hepatitis,
  - cirrhosis,
  - drugs (e.g., antipsychotics and sulphonamides)
  - Gilberts syndrome.

Jaundice of the sclera becomes noticeable when **serum levels 2-3 mg/dl**, jaundice of the skin indicates even higher levels.

Alkaline Phosphatase (ALP)

- is present in all tissues throughout the body.
- ALP is elevated in biliary obstruction, pregnancy and as a by-product of osteoblast activity eg Paget's disease.

Tests of biliary obstruction

- Gamma Glutamyl Transpeptidase (GGT) is present in the cell membrane of many tissues.
- Elevation is seen in liver, biliary system and pancreatic disease.
- Isolated elevation may also suggest significant alcohol ingestion.
- GGT is elevated by several drugs including barbiturates, phenytoin, St John's Wort and non steroidal anti-inflammatory drugs (NSAIDs).
- Elevation is also seen in congestive cardiac failure (CCF)

- Liver disease has a spectrum of severity from subclinical disease to end-stage liver disease
- The range of symptoms a patient has depends on whether the disease presentation is acute or chronic.
- Worldwide the major cause of liver disease **is viral infection and paracetamol overdose.**

Diagnosis of hepatic insufficiency

- ❑ Ascites and distended abdomen
- ❑ Enlarged liver
- ❑ Depression
- ❑ Seizures
- ❑ Weight loss
- ❑ Jaundice
- ❑ Laboratory analysis ▪ Liver enzymes ▪ increased bleeding time ▪ bile acids

- The hepatic dysfunction patients may have **one or all of the following conditions**:

  - Hypoproteinemia
  - Hypoglycemia
  - Bleeding problem
  - Slow to metabolize anesthetics

ACUTE LIVER FAILURE

- ranges from non-specific nausea and abdominal discomfort to confusion, agitation and coma.
- Diagnosis:
  - **abnormalities of liver function tests and coagulation**.
  - **Encephalopathy:**

Hepatic encephalopathy is due to the accumulation of toxic products of protein breakdown and gut bacterial metabolism. When the liver is unable to clear these substances, it can result in elevated ammonia.

Acute liver failure is defined as the rapid **development of**:

1. jaundice,
2. coagulopathy, and
3. encephalopathy, in a patient without prior liver disease.

Common causes of acute liver failure are paracetamol overdose and viral hepatitis.

Chronic liver disease

- The chronic liver disease involves a disease process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis.

- **Common causes include**
  - viral hepatitis B and C, and
  - toxins such as alcohol.

  - **The common complications of chronic liver disease** such as **ascites, hyper-splensism and a collateral venous circulation producing lower oesophageal and gastric varices, all result from portal hypertension**.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH LIVER DISEASE

- **Renal**: renal Impairment is most commonly due to dehydration, sepsis, or nephrotoxic drugs.
- **Hepatorenal syndrome**: the reduced GFR and consequent decline in renal function caused by advanced liver disease.
- **Hepatopulmonary syndrome**: This occurs when intrapulmonary vascular dilations contribute to hypoxia in liver disease.
- **Encephalopathy:** toxic metabolites build up (particularly ammonia), leading to progressive encephalopathy.
- **Hematological changes**: *Anemia may be present secondary to blood loss, hemolysis, bone marrow depression, or nutritional deficiency*.
- Coagulopathy is one of the primary features of advanced liver disease with the liver having a central role in the synthesis of almost all coagulation factors.

ANAESTHESIA IN PATIENTS WITH LIVER FAILURE

- The risks of anesthesia in this group are related to where the patient lies on the liver disease spectrum, from subclinical to endstage liver disease.
- Optimal preparation may decrease both perioperative death and postoperative complications.
- Pre-operative assessment :
- Common preoperative investigations to assess liver disease include:
- 1) Full blood count: to establish anemia, thrombocytopenia, or evidence of infection.

- **Coagulation profile**:
  - bleeding time, clotting time, prothrombin time (PT).
  - Prolongation of PT indicates severe liver disease unless vitamin K deficiency is present.
  - Failure of PT to correct following parenteral administration of vitamin K implies severe liver disease and correction requires 24 hours.
  - Prothrombin time (PTT): as an indicator of hepatocellular function

- Renal function and electrolyte.
- ECG and Echocardiography.
- Chest x-rays and pulmonary function tests.
- Liver function tests and Hepatitis screening.

premedications

- ❑ Depressed patients may **not need preanesthetic premedication**.
- ❑ Avoid premedication in severely **debilitated patients**.
- ❑ Prolonged drug effect - prolonged recovery.
- ❑ Agents of choice:
- ➢ **opioids +/- anticholinergics**.
- ➢ Morphine – delayed elimination d/t reduced hepatic blood flow & extraction ratio May precipitate hepatic encephalopathy in pt – decompensated liver failure
- ➢ Fentanyl – low dose (no active metabolites & renally excreted If repeated / large dose – will accumulate
- ➢ Alfentanil – elimination reduce

- Remifentanil – ideally suit intraoperatively
- Metabolize by tissue & plasma esterase
- Opioids reversible with opioid antagonists

Conduction of anesthesia

- **Elective surgery** only in well compensated liver failure
- Emergency – Initial resuscitation important for emergency surgery. Emphasis on:-

1.Wide-bore IV cannulae for fluid resuscitation.

2. GXM blood products.

3. Invasive monitoring.

4. High risk consent.

Optimizing the medical problem:

- If PT > 1.5 times control – FFP
- Platelet < 50000 – platelet transfusion
- Fibrinogen < 1.0 g/l – cryoprecipitate
- Recombinant factor VIII – prophylaxis 7 therapeutic

- **Correct electrolytes** o Hyponatremia; fluid restriction
- Anaemia – blood transfusion, aim for 10g/dl

- Sedative premed – avoided
- H2 receptor antagonist : ranitidine
- Ascites :Paracentesis – massive ascites compromising the ventilation.
- Spirinolactone (Aldactone)
- Dietary sodium restrictions
- Encephalopathy -Reduce nitrogen load Lactulose Neomycin Protein restriction

Anesthetic technique depends on

- general status of patient and extent of surgery.
- Central neural blockade contraindicated in patients with coagulopathy.
- GA with RSI preferred in emergency situations.
- Reduced and titrating doses of induction agent in hepatic encephalopathy or CVS compromise.

Intraoperative Management

- ❑ Intraoperative monitoring
- ➢ ECG and CVP
- ➢ Invasive and non-invasive BP MAP should be maintained within 10–20% of preoperative levels.
- ➢ Pulse oxymetry
- ➢ End-tidal CO2
- ➢ Peripheral nerve stimulator
- ➢ Urine output
- ➢ Temperature
- ➢ Blood sampling for arterial gases, serum electrolytes & blood glucose

Induction

- Preoxygenation of 2-3 minutes prior to induction to prevent hypoxemia.
- Face mask induction with inhalation agents (isoflurane or sevoflurane)
- (note that 99% of isoflurane is eliminated from respiration and not the liver).
- Desflurane has the advantage of being the least metabolized and providing the quickest emergence.

Induction agent –

- titration of dose to avoid hypotension more important than the particular drug
- Increased sensitivity to benzodiazepines

- **Thiopental**- dose should be reduce d/t reduce plasma proteins – increase unbound protein & prolong duration of action
- **Propofol** – is the most commonly used (extra-hepatic metabolism but increases sensitivity to sedative & cardiorespiratory depressant so the dose should be reduced.
- **Etomidate** – safely but little advantage over thiopental.
- s**uxamethonium** may have a prolonged duration of action due to reduced pseudocholinesterase concentrations slowing its metabolism
- **Vecuronium and rocuronium** have a prolonged elimination phase in severe disease.
- **Atracurium and cisatracurium** are better options as they are not reliant on hepatic excretion.

Intraoperative management

- Good oxygenation, normocarbia, stable heamodynamics to preserve liver perfusion.
- High FiO2 in Prescence of intrapulmonary shunting.
- Adequate fluid replacement with colloids and crystalloids.
- Maintain renal perfusion to prevent hepatorenal syndrome.
- Monitor blood sugars with dextrostix to prevent hypoglycaemia.
- Early replacement of blood products.
- Citrate toxicity treated with IV CaCl2

Maintenance and supportive therapy

- ❑ Isoflurane and sevoflurane are better choice for maintenance.

Liver blood flow:

- ➢ **biggest reduction** with halothane and enflurane
- ➢ **May increase with isoflurane**
- ➢ **Little change with sevoflurane**
- ➢ **Avoid halothane**: higher metabolism and incidence of malignant hepatitis
- ➢ **Portal vein blood flow decreases** but **portal arterial blood flow increases during isoflurane administration**..

- **Therefore isoflurane** is **better choice as it can deliver more oxygen to the hepatic tissue.**
- **Lactated Ringer's solution with 5% dextrose** if plasma glucose level is less than 70 mg/dl.
- **In cases with albumin levels less than 2 g/dL, supplemental colloids such as plasma, dextran, or hetastarch are administered to increase plasma oncotic pressure**.
- **Avoid fluid overloading-**--less protein – and more susceptible to pulmonary edema

Anesthetic management of hepatic dysfunction patients

Potential problems	*Management*
Low hepatic blood flow	• Avoid deep anesthesia • Maintain blood volume and blood pressure • Monitoring oxygenation and prevent hypoxemia by administering 100% oxygen
Prolonged recovery from anesthesia	• Use propofol induction or isoflurane mask induction • Reverse opioids if necessary • Use short half-life drugs.
Hemorrhage	• Pre-treat with vitamin K • Fresh whole blood transfusion • Give plasma to prevent clotting problem
Hypoglycemia	• Give 5% dextrose and other glucose supplements

Recovery and Postoperative considerations:

- Allow recovering in a warm environment
- Under constant surveillance until fully recovered.
- Reverse opioids (with **naloxone or partial reversal with butorphanol) and benzodiazepines (with flumazenil**) if necessary.
- Keep patients warm and observe for bleeding.
- Closely monitor for signs of potential intra-abdominal bleeding .
- Portal hypertension can cause severe discomfort as well as hemodynamic instability.

Analgesia and symptomatic therapy

- Patients with advanced liver disease will need postoperative intensive care.
- **To prevent encephalopathy**, constipating analgesics, such as opioids, should be prescribed with concurrent lactulose.

- **Postoperative ileus** may also precipitate encephalopathy in cirrhotic patients.

- **Complications include** ***delayed wound healing, sepsis, renal impairment, and bleeding.***
- Fluid balance should be carefully monitored postoperatively, aiming for a **urine output of 1mL/kg/h.**
- Coagulopathy increases the risk of postoperative bleeding and hematoma formation.

Post operative pain relief can be challenging.

- **The role of regional techniques is very much restricted** by the high incidence of coagulation defects.
- Placement of epidural catheters should be undertaken with **caution and with careful consideration** to timing of catheter removal.
- Similarly, **intra-muscular and subcutaneous injections can lead to haematoma formation and should be avoided.**
- **Non-steroidal anti-inflammatory medications and their association with increased risk of GI bleeding**, platelet dysfunction and nephrotoxicity mean they are often avoided.

- **Paracetamol** is sometimes used in this patient group, depending on the origin of their liver dysfunction, but this should be done with caution and appropriate monitoring implemented

- **Fentanyl PCA is generally well tolerated**, but accumulation can occur over time and the patient needs to be nursed in an appropriate facility,
- morphine PCA can also be used but a lower bolus dose may be needed, again to avoid accumulation.

Other drugs Associated with liver dysfunction:

- **Valproate, amitriptyline, carbamazepine**
- Tramadol - said to be safe with mild hepatic impairment
- **Local anaesthetics** – amides will have delayed elimination and accumulate

- Paracetamol if severe liver failure – avoid

Thank you

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