10 Anesthetic Management

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Introduction

In 1977, a multicentric study was published involving 621 hepatic resections. In this first report, average mortality stood at 13%, but reached a maximum level of 20% when they involved large resections. Intraoperative haemorrhage was pointed as the most important cause of mortality [1].

In the last two decades, the incorporation of new techniques, better knowledge in the perioperative care, and the development of sophisticated surgical equipment for bleeding control have succeeded in significantly decreasing haemorrhages and massive transfusions.

In the 1990s, mortality in hepatic resections had gone down to 5%, with a lower percentage in centres with high surgical volumes [2, 3].

This step forward has allowed for the geometric growth of the number of hepatic resection surgeries across the world, mainly due to the fact that it is the best treatment that can be offered to date for primary oncologic and metastatic injuries. Its potential in delaying the development of the disease and even offering a cure is higher than any other possible chemotherapy treatment. In a significant percentage of cases, surgical treatment represents the sole potential possibility of a cure [4–7] (Table 10.1).

Table 10.1 Hepatectomies indications

	Number of patients	Percentage (%)
Malignant pathologies	*826*	85.*86*
• Colon metastasis	552	61
• Neuroendocrine		2.9
metastasis	22	4
• Metastasis of another		11.5
origin	31	2.9
• Hepatocellular carcinoma	88	2.3
• Colangiocarcinoma	22	12
• Vesicular cancer	18	
• Others	93	
Benign pathologies	*136*	*14.14*
• Hemangiomas	36	26.5
• Live related donor	35	26
• Adenomas	23	17
• Focal nodular hyperplasia	21	15.5
• Hydatid cyst	8	5.9
• Others	13	9.5

Experience at the Hospital Italiano de Buenos Aires. *N*: 962 patients

Anatomy and Hepatic Physiology

It is vital for the anaesthesiologist carrying out perioperative care in hepatectomies to know the anatomy and physiology of the liver.

It is in these concepts that we shall find the bases for reducing haemorrhages and the way

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towards preventing the increase of cellular injury during the surgical ischemia periods.

Anatomic and Physiological Characteristics of the Liver with Surgical and Anaesthetic Relevance

The liver is the largest solid organ in the body, and weighs about 1.5 kg in an adult. It is placed in the right quadrant of the abdomen and is divided into four lobes: right, left, quadrate lobe, and caudate lobe.

At the same time, the right and left lobes are divided into segments which are defined by the distribution of arterial vessels and the biliary tree.

In the year 2000 in the city of Brisbane, a meeting of specialists was held with the objective of creating a definitive nomenclature to describe the different procedures on the liver. In subsequent years, this nomenclature has been adopted worldwide, and it is currently the most widely accepted one [8].

Hepatic surgery can be carried out according to lobe and segment distribution or disregarding this division.

Thus, the resection of a hepatic lobe will be called hemihepatectomy or right or left hepatectomy (Figs. 10.1 and 10.2).

At the same time, the resection of a single segment is called segmentectomy and when it involves two segments, bisegmentectomy.

The most important hepatic surgery involves the removal of the right or left lobe as well as one or two contralateral segments. This surgery is called hepatic trisegmentectomy [8].

Finally we call it an atypical hepatic resection when the cut on the hepatic tissue does not respect segmentary distribution.

It is important to bear in mind that this organ receives double circulation through the contribution of the portal vein and the hepatic artery. The latter, narrower, is responsible for between 25 and 30% of the hepatic flow but 60% of the oxygen available for this organ. The portal vein contributes 70% of the hepatic flow and 40% of the total oxygen [9].

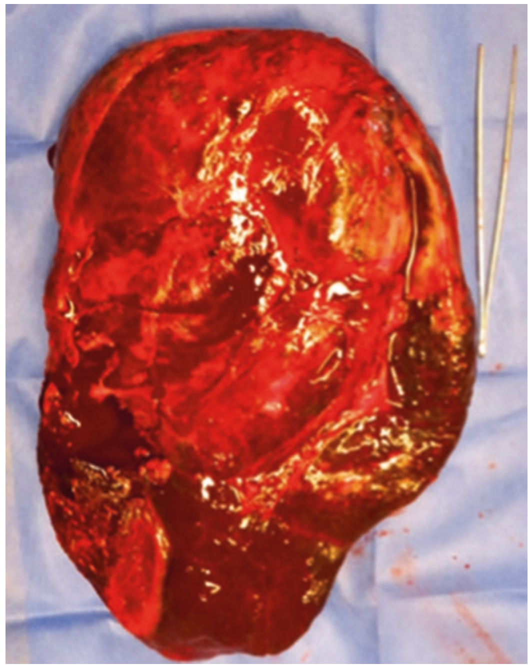

Fig. 10.1 Hepatic tumor

The portal vein branches ramify within the liver, and their division accompanies the hepatic sinusoids. Portal blood goes through these sinusoids and is collected by the centrilobular vein.

The hepatic artery branches run along the portal vein and finally transform into arterioles, precapillaries, and capillaries. Arterioles have sphincters which are part of the hepatic flow regulation [9].

After going through the hepatic sinusoids, blood coming from arterial and portal circulation is collected by three hepatic veins which drain their content into the vena cava [10].

Under normal circumstances, the liver extracts only 40% of the total oxygen delivered, but in patients under surgery or anaesthesia or suffering from diseases such as cirrhosis, the demand for oxygen may increase [9].

Hepatic flow represents about 25% of the total minute volume, which equals the delivery of about 1,500–1,800 ml of blood per minute [10].

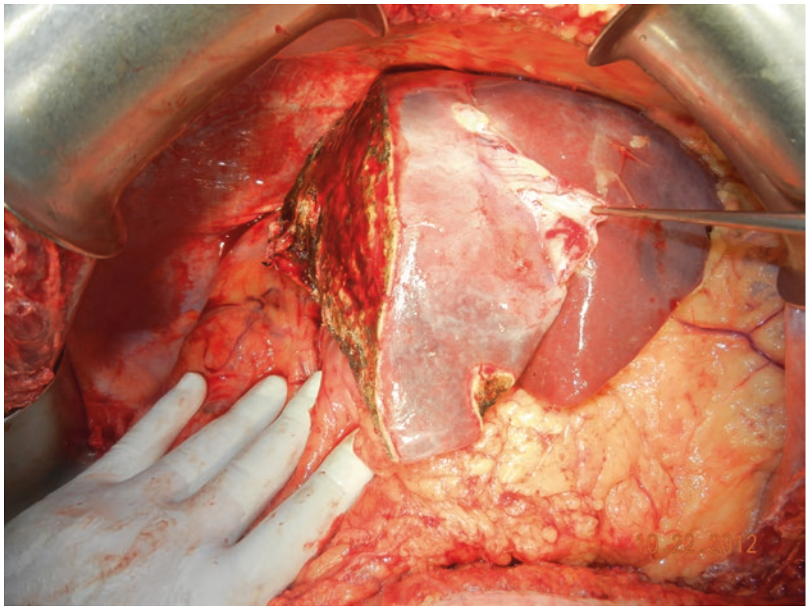

Fig. 10.2 Intraoperative photo of a right hepatectomy

There is a close relationship between the portal vein flow and the hepatic artery. When portal flow decreases, the hepatic artery complements it by increasing its flow [10].

While portal blood flow remains stable, the hepatic artery maintains an intrinsic self regulation system which keeps its volume constant in spite of the systemic pressure variations [11, 12].

Maintaining a stable blood flow towards this organ, under different hemodynamic conditions, is accounted for given the need to support the metabolism of endogenous and exogenous substances, even in critical clinical cases [9, 11, 12].

In other words, hepatic metabolism depends on the blood flow received in the time unit and only stops under extreme circumstances.

Hepatic irrigation is, therefore, an exception system, since it functionally does not respond to the same factors that lead to vasoconstriction or vasodilatation in the rest of the vascular tree.

The effects of the acid base or the concentration of oxygen only alter the diameter of the hepatic arterioles when they reach marginal conditions. Self-regulation would be controlled based on a neural type mechanism [13].

We should also mention, though with a lesser influence on this system:

– Cyclical alterations corresponding to spontaneous ventilation.
– Intrahepatic osmolarity.
– Excessive use of positive end-expiratory pressure (PEEP).
– Hypocapnia and hypercapnia.
– Surgery: surgery itself diminishes hepatic flow. Superior abdominal surgeries are those with the largest influence
– Anaesthesia: inhalatory anaesthetics decrease hepatic flow, although the most modern ones seem to do so in lower quantities (sevorane) and even increase it (isofluorane).
– Intravenous anaesthetics do not appear to have any influence over hepatic flow.

Hepatic Endothelium and Influence on Central Venous Pressure

The vascular endothelial cells in the hepatic sinusoid (mainly those corresponding to the portal vein branches), have fenestrations of a diameter which varies between 100 and 500 nm, and are not supported on any basal membrane.

The importance of these fenestrations lies in that they place the blood perfused to the liver in direct contact with the hepatic interstice. In other words, there is no defence against the changes in hydrostatic pressure [9, 10].

The larger orifices are found in the centrilobular region. These can change their size as a response to intravascular pressures, the action of vasoactive drugs, and the presence of toxins [12].

As incoming blood is controlled by a self-regulating system, there is no possibility for the liver to receive excessive flow that would unproportionally increase the internal volume.

The only way of doing this is through the increase of the central venous pressure which exercises a retrograde strength on the vena cava and the suprahepatic vein. The increase of the central venous pressure successively leads to the increase of the hepatic volume, the increase in the filtration of liquids towards the interstice, a higher lymphatic flow, and finally to the formation of ascitic liquid [9].

The arterioles contract and ease the passage of liquids towards the interstice as a response to the higher central venous pressure.

However, thanks to the lymphatic system which can drain great volumes, there is no accumulation of interstitial fluid in the liver.

Lymphatic vessels have the ability of increasing the density of proteins in their interior. These increase until they reach plasmatic concentration. Thus, oncotic pressures are matched and the interstice does not become a fluid deposit. Additionally, the liver surface can exude liquid, thus ejecting its excess [9–11].

Before reaching this extreme situation, the liver becomes a fabulous blood reservoir due to the increase in its internal volume.

Carrying out a liver resection under these circumstances implies the real possibility of increasing the risk of provoking a significant haemorrhage during surgery.

Surgical Manoeuvres that Diminish Intraoperative Bleeding

Pringle Manoeuvre (PM)

First described by Pringle in 1908, it has proven effective in decreasing haemorrhage during the resection of the liver tissue [14]. It is frequently used, and it consists in temporarily occluding the hepatic artery and the portal vein, thus limiting the flow of blood into the liver, although this also results in an increased venous pressure in the mesenteric territory [15] (Fig. 10.3).

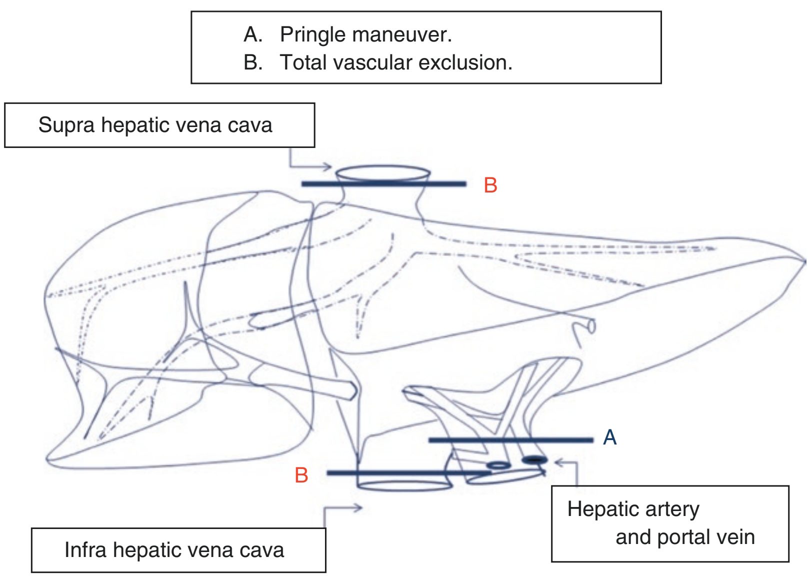

Fig. 10.3 Surgical maneuvers liver vascular occlusion

Hemodynamic repercussion during the PM is rare because it only diminishes the venous return in 15% of cases. The cardiovascular system slightly increases the systemic vascular resistance as a compensatory response, thereby limiting the drop in the arterial pressure. Through the administration of crystalloids, it is possible to maintain hemodynamic stability [16, 17].

In the 1990s, the PM was used continuously for 45 min and even up to an hour because the depth of the potential damage that could occur due to hepatic ischemia was not yet known [14].

During the PM, the lack of oxygen affects all liver cells, especially Kupffer cells which represent the largest fixed macrophage mass. When these cells are deprived of oxygen, they are an endless source of production of the tumour necrosis factor (TNF) and interleukins 1, 6, 8 and 10. IL 6 has been described as the cytokine that best correlates to postoperative complications [15, 17–19].

In order to mitigate the effects of continuous PM, intermittent clamping of the portal pedicle has been developed. This consists of occluding the pedicle for 15 min, removing the clamps for 5 min, and then starting the manoeuvre again.

This intermittent passage of the hepatic tissue through ischemia and reperfusion shows the development of hepatic tolerance to the lack of oxygen with decreased cell damage. Greater ischemic tolerance to this intermittent manoeuvre increases the total time it can be used [17, 20].

Total Vascular Exclusion (TVE)

This was described by Heaney and collaborators and initially associated to 30% mortality due to its use. As a result of this, it was quickly abandoned and only used again when the development of liver transplant programmes led into greater knowledge of the physiopathology of this surgical manoeuvre [21].

The classic vascular exclusion adds to the occlusion of the hepatic artery and the portal vein, and the clamping of the infrahepatic and the superior vena cava. Thus, we prevent retrograde flow of venous blood (Fig. 10.3).

There are variations of this manoeuvre described, with the intention of mitigating its risks; for example, the occlusion of the suprahepatic veins tributaries of the area to be resected, to avoid the total interruption of the flow of the cava. In these cases, the venous return remains undamaged [22].

Used less frequently than the Pringle manoeuvre, the TVE is useful in the resection of tumours adjacent to large vessels to diminish the risks of massive haemorrhage or air embolism [22].

This modality can also be intermitted, alternating periods of ischemia with periods when circulation is re-established to mitigate possible consequences due to the lack of oxygen [23].

Total occlusion of the vena cava damages the filling pressures of the right cardiac cavities, thus causing a drop in the venous return higher than 50% and, consequently, of the minute volume. Its clinical manifestation is a decrease in systemic arterial pressure, which receives an immediate compensatory response through the increase in the systemic vascular resistance (up to 80%), in an effort to decrease the arterial hypotension [22–24]. The anaesthesiologist can help these compensatory mechanisms through the administration of fluids and the use of vasoactive drugs. The intravenous use of fluids during this period must be carefully managed, since when the clamps are released, there can be saturation in the liver capacity and an increase of the haemorrhage from the exposed surface of the organ.

A persistent hypotension during TVE, in spite of the vasoactive drugs, is the main cause of interruption of the manoeuvre [24, 25].

As with PM, TVE should not be used for prolonged periods of time. The choice of an intermittent method allows for greater use of time [21] (Table 10.2).

Table 10.2 Differences between the Pringle manoeuver and total vascular exclusion

Pringle manoeuver	Total vascular exclusion
Greater number of transfusions	Greater number of complications
Greater ischemia/reperfusion effect	Greater hemodynamic instability
Shorter hospital stay	Technically difficult for the intermittent procedure

Morbimortality of the TVE has been related in different series studied with the amount of blood transfused, the clamping time, and the histology of the remaining liver [23].

The limitation of the haemorrhage during TVE is evident and in general, patients are operated on with scarce or no transfusional requirements [14, 26].

Anaesthetic Technique

When an anaesthesiologist is going to take part in a liver resection, he or she should assess the following considerations prior to the surgery: size of the liver resection to be carried out, clinical condition of the patient, preparation for surgery and necessary intraoperative monitoring, possibility of using Fast Track, and the place of post-operative care in the first few hours following surgery (Intensive Care Unit or Anaesthetic Recovery Unit).

Both inhalational anaesthesia and intravenous anaesthesia (total intravenous anaesthesia—TIVA) can be used in all their variations and without restrictions in liver resections. It will only be necessary to avoid those anaesthetics that diminish the hepatic flow, though they are practically out of use nowadays.

Monitoring should be according to the complexity of the surgery and the clinical condition of the patient. Routine monitoring in these types of surgery consists of: dynamic electrocardiography, capnography, oximetry, invasive arterial pressure, and periodic blood tests. Should TIVA be chosen for the anaesthetic technique, BIS is a vital monitor that must be accompanied by an adequate control of muscle relaxation. The control of central temperature and ST segment depression in DII and V5 must also be routine [27].

We should specially mention the central venous pressure (CVP) and its intraoperative control as a parameter highly related to bleeding in patients [28].

Monitoring of the CVP is up to now mandatory, although mini invasive monitoring could replace it in the future. With this method and only by using the invasive arterial pressure can be obtain constant values of systolic volume variation (SVV) or pulse pressure variation (PPV), which provide excellent guidance when restoring the blood [29].

Patients who require a liver resection surgery need at least two venous accesses as large as possible, given the potential need to administer fluids and homoderivatives quickly. Due to the need to measure CVP, one of these venous accesses needs to be central. All venous lines need to be located in the superior vena cava territory (arms and neck), since a vascular exclusion manoeuvre used would limit the desired administration of fluids [27].

Lately, crystalloids are the fluids of choice in high-risk patients, since colloids have been linked to higher renal failure and postoperative mortality [30–32].

Within the group of crystalloids, physiological solution is known for leading to hyperchloremia and acidosis. Both conditions are achieved with little volume, and are clearly damaging in procedures where the metabolic conditions can change quickly [32, 33].

Crystalloids which contain lactate are less criticized, mainly because they can maintain an artificial high level in plasma, which would lead us to conclude that the hyperlactacidemia present is the result of a poor postoperative evolution on the part of the patient [34].

The recommendation regarding the use of crystalloids basically consists of a very balanced solution such as Plasmalyte, whose osmolarity is close to plasmatic, thus contributing more acceptable metabolic results [35].

Nowadays, appropriate anaesthetic technique includes the use of protective mechanic ventilation to prevent pulmonary injury and postoperative complications. Generally speaking, a current volume between 6 and 8 ml/kg is sufficient for effective intraoperative ventilation in patients without prior pulmonary pathologies. The weight used in this equation needs to be ideal for each patient. Constant use of PEEP during mechanical ventilation will prevent pulmonary collapse and very probably the need for pulmonary recruitment with high peaks of positive pressure [36, 37].

Towards the end of the surgery, it is necessary to administer the necessary volume to re establish hemodynamic stability, without the need of pharmacological support or similar to the pre-surgical conditions.

It is desirable not to over-expand patients, among other considerations, because this will help to prevent later complications (e.g., oedemas, anastomosis filtrations).

The anaesthesiologist should have the ability to focus his intraoperative work on keeping the patient in an appropriate balanced metabolic condition which is pain-free and which bears an acceptable level of glycaemia, is normothermic, and has an appropriate concentration of Hb. Additionally, it should be hemodynamically stable, thus ensuring an appropriate consumption of oxygen and a convenient anaesthetic depth with enough muscle relaxation to allow for proper surgical work [38].

Relationship Between Central Venous Pressure (CVP) and Intraoperative Haemorrhage

The relationship between the intraoperative bleeding in liver surgery and CVP was explained in the section where we described the anatomical and physiological dependency between the endothelium, retrograde venous pressure, and intrahepatic blood volume.

Keeping a high CVP implies greater blood loss due to the accumulation of fluids in the liver. On the other hand, when the CVP is low, bleeding will not be a problem, but there might be a higher risk of air embolism [28, 39–43].

It is advisable to keep the CVP below 5 cm of H_2O, at the time of resection. During these periods, it will be necessary to use vasoconstrictive drugs such as phenylephrine or norepinephrine to maintain average arterial pressure between 50 and 60 mmHg [44–46] (Fig. 10.4).

Some authors propose replacing the CVP measure for pressure monitoring in a peripheral vein (in the arm) if it is at the same height as the right atrium. These researchers grant peripheral venous pressure (PVP) the same value as CVP

Fig. 10.4 Hepatic resection surgery with low central venous pressure. No bleeding is observed in the tissue

because they have found an excellent correlation between the two parameters, with a discordance level of just 4% [47, 48].

In order to achieve a CVP below 5 cm of H_2O, it is necessary to impose an intense restriction of the crystalloid infusion from the beginning of the surgery. This measure is frequently not enough on its own, and it is therefore necessary to resort to the administration of drugs in order to achieve the objective set.

The use of venous vasodilators has been described, but the use of diuretics can be a very effective way of obtaining very low levels of CVP without the need of other measures.

Furosemide (0.5 mg/kg), is normally injected in a single dose after obtaining the first basal CVP register at the beginning of the surgery. Its use necessarily implies the serial control of the potassium level in blood during the procedure.

Diuresis, generally speaking, is above 10 ml/kg towards the end of the surgery, which shows the extensive loss of fluids achieved. However, we should note a brief period of interperative oliguria when hypovolaemia is at its highest. Arterial pressure should be maintained through the administration of vasoconstrictive drugs until volemia is recovered at the end of the surgery.

When there is a drop in the effective volemia, the body responds with compensatory mechanisms to maintain constant arterial pressure. In a first phase, the activation of neurohormonal elements takes place which derive flow from the muscle, skin, and splanchnic territory towards vital organs. Up until then, hypovolemia can result in minimal hemodynamic changes.

In more advanced stages, the activation of baroreceptors leads to the release of catecholamines with the subsequent increase in peripheral resistance. This course of action can partially compensate the fall in the venous return and maintain an arterial pressure close to the usual one. Finally, we should add the effect of the renin–angiotensin–aldosterone system, which increases the effect already begun by the sympathetic system [48–50].

The choice of vasoactive drugs to be used during this surgical moment lies within the spectrum of those which ease or even increase mechanisms of compensation. Phenylephrine is the first drug of choice since it behaves lightly and selectively on vascular resistance. A dose of 0.2–0.3 μg/kg/min is first administered, and later increased as necessary. It is unusual to reach a dose of 1 μg/kg/min and, generally, it is not necessary to add other drugs to ensure patients' hemodynamic stability. When thermodilution catheters have been used under these intraoperative conditions, vascular resistance figures registered have never gone above 1,300 dynas.seg.m^2 [51].

Once the hepatic resection period is over, it is necessary to re-establish volemia. Preventing haemorrhages and the absence of transfusions also appears to maintain an adequate immunological level, with considerable improvement in rates of infection. There are hypotheses that even support the possibility of a lower post operative tumoral recurrence [52].

Other Causes that Can Influence Intraoperative Bleeding

Undoubtedly, there are other causes that can strongly influence intraoperative bleeding during a liver reception.

One of them is PEEP, which when increasing transthoracic pressure during a part of the respiratory cycle, increases pressure on the inferior vena cava and its draining territory. There is a notable increase of bleeding if PEEP is maintained during the resection, even with very low CVP [53].

The other situation which can increase the loss of blood from the hepatic surface is Trendelenburg position which undoubtedly increases it, or that of reverse Trendelenburg which decreases it. Both situations can be related to the movement of the blood mass towards one or the other side of the body, according to which one is used [54].

Patients with Preoperative Morbility

The effect of chemotherapeutic drugs on the hepatic tissue does not go unnoticed. Drugs producing the greater organic changes are oxaliplatin, Avastin, and irinotecan, which provoke steatosis, sinusoidal obstruction, and fibrosis [55, 56]. When these patients are later operated on, it is more difficult to diminish the bleeding, even with an adequate reduction of CVP. During the postoperative stage, the changes on the tissue as a result of the chemotherapy increase the possibility of hepatic insufficiency [55]. The theoretical time in which these chemotherapy-associated pathologies diminish their potential to generate greater hepatic damage is 6 weeks after the last treatment [57, 58].

Smokers, diabetics, and morbidly obese patients represent another risk group in hepatic resections [58, 59].

Other Strategies to Diminish Bleeding

Avoiding blood transfusions during any type of surgery is nowadays a mandatory goal for all anesthesiologist doctors. During hepatic resection surgery, haemorrhage is related to the patient's prior conditions, to the technical difficulty presented by the resection, and also very associated with the anaesthesiologist's and surgeon's experience in these procedures [60].

Other strategies have been described in hepatectomies, in addition to the decrease of CVP. These can be used jointly or separately to inhibit haemorrhages.

The anaesthesiologist can continuously administer antifibrinolyctic drugs such as tranexamic acid, although this is not a widely spread practice. It is also possible to use normovolemic hemodilution during surgery with a double objective: to decrease CVP, and to have autologous and fresh blood for the end of the surgery. The latter method has proven to be safe and efficient, especially in live related donors [61]. At many institutions, the use of field blood recovery or cell saver is systematically included when the case calls for it [62].

In the last decade, many anaesthesiologists' adherence to blood administration procedure guidelines has resulted in the avoidance of unnecessary transfusions in patients undergoing high complexity surgeries.

These guidelines are based on scientific research which show that even with critical patients, a haemoglobin level of 7 g/dl does not increase surgical risk [63]. Hypothermia is another condition that anaesthesiologists know very well, and which they seek to prevent to maintain control of haemostasis.

Body temperature easily drops during hepatic resections, given the wide exposure of abdominal organs, cold fluid lavage, and ventilation with gases at room temperature. Control of hypothermia needs active work from the anaesthesiologist: use of thermal blankets, the administration of intravenous hot liquids, abdominal cavity lavage, and the heating of inspired gases, etc. During the hepatic resection surgery, it is necessary to maintain control of body temperature until the patient recovers consciousness during the immediate post-operative stage [64].

The recombinant factor VII, one of the most promising drugs in the field of haemostasis during the last decade, should be included among the possible therapies to be used in liver resections. In the case of coagulation alterations that lead to severe haemorrhage, factor VII will allow for control of the bleeding and sufficient time to make the necessary haemostasis corrections. Although it has been available for several years, its cost seems to be a limiting factor in is frequent use [65].

Finally, we could mention other techniques in the anaesthesia area which help towards preventing the increase of haemorrhage during hepatic surgery: [66, 67].

- Not using heparin, even at very low doses in the arterial line lavage liquids.
- During pre-anaesthesia assessment, we should consider if the administration of iron, erythropoietin/eritropoyetina, or vitamin K is necessary according to the patient's condition.
- Study all patients with Von Willebrand disease and prescribe desmopressin when necessary.
- Send the patient to the hemotherapy service to begin collection of autologous blood before surgery.

Surgery has also contributed, with sophisticated equipment to allow for bleeding-free hepatectomies. Those most used are ultrasonic scalpel, Argon beam, and haemostatic material with fibrin which can be placed on the liver surface to favour coagulation [66–68].

The angiography with arterial embolisation not only allows for the reduction of tumours before surgery but also helps decrease blood flow towards the anatomic sector where the operation is going to take place. It is an excellent and efficient technique to effectively mitigate intraoperative bleeding [69].

New surgical techniques have also been described to carry out small resections with little loss of tissue and a very low possibility of bleeding [70].

Another widely adopted method for preserving healthy tissue surrounding a malignant process or accessing tumours in difficult areas is radio frequency. It consists of using specially designed needles which are located within the metastasis which is destroyed through intense heat. Radio frequency also has the advantage of allowing the treatment of unresectable tumors through a mini invasive technique [71].

Ultrasound helps the placing of the needle when the use of radio frequency is decided upon [72].

Laparoscopic and robotic techniques have also been adopted to carry out hepatic resections, thus avoiding large incisions, hemorrhages, and a low amount of post-operative pain [73, 74].

Nowadays, hepatic resections at high surgical volume centres is a procedure which carries minimal risk of intraoperative bleeding [75].

Hepatic Injury due to Ischemia: Pre Conditioning

The use of hepatic fluid occlusion manoeuvres to diminish bleeding causes liver injury due to ischemia, and its consequences and prevention are studied by many authors, especially because the objective is to preserve the functions of the remaining liver so that the patient can have a swift and appropriate recovery [76].

These ischemia periods can be better tolerated by patients if preconditioning techniques are used.

Any strategy that protects the liver against ischemia is called hepatic preconditioning [77, 78].

Generally speaking, those who benefit the most are younger patients or those who suffer hepatic diseases and are more vulnerable in a surgery [78].

It has been proven in lab animals that hepatic protection strategies against ischemia have allowed for good organ performance even after a 75-min occlusion [79, 80].

One of the techniques to protect the liver against ischemia is to maintain the clamping of the hepatic hilum vessels for 10 min and then releasing them for another 10 min before the clamping. This scheme would produce intracellular biochemical changes that would preserve the ATP for a longer time in a prolonged ischemia period.

Other recommendations include the use of intermittent clamping, definitively discarding permanent ones. A greater amount of research is still needed to more thoroughly know which the most efficient pre-conditioning methods are [81].

In recent years, greater importance has been granted to interleukin 6 (IL 6) as a producer of hepatic injury. This cytokine could be a modulator of the death of the hepatocyte during severe and chronic diseases affecting the liver (Fig. 10.5).

Its action could be mediated by Toll-like receptors, which activate intracellular lines and influence the future destiny of these cells [82]. On the other hand and paradoxically, it is also possible to describe IL6 as a protector during hepatic failure [83].

That is to say, according to the conditions, the same lines that can produce apoptosis and hepatic failure could also counteract these signs and act protectively. In both situations, intracellular factor NF-kB appears to be the key towards determining the foundations of the death process or cellular proliferation. Currently, a significant amount of research seeks to describe the action of factor NF-kB both in animals and in humans during inflammation and ischemia [83, 84].

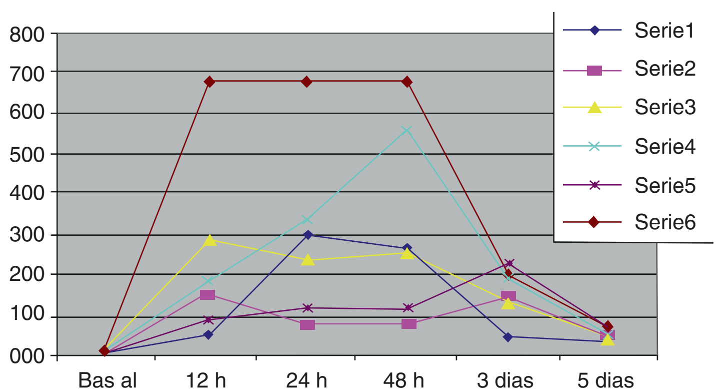

Fig. 10.5 Level reached by IL 6 after liver surgery with Pringle maneuver. Data from six patients treated at Hospital Italiano de Buenos Aires

Post-operative Analgesia and Fast Track Technique

The fast track concept includes different procedures within a multimodal programme to eliminate or diminish the effects of surgical stress on the patient. This technique which initially included almost as a sole objective the early extubation (within the first hours after surgery currently also requires an efficient treatment of post operative pain, perioperative fluid restriction, food and early mobilisation, etc.) [85].

There are programmes called ERAS (enhanced recovery after surgery) which encourage the study and development of techniques that allow for the increase of comfort in patients, the decrease of complications and costs of hospitalisation, thus also easing the medical and nursing staff work [86].

The analgesic technique to be chosen will depend on the patient's clinical condition and mainly on the level of coagulation at the time of administering it or withdrawing the catheters (Fig. 10.6).

Current discussion lies between two options: peridural thoracic analgesia and intrathecal opioids.

Peridural thoracic analgesia with catheter for the administration of local anaesthetics constitutes the higher analgesic standard in abdominal and thoracic surgeries, but in the case of a hepatic resection, the following conditioning elements should be noted: [87].

– In patients with cirrhosis or prior coagulation alterations, placing a large needle in the peridural space could ease the appearance of hematomas with the development of severe neurological injuries.
– Should the patient not have previous coagulation alterations, it is probable they will appear after the liver resection, even in patients with no cirrhosis and with previously normal lab tests. This seriously limits the removal of the catheter, which could extend up to 7 days. Some studies have recently shown that a moderate hepatic dysfunction would not appear to increase the possibility of hematomas above the average level. The causes of alternation of the coagulation profile during hepatic surgery post operative stage could be: intraoperative hemodilution, prolonged hepatic ischemia, or insufficient residual hepatic tissue.
– The removal of the peridural catheter should be preceded by coagulation tests that support the safety of the procedure. In the case of use of anticoagulants during the post-operative stage, they should follow the standards described in procedure guidelines for patients with regional anaesthesia and anti-clotting.

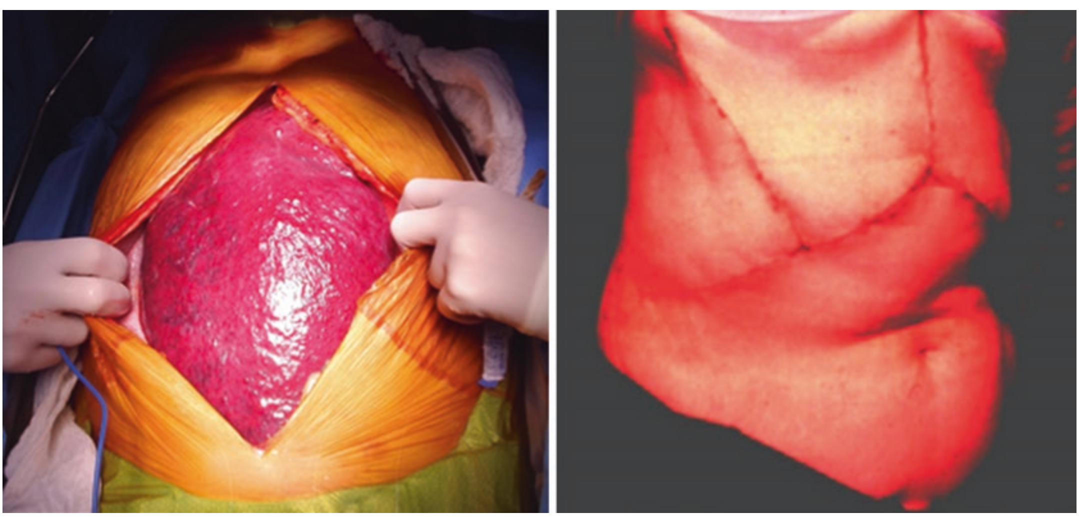

Fig. 10.6 Different incisions used in liver resections

- In addition to local anaesthetics, it is possible to administer low doses of peridural opioids to improve the quality of the analgesia.
- In large hepatic resections, lidocaine alters its metabolism and increases its concentration in blood, with the possibility of reaching toxic levels.
- Local anaesthetics are administered in low doses (ropivacaine 0.15–0.2%) or bupivacaine (0.125–0.150%) at 5–7 ml/h.
- Placing a peridural catheter before the surgery and the continuous administration of local anaesthetics can help diminish CVP during resection, given its light effect on the sympathetic tone.
- Recent studies have associated a great possibility of perioperative transfusion.
- When comparing the use of intravenous analgesia and peridural analgesia, it has been possible to observe a 7% reduction in the possibility of postoperative pulmonary complications with epidural analgesia, and an adequate pain management, though also a 26% increase in the use of colloids [86–89].

Epidural analgesia is prescribed jointly with general anaesthesia. Recently it had been associated with an increased use of blood transfusion and a longer hospital stay. It has a low level of complication, with relevant improvement in the patient's clinical condition in the long term [88–90].

The other analgesic technique also considered among the highest standards for the treatment of acute pain is intrethecal epidural analgesia with morphine. The intradural injection of opioids offers both advantages and disadvantages compared to epidural analgesia with local anaesthetics, which should be considered according to each patient.

Advantages:

- It grants quality analgesia for 24 h and a lower use of intravenous analgesic in the following 48 h.
- Only one injection is administered with a small needle, and therefore there is a lower possibility of hematomas and neurological injury in patients with hepatic dysfunction.
- There is no risk of hematoma resulting from the removal of the catheter in the post-operative period.
- It can be easily used in hospitals with little resources.
- It does not produce sustained hypotension.

Disadvantages: (compared to epidural analgesia with local anaesthetics)

- It produces greater sedation and requires greater re-injection of complementary pain killers.
- It presents typical opioid side-effects: immediate and later respiratory depression, urinary retention, pruritus, nausea, and vomiting [91].

The half-life of the subarachnoid morphine is 18–24 h, while the beginning of the effect is between 45 and 75 min. This leads to many anaesthesiologists choosing to administer a joint doses with fentanil (20–25 μg), since its effects comes within 5–10 min and its duration in not longer than 4 h.

The doses of subarachnoid morphine varies between 100 and 500 μg, but a useful dose could be related to weight, established between 2 and 3 μg/kg [92].

Among the central use coadjuvants along with intrathecal opioids, we should mention clonidine which with very low doses reduces acute pain and produces an adequate sedation. It provokes an increase in the sensitive block time and a decrease of the sympathetic tone, with light hypotension within 30 min of being administered [92, 93].

When analgesia after a liver surgery cannot be achieved through the use of a peridural or intrathecal technique, it will then depend on the intravenous administration of morphine, be it through the PCA (patient controlled analgesia) technique or the use of guided administrations according to the patient's degree of pain. In these cases, it is necessary to remember that the morphine's metabolism in hepatic resections could be altered [94].

In liver resections, the abrupt drop of the mass in the liver prevents the development of compensatory metabolic mechanisms, and thus the impossibility of reducing the concentration of morphine.

A greater plasma concentration of morphine show a higher risk of sedation, respiratory depression, and other side-effects when the same doses are administered in surgeries that do not involve a decrease of hepatic mass [94–97].

Ex-Situ, Ex-Vivo Hepatic Resection

Surgical teams with wide experience who also carry out hepatic transplants can take on surgeries involving great complexity that include patients with unresectable tumours with conventional techniques.

Ex-situ, ex-vivo surgery consists of removing the liver from the abdominal cavity, with the resection technique used in hepatic transplants to be able to resect the tumour on an adequate table. After the resection, the liver is once again implanted in its abdominal position with the corresponding arterial, venous, and biliary anastomosis.

The blood inside the liver is replaced with preservation liquid between 0 and 4°, which will allow for procedures lasting several hours without major problems when it is once again implanted [98].

Although morbimortality of this technique is higher than in conventional hepatic resections, it is also true that a higher percentage of patients survive, patients who would have no possibility of treatment without such surgery [98, 99].

During the ex-situ surgery, dissection and exeresis of the hepatic tissue does not imply any bleeding and, additionally, can be joined to large vessels that in the posterior implant could ease haemorrhage.

There are still few reports on the long-term results of this surgery, and the experiences described are varied and still incomplete [100].

Some conclusions could be added based on personal descriptions which include the following suggestions:

– Renal failure is one of the most frequent complications.
– The anaesthetic technique *SHOULD NOT* include the reduction of the CVP, since it is not necessary due to the vascular clamping and, additionally, because since it is a longer surgery it is more difficult to maintain hemodynamic stability. Hypovolemia and the clamping on the suprahepatic inferior vena cava are responsible for the I/R [101].

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy—ALPPS

This is a recently introduced surgical technique which has been developed to carry out large liver resections avoiding the development of hepatic insufficiency. This technique allows the inclusion in surgeries of patients who a few years ago could not be operated on because the remaining liver was too small.

It consists of two procedures generally carried out a few days apart. In the first one, the right portal vein is occluded which will allow for the progressive atrophy of that hepatic lobe, since it will not receive the usual blood flow, with the subsequent increase of the left liver [102].

In the second procedure, the right liver resection takes place which is generally more compromised, while the left extensive liver remains with enough functionality. Even partial resections can take place in this latter lobe if the growth has been significant. Thus, hepatic insufficiency is prevented.

In the first procedure, the conventional anaesthetic technique with CVP reduction will be used, with the objective of reducing the size of the liver, allowing the adequate work of the surgeon in a reduced space and decreasing bleeding. In the second procedure, it is not necessary to reduce the CVP; the liver is separated into two sectors, one of which (the right one) will finally be resected, but without a significant trans-section of the tissue. After the first surgery, the patient needs to remain in the intensive care unit until the possibility of hepatic insufficiency has passed.

The anaesthetic techniques, monitoring, and post-operative analgesia are carried out according to the criteria prescribed for general hepatic resections [103].

Final Considerations

It is clear that surgery continues to move forward, and that there are nowadays few patients who can be considered unresectable. In the last few decades, surgery, and anaesthesia have contributed with marvellous advancements which favour the concept of safety. Patients who previously suffered a surgery which left a physical and psychological imprint, and whose recovery would take several months, today are released a few days after surgery. The speed of change in current medicine brings us hope for the future. It is probable we will continue to be astounded by the progress made by medical science [104].

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