Hepatic Resection Surgeries: Perioperative Management and Prevention of Ischaemia Reperfusion Injury- An Anesthesiologist's Perspective

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Abstract: *Improvements in the understanding of liver anatomy, patient selection, and also surgical and anaesthetic techniques have contributed to a reduction in perioperative mortality although patients with parenchymal liver disease (e.g. cirrhosis) have significantly higher rates of complications and mortality. This decline in postoperative mortality after hepatic resection has encouraged surgeons for more radical liver resections, leaving behind smaller liver remnants in a bid to achieve curative surgeries. But despite advances in diagnostic, imaging and surgical techniques, postoperative liver dysfunction of varied severity including death due to liver failure is still a serious problem in such patients. In this paper, the anesthetic considerations during hepatic vascular occlusion techniques are reviewed along with special emphasis on ischaemic and pharmacological preconditioning which can be easily adapted clinically.*

I. Introduction

The first ever recorded liver resection was performed in Germany by Carl von Langenbuch in 1887, who removed a pedunculated tumour from the left lobe of a thirty year old woman. Despite major haemorrhage, she survived. Advances in anaesthetic and surgical management of patients undergoing liver resection have lead to a significant reduction in perioperative risk. The techniques of vascular control during hepatectomy are highly demanding and should be performed under special anesthetic considerations.

II. Liver Anatomy

The liver is highly vascular, receiving a total blood flow of 1.5 litre/ min, of which 80% is supplied by the portal vein and 20% from the hepatic artery. The liver can be divided into five sectors and further sub-divided into eight functional segments (Fig. 1), described by their blood supply and biliary drainage. The portal vein divides successively to supply each liver segment, reflecting similar divisions of the hepatic artery and bile duct. Segmental portal and hepatic arterial blood supply and biliary drainage are unique, so contiguous segments can be resected without disrupting the vascular supply to neighbouring tissue.
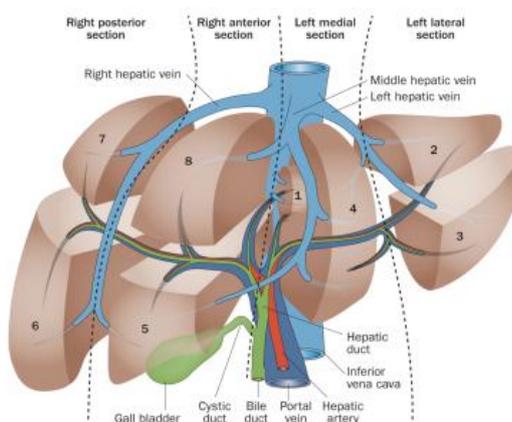
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Figure 1

The liver is metabolically very active providing a number of essential functions including carbohydrate and lipid metabolism, protein synthesis such as coagulation factors and albumin, and the breakdown of various hormones and drugs. Despite this, it is an incredibly resilient organ, tolerating up to two-thirds of its mass being resected without leading to liver failure. It can also regenerate. Liver regeneration occurs by hyperplasia of the remnant. Liver cells can replicate within 24 hours, and discovery of this fact has made modern day liver surgery a reality.[1-3]

III. Preoperative Assessment

Healthy patients undergo a routine preoperative assessment including a full blood count and a standard biochemical and coagulation test. The ASA and Child pugh scoring system (table 1) have been used previously but a newer multivariate analysis of assessing the perioperative mortality after general surgery in cirrhotic patients have been described (table 2). In this, the risk factors are additive.[1]

Table 1

Child-Pugh Scoring System

Points	1	2	3
Ascites	None	Small or diuretic controlled	Tense
Encephalopathy	Absent	Mild	Significant
Albumin (g/L)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2	2-3	>3
PT (sec > control) or	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

INR, International normalized ratio; PT, prothrombin time
Class A: 5 to 6 points; class B: 7 to 9 points; class C: 10 to 15 points

Preexisting hepatic impairment is a risk factor, even for nonhepatic surgery, with higher blood transfusion requirements, a longer hospital stay, a higher number of complications, and increased mortality rates of 16.3% in cirrhotic patients as compared to 3.5% in controls.[2,3] Estimating the health status of patients presenting for hepatectomy is quite challenging: coagulopathy, volume and electrolyte disturbances, viral infections (Hep C), hepatorenal and hepatopulmonary syndrome, portopulmonary hypertension, and low cardiovascular reserve capacity can occur in patients with chronic liver disease.[1,4] Although vascular occlusion techniques have minimized hepatic bleeding, the risk for postoperative liver and/or renal failure remains high for patients of advanced age and those with steatosis and cirrhosis, on preoperative chemotherapy and with small remnant liver volumes.[5]

Vascular control techniques during hepatectomy require optimization of the cardiac and pulmonary function.[1,6] Hepatic ischemia and reperfusion on subsequent liver dysfunction is associated with unexpected responses to surgical stress and poor prognosis.[7] Patients with endstage liver disease have a characteristic hemodynamic profile: increased cardiac output with blunted response to painful stimuli, splanchnic vasodilatation and central hypovolemia. As a result, silent moderate-to-severe coronary artery disease cannot be easily recognized.[1,8]

Preoperative invasive assessment of preexisting cardiovascular dysfunction is indicated only for high risk patients, provided that any coagulopathy is corrected.[4] Furthermore, beta blockade discontinuation in order to permit adequate cardiac function assessment may be hazardous in patients with advanced liver disease.[9] Beta blockers reduce portal hypertension, decrease cardiac workload, and their use seems to be beneficial to both the liver and the heart in the setting of hepatectomy.

Table 2

Multivariate associations with the presence of complications in Ziser and colleagues' study			
Risk factors	Morbidity rate (%)	30 day mortality rate (%)	6 month mortality rate (%)
Pugh score: 7-10	42	15	31
Ascitis	48	20	39
High creatinine concentration	42	21	36
Chronic pulmonary disease	41	18	29
Preoperative infection	74	49	60
Upper gastrointestinal bleeding	70	12	23
ASA IV-V	68	32	52
Major surgery	39	12	23
Intraoperative low blood pressure	45	15	26
Cryptogenic cirrhosis	33	14	24

Indications

Lesions requiring resection may be benign or malignant. Approximately 10% of liver resections are for benign lesions and 90% are for malignant. Of the latter 20% are primary and 80% metastatic. By far the most common indication for liver resection surgery is for metastatic spread of colorectal cancer. The most common primary liver carcinoma is hepatocellular carcinoma which accounts for around 80% of lesions.[9-11] The second most common is cholangiocarcinoma, which usually arise from the bile duct and can present with pain and jaundice. Liver cirrhosis is not an absolute contraindication to resections although it does limit the ability for the liver to regenerate, and these patients will be more at risk of postoperative complications.[4,15] However other techniques can be used to avoid the more invasive surgery such as image guided, percutaneous ablative techniques.[14]

IV. Intraoperative Haemodynamic Monitoring

Central venous line pressure monitoring-
CVP monitoring is not reliable during liver resection. During liver resection, the pressure of the surgical retractors on the diaphragm increases the intrathoracic pressure and consequently increases the CVP. Clamping of liver vessels reduces the venous return of blood to the heart and therefore decreases CVP.[1,16] In addition central venous catheters are longer than peripheral venous cannulae and cause a higher resistance to fluid flow. Consequently, blood transfusion is more easily performed through a peripheral cannula than through a central venous catheter. Moreover, measurement of CVP is not needed to guide intraoperative fluid infusion or to keep the systemic arterial pressure as low as haemodynamically tolerated and therefore to limit blood loss during parenchymal sectioning. Finally should massive bleeding occur, the major criteria for blood volume expansion are the adequacy of systemic arterial pressure and expired CO2 plus the adequacy of waveform of peripheral pulse oximetry curve.[1,4,17]

Transoesophageal Echocardiography- Best assess the volume status, left ventricular function , kinetic abnormalities and afterload indices.[4]

Arterial Catheter- A must for long lasting procedures or circulatory impairements. It allows frequent blood samples to be taken and displays systemic arterial pressure continuously.[4,18]

V. Induction And Maintainence

General Considerations-
All patients require general anaesthesia with endotracheal intubation as standard. As there is potential for massive sudden blood loss, large-bore venous access must be secured. Temporary dialysis catheters (vascath) and pulmonary artery introducer sheaths have even been used.[19] Patients with ascites undergo rapid sequence induction.[19,20] Cis-atracurium is the nondepolarizing muscle relaxant of choice in patients with liver disease as it is hydrolyzed by Hoffman elimination. Moreover, it is haemodynamically stable due to its scarce release of histamine.[1,4] Atracurium can provide stable neuromuscular blockade, as its requirements remained unchanged during exclusion of the liver from the circulation.[1,21] Hepatic vascular control techniques depress cardiovascular function in addition to the depression caused by general anesthesia. Most commonly used volatile anesthetics for maintenance are isoflurane and sevoflurane. Isoflurane has mild cardiodepressive effects but maintains hepatic oxygen supply, due to vasodilatation in the hepatic artery and portal vein.[22] Beck-Schimmer et al., in a randomized controlled trial on patients undergoing liver surgery, showed that ischemic preconditioning with sevoflurane before inflow occlusion limited postoperative liver injury, even in patients with steatosis.[23] Desflurane appears to have no greater liver toxicity than currently used volatile anesthetic agents. Additionally, desflurane undergoes only minor biodegradation (it is metabolized at a ratio of 0.02%) and in fact it may cause less hepatocellular damage due to its reducedmetabolism.[4,24]
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VI. Haemodynamic Management

Inflow Vascular Occlusion. CPM, IPM, and selective inflow occlusion share common hemodynamic management. Portal triad clamping increases systematic vascular resistance by up to 40% and reduces cardiac output by 10%. Mean arterial pressure increases about 15%. Following unclamping, hemodynamic parameters gradually return to baseline values.[1,25] However, the systemic circulation in patients with cirrhosis is hyperdynamic and dysfunctional, with increased heart rate and cardiac output, decreased systemic vascular resistance, and low or normal arterial blood pressure.[26] Thus, maintaining adequate organ perfusion may be difficult to achieve and preoperative optimization of the patient is required.

The anesthetic management is dictated by the surgical approach and the patient's health status. For healthy patients, routine monitoring is used. Monitoring can even be limited to just peripheral vein catheters.[26] During resection of liver parenchyma the main source of bleeding is from valveless hepatic veins. As such it is important to control central venous pressure, and so therefore hepatic venous pressure, in order to minimise blood loss. If CVP was >6 cm H2O blood loss was 1litre, but was only 200mls if CVP was <6; with blood

transfusion requirements dropping from 48% to 5%.[28] Techniques used to maintain a low CVP can include: head-up position, known as reverse-trendelenburg, avoidance of positive end expiratory pressure (PEEP), minimal fluid administration, diuretic use i.e. frusemide, vasodilators such as glyceryl trinitrate (GTN), and epidural use, which can help reduce systemic vascular resistance and CVP.[1,2,29] However maintaining a low CVP, to reduce blood loss, must be balanced with the potential risk of organ hypoperfusion as well as the low but potentially serious risk of air embolus. Patients with preoperative cirrhosis have a much lower tolerance to a reduction in renal perfusion pressure and therefore the anaesthetist must maintain an adequate perfusion pressure to try and preserve the renal function.[29,30] In an experimental animal study, Sivelestat, a neutrophil elastase inhibitor, reduced hepatic injury and stabilized hemodynamics after ischemia-reperfusion following IPM. A 15◦ Trendelenburg position protects against air embolism.[31,64]

Inflow and Outflow Vascular Occlusion
(1) Total Hepatic Vascular Exclusion (THVE). In THVE, rapid hemodynamic changes are frequent due to surgical events such as caval clamping, sudden blood loss, and hepatic reperfusion. Cross-clamping of the inferior vena cava and portal vein result in a 40–60% reduction of venous return and cardiac output, with a compensatory 80% increase in systemic vascular resistance and a 50% increase in heart rate.[32] Unclamping is followed by an increase in cardiac index and a significant reduction in systemic vascular resistance.[33-35] The anesthetist should take prompt steps to manage the preload reduction and the sudden decrease in cardiac output evoked by the inferior vena cava and portal vein clamping. Patients with pulmonary hypertension require pulmonary artery catheterization. In addition, the presence of a pulmonary artery catheter allows the tailored administration of vasopressors in case of massive hemorrhage due to vena cava injury.[1,4,36] Before THVE, colloids can be administered to prevent the abrupt decrease in cardiac output. Colloids, beyond correcting volume deficits, improve splanchnic circulation, displace fluid into the blood compartment, and reduce bowel edema.[37] Vasoactive agents should be used carefully, as they improve cardiac output at the expense of microcirculatory blood flow.[38] Preventing renal impairment is another important consideration for the anesthesiologist. Renal autoregulation ceases below a renal perfusion pressure of 70 to 75mmHg, below which, flow becomes pressure dependent.[38,39] Mannitol, furosemide, and "low dose dopamine" have been used with the aim of preventing intraoperative renal injury without evidence of substantial benefit. Recently, terlipressin along with volume expansion have been shown to improve renal function, without, however, improving survival.[4,40-42]

(2) Selective Hepatic Vascular Exclusion (SHVE).
SHVE is the method of choice in cases when CVP cannot be lowered (i.e., right heart failure, poor cardiovascular status).[43] Although the performance of SHVE requires significant surgical expertise, it is tolerated by most patients and has a hemodynamic profile similar to that of CPM. Furthermore, it controls backflow bleeding of the hepatic veins. In a large clinical study, SHVE proved to be more effective than CPM in controlling intraoperative bleeding, preventing blood loss, and reducing postoperative complications and mortality rates (Table 2).[44,45]

VII.   Vascular Air Embolism
Factors predisposing to vascular air embolism during liver resections include: (a) surgical technique, (b) size and place of the tumor, (c) blood loss, and (d) low CVP anesthesia. Clinical signs of vascular air embolism during anesthesia with respiratory monitoring are: a decrease in end-tidal carbon dioxide and decreases in both arterial oxygen saturation (SaO2) and tension (PO2), along with hypercapnia.[4,46-48] From the cardiovascular system monitoring, tachyarrhythmias, electromechanical dissociation, pulseless electrical activity as well as ST-T changes can be noted.

Resection of large tumors situated in the right lobe, close to the inferior vena cava or the cavohepatic junction, put the patient at risk of venous air embolism. Those tumors should therefore be resected under THVE or SHVE if possible. Massive bleeding (>5000 mL) and subsequent air embolism can even result in intraoperative death in patients undergoing major liver resections.[49,50] The adult lethal volume has been described as between 200 and 300mL or 3–5mL/kg. Low CVP further enhances the negative pressure gradient at the surgical field compared to the right atrium and increases the possibility of air embolism.

Currently, the most sensitive monitoring devices for vascular air embolism are transesophageal echocardiography and precordial Doppler ultrasonography, detecting as little as 0.02 mL/kg and 0.05 mL/kg of air, respectively.[51,52,64]

The consequences of air embolism can be minimized by placing the patient in a 15 degree trendelenburg position. Vascular air embolism is a potentially hazardous complication.

Additionally, cirrhotic patients undergoing hepatectomy have pulmonary abnormalities including intrapulmonary shunting, pulmonary vascular dilatation, and arteriovenous communications.[53] In these patients, air can pass into the systemic circulation (paradoxical air embolism), even if cardiac abnormalities (patent

foramen ovale) are not present, evoking fatal consequences. Recognizing the risk for vascular air embolism and planning the appropriate level of monitoring and treatment is the key to patient safety.[54]

VIII.   Strategies To Reduce Intra-Operative Bleeding

Blood loss of 10 litre has been reported after liver resection, and large transfusions are a risk factor for major postoperative complications and liver failure. Patients with cirrhosis, steatosis, and after chemotherapy are at especially increased risk of coagulopathy and bleeding. However, modern, multi-modal perioperative techniques have reduced mean blood loss to 300–900 ml. The use of intra-operative cell salvage in surgery for malignancy remains controversial.[1,4]

Transfusion- Liver resections may result in transfusion of RBC (red blood cells) in about 25%−30% of patients. Blood transfusions are well known to carry the risk of transmitted infections, acute or delayed reactions and "wrong blood" incidents. In liver resections, blood transfusions are associated with suppression of the immune system.[55,56] Transfusion evoked immunosuppression is also responsible for TRALI (transfusion-related acute lung injury). Dyspnea, hypotension, fever, and bilateral noncardiogenic pulmonary edema, present within 6 h of transfusion and complicate the postoperative outcome of patients following major liver surgery.[57] Although all blood products can lead to this life-threatening situation, plasma-containing products especially from multiparous female donors with leukocyte antibodies, were responsible for the majority of cases in patients undergoing liver transplantation.[58]

Aprotinin-

Significant reductions in blood transfusion requirements have been shown in liver resection using aprotinin although serious safety concerns have been raised about the incidence of life threatening allergic reactions, thrombotic potential, and renal failure. After the BART study, the license for aprotonin has effectively been withdrawn because of a 1.5 times increase in mortality compared with tranexamic acid and aminocaproic acid and an inability to identify specific patients who might benefit from the drug.[59-62]

Tranexamic acid has also been shown to reduce blood requirements in liver resection surgery but safety concerns have been raised and require further investigation.[63,64] In the future, two artificial oxygen carriers (haemoglobin solutions and perfluorocarbons) may become essential in reducing the need for allogeneic RBC transfusions.[65] Artificial oxygen carriers improve O2 delivery and tissue oxygenation as well as the function of organs with marginal O2 supply. A transfusion risk score, including variables of: (a) preoperative hemoglobin concentrations below 12.5 g/dL, (b) largest tumor more than 4 cm, (c) need for exposure of the vena cava, (d) need for an associate procedure, and (e) cirrhosis, accurately predicted the likelihood of blood transfusions in liver resections.[66-68]

IX. Pain Management

Regardless of the incision, postoperative pain must be managed for patient comfort. Adequate analgesia also decreases the incidence of respiratory complications (ie, atelectasis or pneumonia) and facilitates early ambulation.[4,110] Second, there is general agreement that a well-functioning epidural catheter provides the best perioperative pain relief following major abdominal surgery. However, 2 recent randomized, prospective trials comparing combined intraoperative general and epidural anesthesia with postoperative epidural pain control vs the regimen of general anesthesia followed by pain control with intravenous (IV) narcotics failed to show any difference in overall mortality or major complications.[69,70,110-112] Nonetheless, in the MASTER Anaesthesia Trial Study Group, the use of an epidural catheter was associated with significantly less pain during the first 3 postoperative days. The epidural drugs used also appear to have an impact on postoperative morbidity. In a recent report describing the anesthetic management of living liver donors for organ transplantation, thoracic epidural catheter was the preferred method of postop pain management.[110-113]

This question also raises a valid point that occasionally the epidural catheter is not effective and requires alternative analgesia. In our institution, the next best choice is IV narcotics with a patient-controlled analgesia (PCA) pump. Morphine sulfate is the drug used most commonly. Although excessive opioids can compromise respiratory function as suggested, it is our experience that inadequate pain control leads to shallow respirations, decreased cough, and splinting with an overall increase in respiratory complications.[71-74] Therefore, a well-titrated PCA with careful monitoring of respiratory status is usually adequate for pain control when you do not have the luxury of a functioning epidural catheter. The IV PCA is weaned to oral narcotics typically on the third or fourth postoperative day.[75,77] One caveat with narcotics is altered drug metabolism seen with marginal liver function, so this should be taken into consideration when dosing postoperative analgesia after major liver resections.

NSAIDs can be used on occasion when the patient cannot tolerate opioids. However, they do carry the theoretical risk of increased gastritis, bleeding, renal dysfunction, and altered liver regeneration.[78-80]

X. Ischemia Reperfusion Injury

(IRI) is defined as the phenomenon during which cellular damage in an organ, caused by hypoxia, is paradoxically exacerbated after the restoration of oxygen delivery. It is a dynamic process which involves the two interrelated phases of local ischemic insult and inflammation-mediated reperfusion injury.[81-83] If severe enough, the inflammatory response after IRI may even result in the systemic inflammatory response syndrome (SIRS) or the multiple organ dysfunction syndrome (MODS).[84-87] Liver, being an organ with high energy requirements, is highly dependent on oxygen supply and susceptible to hypoxic or anoxic conditions.

We are discussing surgical and non-surgical measures that can be adopted to minimise the risk of postoperative liver failure following liver surgeries. With emphasis on ischaemic and pharmacological preconditioning (PP) which can be easily adapted clinically.

Surgical measures
1 continuous portal triad clamping
2 intermittent clamping
3 preconditioning-

Ischaemic preconditioning(IP) is defined as a process in which a short period of ischemia, separated by intermittent reperfusion, renders an organ more tolerant to subsequent episodes of ischemia.[88,89] Clavien et al. provided the first clinical evidence of benefit in patients undergoing hemihepatectomy. It leads to improvement of hepatic microcirculation, reduction in tissue apoptosis, and improvement of survival. IP stimulates adenosine receptors on Kupffer cells in nonischemic lobes to produce oxygen radicals, leading to the promotion of liver regeneration after partial hepatectomy.[90-92] The benefit of ischemia is restricted by old liver. Similarly, the effect of preconditioning was lost in patients undergoing tissue loss above 50%. In small liver remnants of about 30%, it may in fact have detrimental effects.[93,94] This is because the small remaining tissue suffers from shear stress-associated microvascular injury.[114]

Pharmacological preconditioning-

Volatile anaesthetic agents- The preservation of mitochondrial function by sevoflurane resulted in reduced hepatic parenchymal damage and lower transaminase levels. It is possible that sevoflurane activated $mitoK_{ATP}$ channels and therefore decreased the intracellular calcium concentration, thus reducing mitochondrial damage in hepatic I/R injury.[95,96,114]

Protective role of nitric oxide

It has been shown that both endogenously generated and exogenously administrated NO plays an important role in protecting the liver from IRI[31 NO-based therapy has been applied for many years to patients with pulmonary hypertension or cardiopulmonary disorders. The therapeutic application of NO in protecting the liver from IRI has just been emerging.[97,98]
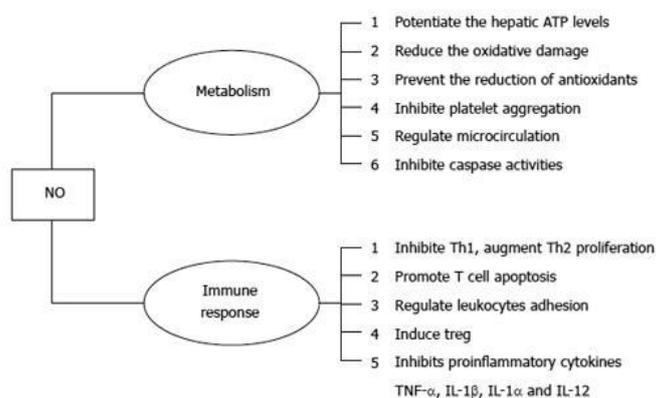

Figure 2- Role of nitrous oxide in IR injury

Other pharmacological agents (dextrose, intraoperative use of methylprednisolone, trimetazidine, ulinastatin and lignocaine), and opioids (remifentanil) have demonstrated the potential benefit and minimised the adverse effects of surgery.[99-102]

More recent being virapamil, lignocaine and adenosine. However, according to Wang et al., propofol also seems to have the ability to protect human hepatic cells from H2O2-induced apoptosis. Intraportal administration of L-arginine, a precursor of NO, has been recently studied in pigs and appears to reduce cell

damage during the early phase of reperfusion, by downregulating capsase-3 activity and by preserving mitochondrial structure.[103-107]

Finally, it is reported that angiotensin II type I receptor (AT1R) antagonist increased regeneration in nonsteatotic livers, while in the presence of steatosis both AT1R and AT2R antagonists increased liver regeneration.[108-110]

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