Microcirculation of the Liver

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Abstract

The microcirculation of the liver has important roles in maintenance of liver function. It guarantees the supply of the parenchymal tissue with oxygen and nutrients, serves as the gate for leukocyte entrance in hepatic inflammation, and is responsible for the clearance of toxic materials and foreign bodies from the bloodstream. The morphology and physiology of the hepatic microcirculation are described in this chapter to help the understanding of the physiology of the hepatic microcirculation.

Keywords

Microcirculation of the liver • Liver microcirculation • Liver function • Hepatic microcirculation • Physiology of hepatic microcirculation

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2.1 Dual Blood Perfusion of the Liver and Hepatic Arterial Buffer Response

The liver constitutes about 2% of the body weight in adults, thus being the largest organ in the body. It receives 25% of the cardiac output via two inflows, the portal vein and the hepatic artery. Total amount of hepatic perfusion is about 1 mL/min per 1 g liver tissue, and oxygen consumption by the liver accounts for 20% of total body oxygen consumption.

The portal vein is a valveless afferent vessel that drains the splanchnic blood flow from the capillary system of the intestine, spleen, pancreas, omentum, and gallbladder. Portal blood flow occupies about 75% of total hepatic inflow, or 90 mL/min per 100 g liver, and the remaining 20–25% is supplied by the hepatic arterial flow. The hepatic circulation drains into the hepatic venous system. The hepatic artery is a vessel of

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resistance, whereas the portal and hepatic veins are vessels of capacitance. The resistance in the hepatic arterial bed is 3–40 times that in the portal venous bed.

The hepatic arterial blood is well-oxygenated, whereas the portal vein carries partly deoxygenated, but nutrient-rich blood after passing the splanchnic system. Since half of the hepatic oxygen requirements are supplied by portal venous blood due to its high flow rate, both hepatic artery and portal vein nearly equally provide hepatic oxygenation.

The dual blood supply of the liver is a unique feature of the hepatic vasculature and distinctly determines the regulation and distribution of blood flow. There is an intimate relationship between the two vascular systems, named the "hepatic arterial buffer response," representing the ability of the hepatic artery to produce compensatory flow changes in response to changes in portal venous flow.[1,2] The artery usually has an intrinsic regulatory mechanism showing the myogenic constrictive response of the hepatic artery on rise of arterial pressure. In addition to this intrinsic autoregulation of arterial flow, the hepatic artery has another intrinsic mechanism showing regulatory responses on the change of portal flow. If the portal flow decreases, the hepatic artery dilates to increase its flow, whereas it constricts to decrease arterial flow on increase of portal flow.[3] This increase in hepatic arterial blood flow is capable of buffering 25–60% of the decreased portal flow. The hepatic arterial buffering mechanism makes the liver being perfused by a steady rate in order to cope with the wide fluctuation of splanchnic blood flow. The hepatic arterial flow also serves the hepatic role as a regulator of blood levels of nutrients and hormones by maintaining blood flow, by which hepatic clearance becomes steady.[4,5] In contrast, the portal vein cannot control its blood flow, not showing reciprocity of the hepatic arterial buffer response.[2,6] Changes in the hepatic arterial flow do not induce compensatory changes of the portal vascular flow or resistance.

The underlying mechanism of the hepatic arterial buffer response is not associated with the neural or myogenic control. Instead, adenosine is known as the putative mediator in the space of Mall driving the communication between the hepatic artery and the portal vein. The space of Mall surrounds the hepatic arterial resistance vessels and portal venules and is contained within a limiting plate that separates this space from other fluid compartments. According to the wash-out hypothesis of adenosine, adenosine accumulates in or less adenosine is washed away from the space of Mall, if portal blood flow is reduced. Elevated adenosine concentrations lead to a dilation of the hepatic artery with a subsequent increase of hepatic arterial flow.[1,7,8] In addition to adenosine, other vasoactive substances such as nitric oxide, carbon monoxide, and hydrogen sulfide, might contribute to this regulatory mechanism.[9,10]

The intrinsic arterial buffer response of the liver is preserved in cirrhotic livers.[11-13] Decreased portal venous inflow to the liver leads to a decrease in oxygen supply and thus induces a compensatory increase of hepatic arterial blood flow. This arterial buffer mechanism is maintained even after liver transplantation.[14,15] After implantation of a small-for-size liver graft, increased portal flow and pressure usually lead to reduction of the hepatic arterial flow, leading to functional dearterialization, ischemic cholangitis, and parenchymal infarcts. Reduction of portal inflow through various inflow modulation methods such as hemi-portocaval shunt or splenic artery embolization appears to be beneficial for amelioration of the overactive hepatic arterial buffer response.[15,16]

2.2 Anatomy of the Hepatic Microvascular Bed

The microcirculation is the most active part of the hepatic circulation because it regulates nutrition and function of the hepatic parenchyma and its supporting tissues. The anatomy of the hepatic microvascular bed is illustrated at Fig. 2.1.[17] Communicating networks are developed between the portal venous and the hepatic arterial circulation.[18,19] After repeated branching, the terminal hepatic arterioles and terminal portal venules supply the blood to the hepatic sinusoids. The inlet sphincters are located at the transition of the terminal portal venule to the sinusoid. The hepatic arterioles wind themselves around the portal venules sending short branches to the portal venules as arteriolo-portal anastomoses and also to the capillaries of the peribiliary plexus, which nourish the bile duct and drain into the sinusoids via arteriosinus twigs. Within the periportal tissue at the periphery of the lobule, these twigs have a complete basement membrane and unfenestrated endothelium, still resembling capillaries. A short distance downstream into the parenchyma they lose their basement membrane, become fenestrated, and

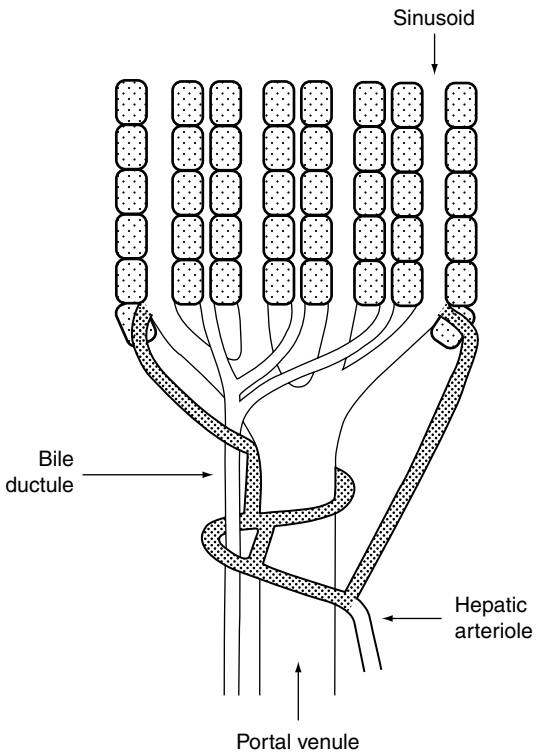

Fig. 2.1 Illustrative presentation of the microvascular bed of the liver. The hepatic arterioles, portal venules, and bile ductules are anatomically associated. The shaded area at the hepatic arterioles indicated the probable site of action responsive to vasoactive agents on the hepatic arterial circulation (From Mathie[17] with permission of Elsevier)

are true sinusoids. The terminal hepatic arteriole-derived capillaries further supply the portal venular wall as vasa vasorum and the connective tissue including the nerves of the portal tract.[19,20]

The hepatic sinusoids correspond to the capillary bed of the liver and represent the segment of the microcirculation in which supply of nutrients and removal of metabolic products take place. Main sinusoids run straight between the liver cell cords and communicate with each other through shorter interconnecting sinusoids running across the liver cell cords. Sinusoids are invested with a unique type of lining consisting of endothelial cells with flattened processes perforated by small fenestrae. These open fenestrations are arranged in clusters of 10–50 pores forming so-called "sieve plates" and represent, apart from the absence of a basement membrane, the structural peculiarity of hepatic sinusoids.[1,21,22] There is a decrease in diameter but an increase of frequency from periportal to centrilobular zones, which results in higher centrilobular porosity.

A unique cellular component of the hepatic sinusoids is the fat- and vitamin A-storing perisinusoidal cell, known as stellate cell.[23,24] External to the endothelium stellate cells are located in the space of Disse, which is the space between the basal microvilli-rich surfaces of the hepatocytes and the sinusoidal lining cells. The stellate cells not only involve in retinol metabolism and hepatic fibrogenic response to injury but also play a central role in the regulation of blood flow through hepatic sinusoids.

After flowing through the sinusoids, blood passes through outlet or efferent sphincters composed of sinusoidal endothelial cells and collected in the terminal central veins. Several of these terminal central veins may combine, increasing in diameter and reaching the sublobular vein and hepatic veins, which leave the liver on the dorsal surface and extend to the extrahepatic inferior vena cava.[18] Thus, the hepatic microcirculatory unit consists of the two terminal afferent vessels, the network of sinusoids running between the liver cords and the efferent terminal hepatic venule. The classic lobule, comprising several cone-shaped primary lobules, is a polygonal structure featured by placing the terminal central vein in the center with portal tracts distributed along its periphery. Primary lobules were renamed as hepatic microvascular subunits, consisting of a group of sinusoids supplied by a single inlet venule and its associated termination of a branch of the hepatic arteriole, finally draining into a central venule.

2.3 Regulation of the Hepatic Microvascular Blood Flow

The liver is morphologically and structurally multifaceted and has been considered second only to the brain in its complexity. All vascular segments of the hepatic microvascular subunit represent potential sites of regulation of blood flow. Regulation of portal flow by the terminal portal venule is nearly absent because its wall has no smooth muscles, but it can adjust its width to the volume flow that is determined by constriction or dilatation of the splanchnic arterioles. The hepatic arterioles are highly sensitive to metabolites, electrolytes, and vasoactive substances. These make the arterial microcirculation be adjusted to the local requirements. Various endothelial mediators,

including thromboxane A2, prostaglandin I2, angiotensin II, nitric oxide, endothelin-1, carbon monoxide, and hydrogen sulfide, are known to delicately control vascular tone under both physiological and pathological conditions.[1,2,9,10]

In addition to the presence of smooth muscle cells restricted to the afferent and efferent vessels and its branches, the sinusoids contain contractile cells, such as stellate cells, sinusoidal endothelial cells, and Kupffer cells, which all are involved in the regulation of blood flow through sinusoids. The hepatic microvascular blood flow is regulated and redistributed at the level of the microcirculation, in which both stellate cells and endothelial cells can actively control various functions of the microvasculature.

There is adjustment of microcirculation for bile secretion through a direct link between food ingestion and absorption and increased hepatic arterial flow mediated by the dilated arterioles of the peribiliary plexus. Increase in the arterial supply further leads to maintain the ratio of arterial to portal flow that is augmented during digestion.[25]

Sinusoidal perfusion failure is critically associated with the pathogenesis of tissue injury from warm ischemia-reperfusion, cold preservation and transplantation, acute liver failure, and drug-induced hepatotoxicity.[26-29] Several mechanisms are well established to contribute to sinusoidal perfusion failure, including sinusoidal narrowing caused by sinusoidal endothelial cell edema or stellate cell-mediated vasoconstriction. These cause a gradient of perfusion failure, which is most pronounced in the periportal segment of the sinusoids.[30] Upon entrapment of activated leukocytes, sinusoidal flow velocity decreases due to increased hindrance, further inducing perfusion heterogeneity and perfusion deficits. In addition, inflammation- and injury-associated adherence of leukocytes in outflow venules may alter sinusoidal perfusion due to an increase of blood viscosity and vascular resistance. Perfusion failure in sinusoids is thought to be caused by sluggish blood flow, intravascular hemoconcentration, and procoagulant conditions.[31,32]

Vascular remodeling is an important component contributing to increased intrahepatic resistance in portal hypertension in addition to alterations in vasoreactivity. Different anatomic lesions are apparent as important structural changes to the vascular compartment, including fibrosis, sinusoidal collapse, defenestration of sinusoidal cells (capillarization), hepatocyte enlargement, and formation of a basement membrane in the space of Disse, all narrowing the sinusoid.[33,34] These changes result in a reduced access of plasma and plasma-dissolved substances to hepatocytes due to their limited diffusion in the extravascular space. Capillarization of hepatic sinusoids is known to occur only in very limited regions of the cirrhotic parenchyma and seems to be less relevant for functional consequences in cirrhotic livers than the markedly smaller areas occupied by sinusoids per unit of parenchyma and the sinusoid/hepatocyte interfaces disposable for metabolic exchanges.[35] Sinusoids of cirrhotic livers further lack features of zonation, thereby contributing to the development and progression of liver failure.

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