Anaesthesia For Liver Resection: The Physiology
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The anaesthetic issues relating to patients undergoing liver resection need to be considered hand in hand with the relevant anatomy and physiology. The anatomy of the liver has been described in terms of liver segments. These segments are defined predominantly by their venous drainage. There are eight liver segments, as shown on the first slide. In terms of its functional anatomy, the liver is the largest solid organ of the body. It typically weighs around 1.5 kg, and is located in the right upper quadrant of the abdomen. It is divided into four globes, and eight segments. Posteriorly, it is attached to the vena cava by the three hepatic veins. Its blood supply comes from the portal vein and hepatic artery. The bile ducts descend from the right and left lobes of the liver and converge to the common bile duct. The entire liver is enclosed in a richly innervated and non distensible capsule. A number of cell types are present, each with their own distinct functions. The cells are supported in a connective tissue matrix.

The liver derives its blood supply both from the portal vein and from the hepatic artery. This follows the “law of thirds”. Approximately one third of cardiac output is distributed to the liver. The hepatic artery provides approximately one third of the liver’s blood flow, and the portal vein the remaining two thirds. However, oxygen delivery to the liver is in a reverse ratio; the hepatic artery provides two thirds of this, and the portal vein approximately one third. There is complex auto regulation of these processes which will be discussed later.

Variations in the anatomy of the hepatic artery are relatively common (up to 50%). The hepatic artery arises from the coeliac axis from the intra-abdominal aorta. The common hepatic artery is derived from the right side of the coeliac artery, and divides to give right and left arteries at the Porta Hepatis. The right hepatic artery gives off the cystic artery and supplies the right lobe of the liver; the left supplies quadrate and caudate branches and the left lobe of the liver.
The portal vein is the terminal vein of the entire splanchnic circulation. It forms behind the head of the pancreas from a confluence of the splenic and superior mesenteric veins.

Venous drainage from the liver is via three hepatic veins. These represent venous drainage from the hepatic sinusoids, whose blood supply is derived from both arterial and portal venous blood. The right hepatic vein is the largest of these and arises in the right lobe between segments five and six anteriorly and segments seven and eight posteriorly. The left vein arises between the medial and lateral segments of the left lobe.

The middle hepatic vein drains the left medial segment and a variable part of the right anterior segment. All three veins drain directly to the cava at the level of the diaphragm.

The hepatic portal veins subdivide within the liver parenchymal to give a number of interlobular or conducting veins. These run in continuity with the hepatic sinusoids. A number of hepatic artery branches run with these portal vein branches, giving off precapillaries and capillaries. These go on to form a general plexus supplying the portal tract and peri-biliary plexus. There are also arterial capillaries emptying directly into hepatic sinusoids via richly innervated sphincters.

The microcirculatory unit of the liver is the acinus. The portal system flows into this, usually at low pressure (6 mm of mercury) and high flow. The hepatic artery is a high-pressure system but with somewhat lower flow. These two systems meet within the sinusoidal bed of the liver acinus. Pressure within the sinusoid is two to 4 mm of mercury above vena cava pressure. The acinus is a three-dimensional, microscopic mass, arranged around a triangular vascular axis. This is composed of the arteriolus, the venulus, and bile duct together with an accompanying nerves and lymphatics. Blood exits the acinus by two or more hepatic veins (central lobular veins). The hepatic sinusoids have structurally unique vasculature. There are three main cell types present. The endothelial cells and Kupffer cells are in contact with the bloodstream. The hepatocytes and Ito cells are in contact with plasma only in the space of Disse.
44% of liver cells are endothelium. Hepatic endothelial cells are unique. They have a cell body with a nucleus and an extended process with clusters of pores. There is no basement membrane. Hence, there is unrestricted communication of plasma between the vascular space and the space of Disse.

One third of liver cells are Kupffer cells. These are in essence fixed macrophages. The remaining sinusoidal cells are pit cells, a variant of a natural killer cell.

Hepatocyte location is important. So-called Zone 1 cells are located near the hepatic artery. They are bathed by predominantly arterial blood. Zone 3 cells are peri-venular and are located at the periphery of the acinus. These are bathed in a solute modified by the metabolic action of the zone one and two cells. There is increasing sensitivity to nutritional ischaemic and anoxic damage as we move from zone one to zone three. Zone one cells are equipped for oxidative functions whereas zone three cells are equipped for less oxygen dependent processes.

Liver blood flow is a function of splanchnic blood flow, hepatic arterial resistance and portal venous (intra hepatic) resistance. There is an important and well-known interaction between arterial and portal venous blood flow. This is known as the hepatic artery buffer response. In essence, there is partial reciprocity; a reduction in portal venous flow results in an increase in hepatic artery flow. This is thought to be mediated by washout of adenosine from the hepatic sinusoid. It is important to note that this is one-way reciprocity; changes in hepatic artery flow do not bring about consequent changes in portal vein flow.

Many anaesthetic drugs are known to attenuate the hepatic artery buffer response. In particular, the volatile anaesthetic agents all have some effect on this, although there is a progression of severity. Halothane is thought to have the greatest effect, with enflurane and isoflurane showing a progressively lesser effect. There is a similarly minimal effect (although still some) with desflurane and sevoflurane. Agents such as propofol and fentanyl are not thought to influence the hepatic artery buffer response. Many anaesthetic agents compromised liver blood flow not only because of their effect on regulation of hepatic flow, but also because of a global reduction in blood
pressure and cardiac output. Additionally, recent work has shown that epidural analgesia also compromises splanchnic and liver blood flow proportional to the reduction in mean arterial pressure. The effects of epidural induced reductions in hepatic blood flow can be reversed by elevating the arterial pressure, either by volume or by low-dose vasopressors.

Changes in central venous pressure are also important. Because there is no effective colloid oncotic gradient across liver endothelium, there is a tendency for liver oedema to form extremely rapidly. This can also result in increased lymphatic flow and formation of ascites. To some extent, the effects of venous pressure changes can be offset by constriction of the pre capillary sphincters reducing overall hepatic perfusion and pressure, possibly by a myogenic mechanism.

There is also pressure-flow auto regulation in the hepatic artery. This has been seen both in innervated and denervated liver, again possibly by a myogenic mechanism. In addition to these mechanisms, there is extrinsic regulation of liver blood flow. This is mediated both by sympathetic and para-sympathetic plexuses; sympathetic stimulation can result in increased vascular resistance and a reduction in hepatic artery flow. While portal vein pressure also rises, its flow is unchanged. Cessation of sympathetic stimulation is followed by transient hyperaemia.

There is also an important interaction between respiration and liver blood flow. This is mediated via simultaneous changes in diaphragm position, resulting in distortion and compression of hepatic veins, together with changes in vena cava pressure. Together, these effects maintain hepatic venous blood flow during spontaneous respiration. However, the compensating effects of reduced venous pressure in inspiration is lost during artificial ventilation. Theoretically, therefore, there is significant compromise of liver blood flow during intermittent positive pressure ventilation.

There are a number of other important determinants of liver blood flow, including osmo-receptors and the effects of gastrointestinal hormones.
The interposition of the liver and in its cells between the digestive tract and systemic circulation is necessary both for normal hepatocellular function, and gives rise to important modulating and protective effects on the systemic circulation. These include synthetic, catabolic and other effects; drug metabolism; and a reticulo-endothelial “barrier” effect.

Liver resection and results in the compromise of many of these functions. There is a loss of cellular mass, which will necessarily include a loss of hepatocyte mass. The physiological consequences of this vary on the nature of the tumour and the tumour load in the resected specimen. While colorectal metastases may be resected with relatively little functional consequence for the liver, hepatomas may be metabolically active.

Additionally, there is compromise of the gastrointestinal and circulatory barrier. There may also be haemorrhage, not only due to transected parenchyma, but also due to the effects of venous back - bleeding. These effects are likely to be compounded by an evolving coagulopathy. Additionally, the liver may be subjected to intermittent clamping during the course of surgery, in an attempt to limit bleeding. This can result in a series of ischaemia reperfusion insults, which can give rise to accelerated coagulopathy and genesis of fibrinolysis. Additionally, there may be distant haemodynamic effects from ischaemia reperfusion sequences. These may include myocardial depression and vasodilatation.

The time course of the derangement may be significant: data from our unit as well as others suggest that a significant coagulopathy is present for up to a week after surgery.

The Pringle manoeuvre is used to clamp portal inflow and limit bleeding. It has been shown to be highly effective at reducing blood loss. However, this is not without a cost. Ischaemia and subsequent reperfusion can result in both apoptosis and necrosis. This may be too great a price to pay. Cross clamping may be performed either continuously (for example 30 to 60 minutes of transection) or intermittently, with 10 minutes on and five minutes off. The intermittent technique is associated with less hepatic damage. Additionally, a short period of ischaemic preconditioning
prior to application of the clamp has been shown to limit ischaemic damage of the liver and reduce both cell necrosis and apoptosis consequent on a long period of subsequent clamping. The putative mechanisms of ischaemic preconditioning are shown schematically on the slide. These are thought to be mediated by a number of factors, including nitric oxide and adenosine. The final common pathway for early or classical ischaemic preconditioning (protection occurring for up to one or two hours after the episode of preconditioning) is thought to be an effect on the mitochondrial ATP dependent potassium channel and a reduction in calcium influx. Late preconditioning (protection occurring several hours after the initial brief period of ischaemia) is thought to result from gene transcription and expression of new proteins within the cell including heat shock proteins and antioxidants. Other preconditioning techniques – including pharmacological - have also been shown to be of value in experimental animal models. These include the infusion of drugs such as adenosine and dipyridamole.

In summary, anaesthesia for liver resection is potentially very challenging. These challenges are related in part to the anatomy of the liver and its rich blood flow. They may be enhanced in individual patients because of tumour location. Anaesthesia has the potential to modulate the balance between hepatic oxygen supply and demand, and to compromise hepatic blood flow. Added to this, that there are the challenges posed by the nature of surgery which can compromise both metabolic and reticulo-endothelial functions of the liver. These may be further compounded by the effects of massive blood loss, and the effects of portal and arterial clamping, resulting in coagulopathy and both local and distant ischaemia reperfusion phenomena. Despite these challenges, liver resection is an increasingly widely practised surgical solution for both primary and metastatic malignant disease. Good outcomes are not only possible, but have become the norm.