

## Chapter 2

# Anatomy and Physiology of the Liver

### 2.1 Anatomy

The liver is the largest organ of the human body (Figure 2.1), weighs approximately 1500 g, and is located in the upper right corner of the abdomen. The organ is closely associated with the small intestine, processing the nutrient-enriched venous blood that leaves the digestive tract. The liver performs over 500 metabolic functions, resulting in synthesis of products that are released into the blood stream (e.g. glucose derived from glycogenesis, plasma proteins, clotting factors and urea), or that are excreted to the intestinal tract (bile). Also, several products are stored in liver parenchyma (e.g. glycogen, fat and fat soluble vitamins).

Almost all blood that enters the liver via the portal tract originates from the gastrointestinal tract as well as from the spleen, pancreas and gallbladder. A second blood supply to the liver comes from the hepatic artery, branching directly from the celiac trunc and descending aorta. The portal vein supplies venous blood under low pressure conditions to the liver, while the hepatic artery supplies high-pressured arterial blood. Since the capillary bed of the gastrointestinal tract already extracts most  $O_2$ , portal venous blood has a low  $O_2$  content. Blood from the hepatic artery on the other hand, originates directly from the aorta and is, therefore, saturated with  $O_2$ . Blood from both vessels joins in the capillary bed of the liver and leaves via central veins to the inferior caval vein.

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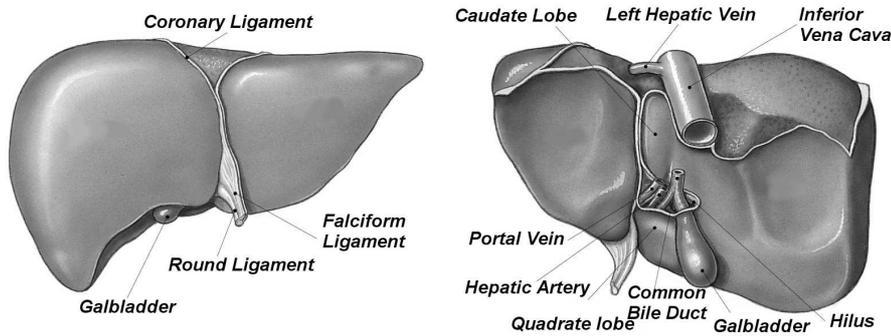


Figure 2.1: The liver.

### 2.1.1 Basic liver architecture

The major blood vessels, portal vein and hepatic artery, lymphatics, nerves and hepatic bile duct communicate with the liver at a common site, the hilus. From the hilus, they branch and rebranch within the liver to form a system that travels together in a conduit structure, the portal canal (Figure 2.2). From this portal canal, after numerous branching, the portal vein finally drains into the sinusoids, which is the capillary system of the liver. Here, in the sinusoids, blood from the portal vein joins with blood flow from end-arterial branches of the hepatic artery. Once passed through the sinusoids, blood enters the collecting branch of the central vein, and finally leaves the liver via the hepatic vein. The hexagonal structure with, in most cases, three portal canals in its corners draining into one central vein, is defined as a lobule (Figure 2.3). The lobule largely consists of hepatocytes (liver cells) which are arranged as interconnected plates, usually one or two hepatocytes thick. The space between the plates forms the sinusoid. A more functional unit of the liver forms the acinus. In the acinus, the portal canal forms the center and the central veins the corners. The functional acinus can be divided into three zones: 1) the periportal zone, which is the circular zone directly around the portal canal, 2) the central zone, the circular area around the central vein, and 3) a midzonal area, which is the zone between the periportal and pericentral zone.

### 2.1.2 Sinusoids

Sinusoids (Figure 2.4) are the canals formed by the plates of hepatocytes. They are approximately 8-10  $\mu\text{m}$  in diameter and comparable with the diameter of normal

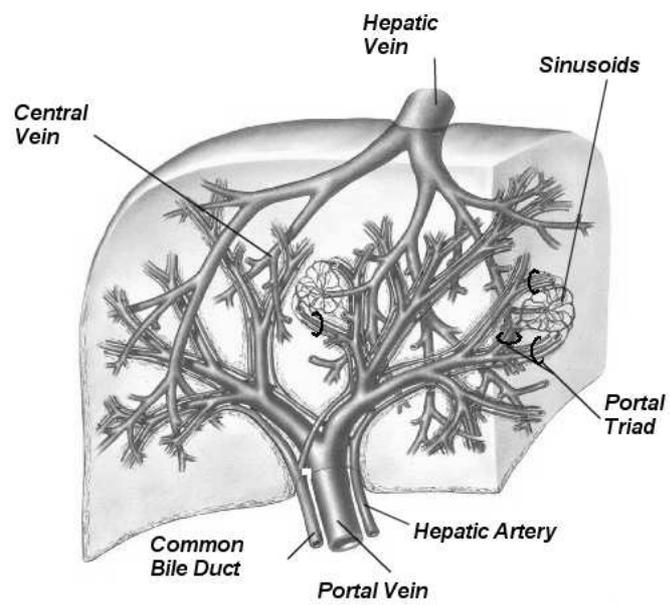


Figure 2.2: Network of branching and rebranching blood vessels in the liver.

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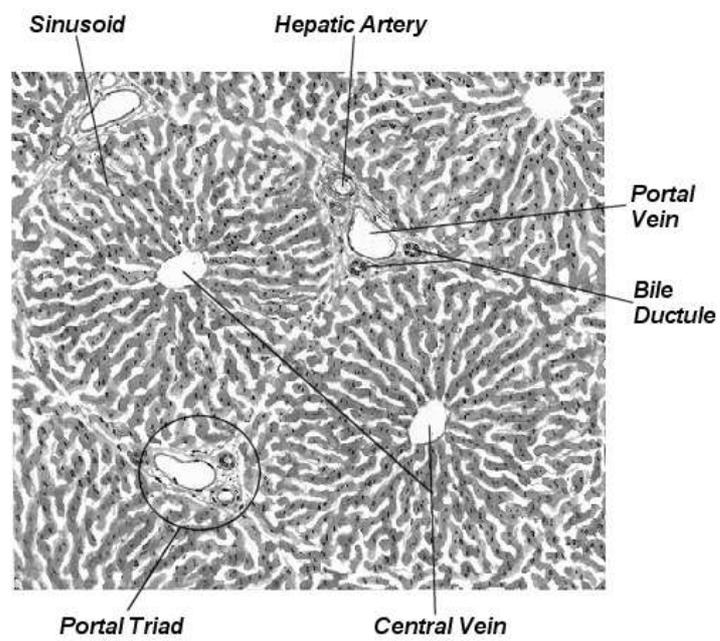


Figure 2.3: The liver lobule with portal canals (hepatic artery, portal vein and bile duct), sinusoids and collecting central veins.

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capillaries. They are orientated in a radial direction in the lobule. Sinusoids are lined with endothelial cells and Kupffer cells, which have a phagocytic function. Plasma and proteins migrate through these lining cells via so-called fenestrations (100-150 nm) into the Space of Disse, where direct contact with the hepatocytes occurs and uptake of nutrients and oxygen by the hepatocytes takes place. On the opposite side of the hepatocyte plates are the bile canaliculi situated (1  $\mu\text{m}$  diameter). Bile produced by the hepatocytes empties in these bile canaliculi and is transported back towards the portal canal into bile ductules and bile ducts, and finally to the main bile duct and gallbladder to become available for digestive processes in the intestine. The direction of bile flow is opposite to the direction of the blood flow through the sinusoids.

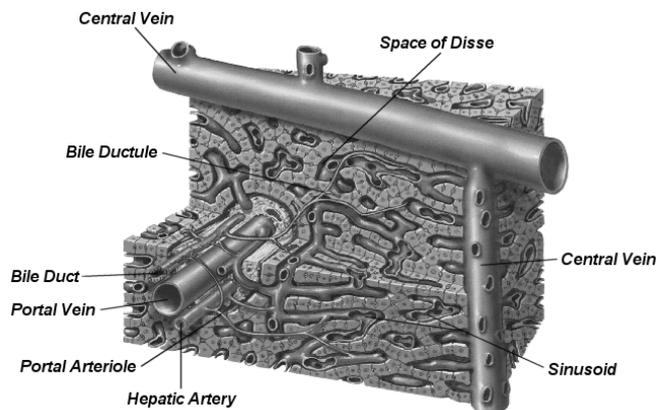


Figure 2.4: Detailed view of the liver sinusoidal structure.

## 2.2 Physiology

### 2.2.1 Pressure distribution

Blood pressure in afferent vessels and pressure distribution inside the liver, is essentially similar for most species. Pressure in the hepatic artery, originating from the descending aorta and the celiac trunc, is considered to be the same as aortic pressure. This includes a high pulsatile pressure between 120 and 80 mmHg with a frequency equal to the heart rate. Vessel compliance causes a gradual decrease in pulsation as the hepatic artery branches and rebranches inside the liver. Once

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at the sinusoidal level, pulsation amplitude decreases to virtually zero and pressure drops to approximately 2-5 mmHg. On the other hand, pressure in the portal vein, originating from capillaries of the digestive tract, has no pulsation and a pressure of 10-12 mmHg. In the sinusoids, both portal venous and hepatic arterial pressure is 3-5 mmHg. Consequently, the pressure drop inside the liver is much less in the portal venous system than in the arterial system. The pressure drop from the collecting central veins to the vena cava is then approximately 1-3 mmHg, fluctuating slightly with respiration.

### 2.2.2 Flow distribution

Total human liver blood flow represents approximately 25% of the cardiac output, up to 1500 ml/min. Hepatic flow is subdivided in 25-30% for the hepatic artery (500 ml/min) and the major part for the portal vein (1000 ml/min). Assuming a human liver weighs 1500 g, total liver flow is 100 ml/min per 100 g liver. Comparing this normalized flow rate to other species, it can be concluded that total liver blood flow is 100-130 ml/min per 100 g liver, independent of the species. The ratio of arterial:portal blood flow, however, is species-dependent. The hepatic artery originates directly from the descending aorta, and is therefore saturated with oxygen. It accounts for 65% of total oxygen supply to the liver. The hepatic artery also plays an important role in liver blood vessel wall and connective tissue perfusion. It also secures bile duct integrity. The blood from the portal vein is full of nutrients derived from the intestine and allows the hepatocytes to perform their tasks. Blood from the hepatic artery and the portal vein joins in the sinusoids. However, recent studies by others as well as our own observations, have revealed that there are both common and separate channels for arterial and portal blood. The hepatic artery perfuses the liver vascular bed in a 'spotty' pattern, while the portal vein perfuses the liver uniformly. The liver is able to regulate mainly arterial flow by means of so-called sphincters, situated at the in- and outlets of the sinusoids. One of the most important triggers for sphincter function is the need for constant oxygen supply. If the rate of oxygen delivery to the liver varies, the sphincters will react and the ratio of arterial:portal blood flow alters.

## 2.3 Physiology of Liver Preservation

Liver transplantation requires a period of preservation time, during which the liver after explantation is stored and transported outside its natural environment. The

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length of this preservation or better bridging period from donor to recipient depends on a large number of donor and recipient as well as logistical factors. Nowadays this time zone is kept between 6-15 hours of preservation, while the liver is cut off from its life sustaining mechanisms, i.e. blood flow and oxygen supply, and consequently, ischemic damage will occur. Three periods of ischemia are distinguished in a donor and transplantation procedure.

1. The first period is defined as the time in between clamping of the liver's afferent vasculature and start of the wash-out with ice-cold preservation solution during the procurement phase in the donor. In this period of ischemia, blood flow to the liver is stopped and perfusion with the preservation solution via a cannula takes place. During this period of ischemia the liver is still at body temperature, for which reason this is called warm-ischemia. During this warm-ischemic time, mainly damage to the hepatocytes occurs, and it is therefore very important to keep this period as short as possible. Especially in non-heart-beating donors (NHBDs) after cardiac arrest and awaiting the donor operation and start of cold preservation, the warm-ischemic period can become too long, and result in a serious injury of hepatocytes with non-function after transplantation.
2. The second period of ischemia starts at the moment when the ice-cold preservation solution enters the microvasculature of the liver to wash-out the blood. A good wash-out of blood cells is important to obtain optimal and uniform perfusion and cooling of the liver. Furthermore, remaining blood cells could cause inflammatory reactions and trigger the immune response of the receiving patient against these donor cells. This cold ischemic period continues during the preservation period, in which the liver is transported to the recipient, and ends at the moment that the liver is taken out of its cold environment just prior to be placed in the 'warm' recipient's abdomen during the actual implantation. This second period takes place at 0-4°C, including the wash-out with ice-cold solution and cold storage preservation period, and is defined as the period of cold ischemia. During this period of cold ischemia, not so much hepatocytes, but more endothelial and biliary epithelial cells appear to be injured.
3. The last period of this bridging ischemia is the period needed to complete the vascular anastomoses during implantation. This procedure could take 30-60 minutes, a period in which the liver lies in the abdominal cavity and is thus rewarmed by temperature of the body. Once all vessels are connected

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between donor organ and recipient vasculature, the liver is reperfused with blood and after the biliary anastomosis the transplantation is complete.

To minimize the impact of cold ischemic injury, two principal requirements for successful preservation have to be considered: the temperature effect using hypothermia and the effect of the preservation solution.

- Cooling the liver to hypothermic temperatures (0-4°C) lowers the rate of metabolism and the rate at which cellular components degrade. As a result, the need for nutrients and oxygen decreases and the organ can be preserved in a viable state for several hours (see further § 6.4).
- Although hypothermia is a key to successful preservation, it has negative side effects as well. The major drawback of hypothermia is the induction of cell swelling due to suppressed functioning of the cellular ion pumps. This can be counteracted, however, by the use of an effective preservation solution containing so-called impermeants, the use of intracellular-like solution and possibly colloids. Another reason for using a specially developed preservation solution is to prevent ischemia-induced cellular acidosis, which requires a powerful buffer. Finally, in the initial reperfusion phase during transplantation the sudden increase in available oxygen ('respiratory burst') results in the formation of toxic oxygen radicals. To counteract this last drawback, the preservation solution should contain agents that are able to scavenge oxygen free radicals (see further § 6.2).

The combination of hypothermia and the use of an adequate preservation solution prevent hypothermic and preservation-induced injury, and make it possible to keep the liver for a limited amount of time outside its physiologic environment. Cold storage allows preservation for 12-15 hours in the clinics and even beyond 48 hours in the experimental setting. This time period is considered short to fulfill all requirements of an appropriate match between donor and recipient as well as of complex logistic factors. Also, despite major achievements in organ preservation, and especially in older donors, prolonged static cold storage is still accompanied by an increased primary non-function as well as reduced long term functional outcome after liver transplantation. To date, preservation times are kept short and any prolongation without a compromise to the viability of the liver would be a significant improvement. Thus, hypothermic machine perfusion preservation could substantially increase the quality of preservation and lengthen the preservation period.