Physiology and Anatomy of the Liver

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Teresa A. Mulaikal and Jean C. Emond

Introduction

This chapter will review the anatomy and physiology of the liver relevant to anesthetic management during complex liver surgery. Anesthetic management of the patient with chronic liver disease requires an understanding of the alterations induced in cirrhosis that affect many organ systems. Liver surgery for ablation of tumors may reduce the functional mass of the liver resulting in systemic changes that alter hemodynamics and renal function. In liver transplantation, the body is deprived of all liver function during the implantation and may receive a new liver with impaired initial function. All types of liver surgery may accentuate hepatic ischemia with reperfusion, inducing systemic changes both acute and chronic. Thus, an understanding of the liver, and its structure and function, is critical in managing the changes of the liver induced during surgery. This knowledge, applied throughout the perioperative period by anesthesiologists with interest in liver disease, has been a major factor in the markedly improved outcomes of liver surgery during the past 50 years, and especially since the era of liver transplantation.

The liver is the largest gland in the human body and the only organ capable of regeneration [1]. This unique ability has been both the subject of ancient Greek mythology and modern medicine best illustrated by the Promethean myth in which the injured liver is restored daily as Zeus' eternal punishment to Prometheus. While advances in science allow for the temporary support of renal function in the form of dialysis, and of cardiovascular and pulmonary function in the form of veno-arterial extracorporeal membrane oxygenation (VA ECMO), there is currently no effective substitute for the immune, metabolic, and synthetic functions of the liver other than transplantation (Table 1.1). The absence of artificial liver support makes a strong understanding of hepatic physiology and pathophysiology imperative to the care of critically ill patients with liver injury as management requires careful protection of remnant function while regeneration occurs.

This chapter will review normal liver anatomy, histology, and physiology. The first section covers basic liver anatomy and describes Couinaud's classification, which divides the liver into eight segments as a function of its portal venous and hepatic arterial supply. These segments serve as boundaries for the modern hepatectomy. A knowledge of each segment's vascular supply, proximity to the vena cava, and spatial orientation

T.A. Mulaikal
Department of Anesthesiology, Columbia University Medical Center, New York, NY, USA

J.C. Emond (✉)
Department of Surgery, New York Presbyteria Hospital, Columbia University Medical Center,
622 West 168th Street, PH 14 East RM 103, New York, NY 10032, USA
e-mail: je111@columbia.edu

G. Wagener (ed.), *Liver Anesthesiology and Critical Care Medicine*,
DOI 10.1007/978-1-4614-5167-9_1, © Springer Science+Business Media New York 2012

Table 1.1 Functions of the liver

Metabolic	Synthetic	Immunologic	Regenerative	Homeostasis
Xenobiotic metabolism	Coagulation factor synthesis Pro-coagulants Anticoagulants Fibrinolytics Antifibrinolytics	Innate immunity	Restoration after hepatectomy or trauma	Regulation of intravascular volume Renin Angiotensin Aldosterone
Protein metabolism Ammonia Detoxification	Plasma protein synthesis Albumin	Adaptive immunity		Glucose homeostasis
Lipid metabolism B-oxidation F.A. Triglyceride	Steroid hormone synthesis Cholesterol	Oral and allograft tolerance		Regulation of portal inflow Hepatic arterial buffer hypothesis
Glucose metabolism Gluconeogenesis Glycogenolysis Glycogenesis	Thrombopoietin Angiotensinogen Insulin-like growth factor 1 (IGF-1)			

F.A. fatty acids

is useful in judging the difficulty of resection and use of surgical techniques such as total vascular isolation to minimize blood loss. Lesions located posteriorly and adjacent to the vena cava for example may necessitate total vascular isolation.

The next section covers basic liver histology, including a discussion of microanatomy and cellular function, which has implications for the regulation of portal blood flow and the pathophysiology of cirrhosis and portal hypertension. The last section focuses on basic liver physiology, including the immunological role of the liver, the regulation of hepatic blood flow and its impairment in small for size syndrome, as well as the metabolic and synthetic functions of the liver.

Embryology

The liver derives from the ventral foregut endoderm during the fourth week of gestation, responding to signals from the cardiac mesoderm for hepatic differentiation [2–4]. The ventral foregut also gives rise to the lung, thyroid, and ventral pancreas while the dorsal foregut gives rise to the dorsal pancreas, stomach, and intestines [5]. The ventral endoderm responds to signals from the cardiac mesoderm to generate the hepatic diverticulum that transforms into the liver bud, and hepatic vasculature [6]. The portal vein derives from the vitelline veins [4]. The ductus venosus shunts blood from the umbilical vein, which carries oxygenated blood from the placenta to the fetus, to the vena cava thereby supplying oxygenated blood to the brain. The ligamentum venosum is the remnant of the ductus venosus and the ligamentum teres is the remnant of the umbilical vein.

The extrahepatic and intrahepatic biliary tracts have different origins. The extrahepatic biliary tract, which includes the hepatic ducts, cystic duct, common bile duct, and gall bladder, develops from the endoderm. The intrahepatic biliary tract, however, develops from hepatoblasts [2].

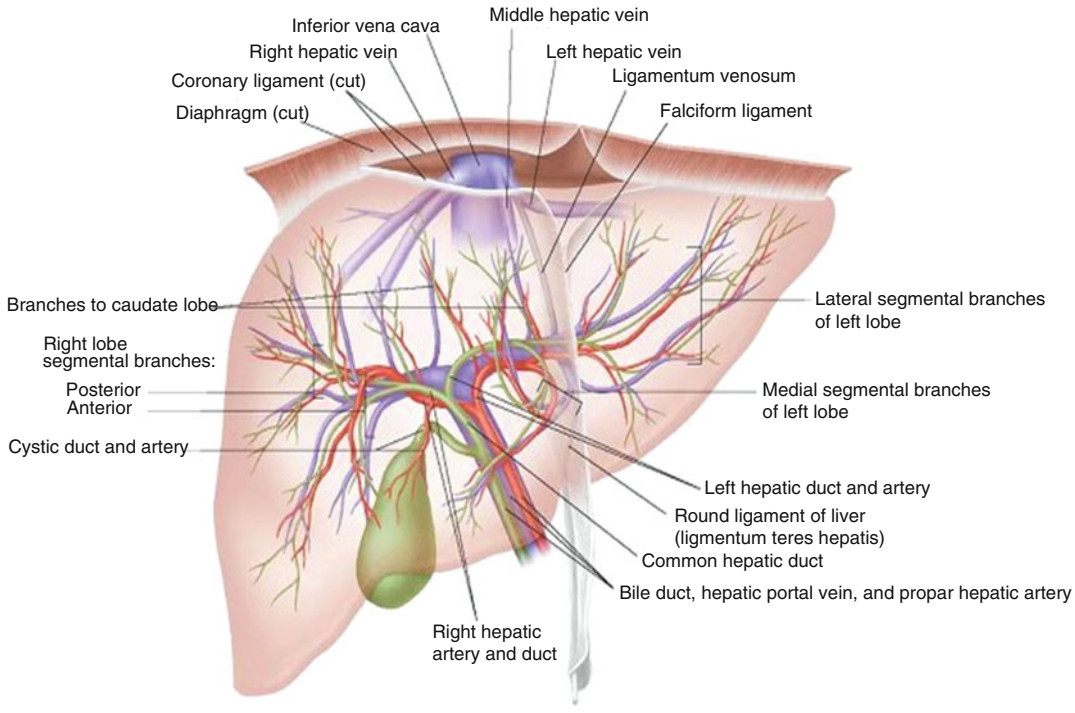

Fig. 1.1 Arterial and venous circulation of the liver. With kind permission from Lippincott Williams and Wilkins: Tank, Gest, Burket et al.; Atlas of Anatomy 2009 (Chapter 5 "The Abdomen," plate 5–22, figure A, pg 234)

Macroscopic Anatomy of the Liver and the Visceral Circulation

Anatomy relevant to surgical management and liver anesthesia includes the blood supply and the intrahepatic architecture of the liver. A much more specific knowledge of liver anatomy is required to plan and execute the operations and is beyond the scope of this chapter. The afferent bloodflow to the liver is composed of both arterial and portal blood and accounts for 20–25% of the cardiac output, and all the blood exits the liver through the hepatic veins (Fig. 1.1). The hepatic artery is derived from the celiac artery in most cases but may receive some or all of its supply from the superior mesenteric artery. The artery divides in order to supply the right and left lobes and the intrahepatic segments, and the anatomy includes several variants that are relevant in hepatic resections and biliary surgery. These variants do not affect anesthetic management other than the recognition that surgical errors may result in ischemic injury to segments of the liver. Furthermore, since the biliary tree is primarily supplied by the arterial system, bile duct ischemia may result in postoperative complications.

The portal blood accounts for the majority of the hepatic blood flow and unites the venous return from the entire gastrointestinal (GI) tract with the exception of the rectum that drains into the iliac vessels. The foregut, including the stomach, spleen, pancreas, and duodenum drain directly into the portal vein and the splenic vein, while the small intestine and the right colon drain into the superior mesenteric vein. This means that the splenic vein contribution to the portal blood is rich in pancreatic hormones and cytokines while the superior mesenteric vein brings nutrients, toxins, and bacteria that are absorbed

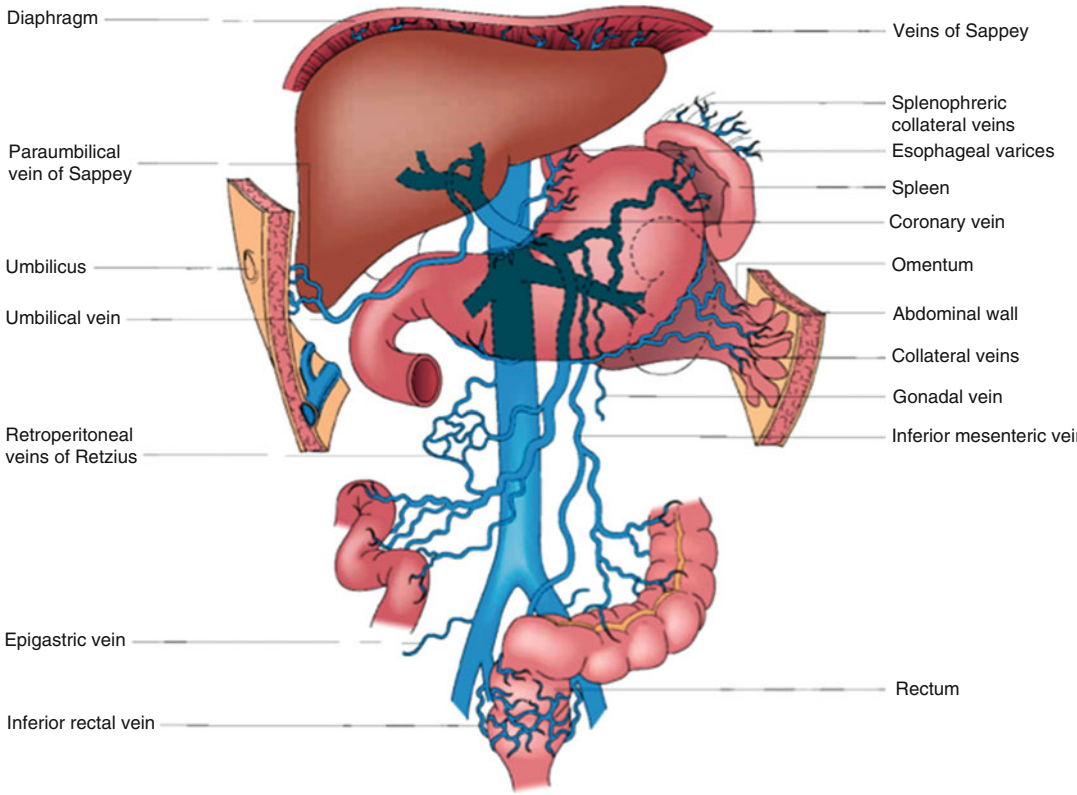

Fig. 1.2 Sites of collaterals in portal hypertension. With kind permission from Lippincott Williams & Wilkins: Greenfield's Textbook of Surgery, 5th edition 2011 (Chapter 58: "Cirrhosis and Portal Hypertension" (Emond) Figure 58.8, pg 914)

by the gastrointestinal tract. In situations of increased portal vein pressure such as cirrhosis and portal vein thrombosis, collateral veins known as varices can develop as connections between the portal vein and the systemic circulation that become enlarged and shunt blood away from the liver (Fig. 1.2). Shunting results in impaired liver function and is most pronounced in alterations of brain function discussed later in the chapter. Clinically significant varices result in gastrointestinal bleeding, including the esophagus, stomach, and duodenum, as well as the rectum. Other collateral shunts occur in the retroperitoneum and the abdominal wall, and may accommodate large amounts of portosystemic shunting without bleeding but with other consequences of impaired portal blood flow. In addition to the loss of metabolic transformation, the reticulo-endothelial protective function of the liver is also bypassed in the presence of large shunts and may result in sepsis and contribute to the hemodynamic alterations of cirrhosis discussed below.

The hepatic veins are of great functional significance to the liver and are of surgical and anesthetic importance. They join at the diaphragm and enter the right chest, therefore, unlike the remainder of the abdominal circulation, are exposed to alterations in intrathoracic pressure. The liver is exquisitely sensitive to outflow pressure, and obstruction of the hepatic veins, for example in Budd-Chiari syndrome or right heart failure, causing severe functional impairment of

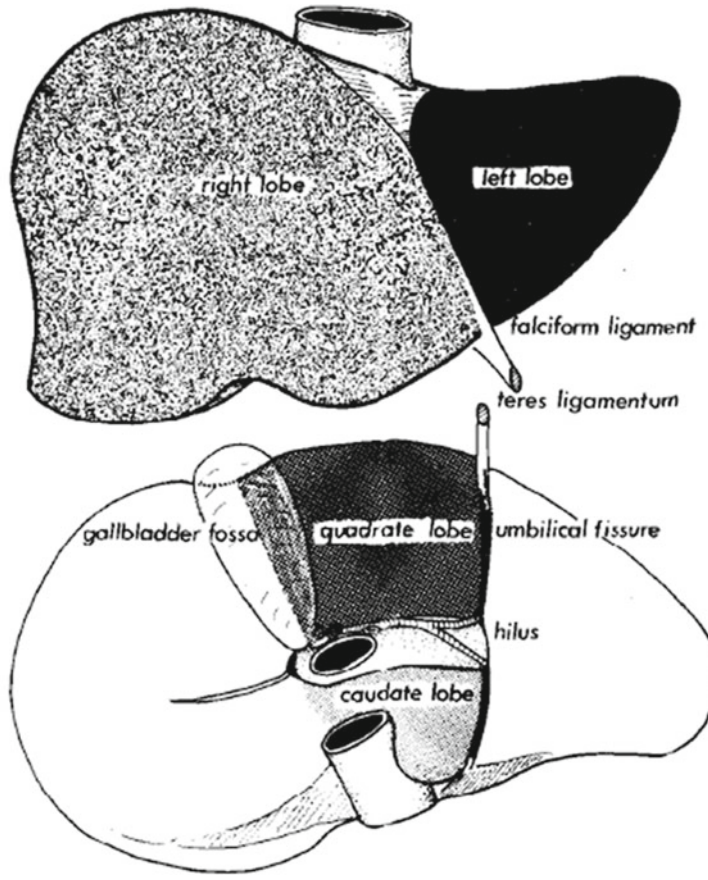

Fig. 1.3 External anatomy of the liver. With kind permission from Springer Science + Business Media [7]

the liver. During liver surgery, obstruction of the hepatic outflow especially if combined by vena cava clamping or twisting, may result in acute hemodynamic instability. To avoid hemodynamic collapse as the liver is being manipulated, minute to minute communication between the surgeon and anesthesiologist is critical.

The external anatomy is described from gross landmarks including the gallbladder, the vena cava, and the hepatic ligaments (Fig. 1.3) [7]. The internal anatomy is defined by the vessels, and eight functionally independent segments each with an afferent pedicle including artery, portal vein and bile duct, and efferent hepatic vein (Fig. 1.4). From the exterior, the apparent right lobe of the liver is defined by the vena cava and the gallbladder fossa. This is typically 55–70% of the hepatic tissue and is supplied by the right hepatic artery and the right portal vein, and is drained by the right hepatic vein and comprised of segments V–VIII. The central plane between the right and left lobes of the liver is defined by the middle hepatic vein. The left lobe is more complex. An external left lobe is defined by the falciform ligament (and is termed by some surgeons as the "left lateral segment," but consists anatomically of two segments, II and III). The medial portion of the left lobe is morphologically described as the quadrate lobe and is actually segment IV. The left lobe segments are supplied by the left hepatic artery and portal vein, and drained by the left and middle hepatic veins. The caudate lobe (segment I) is central and fully independent of either right or left livers.

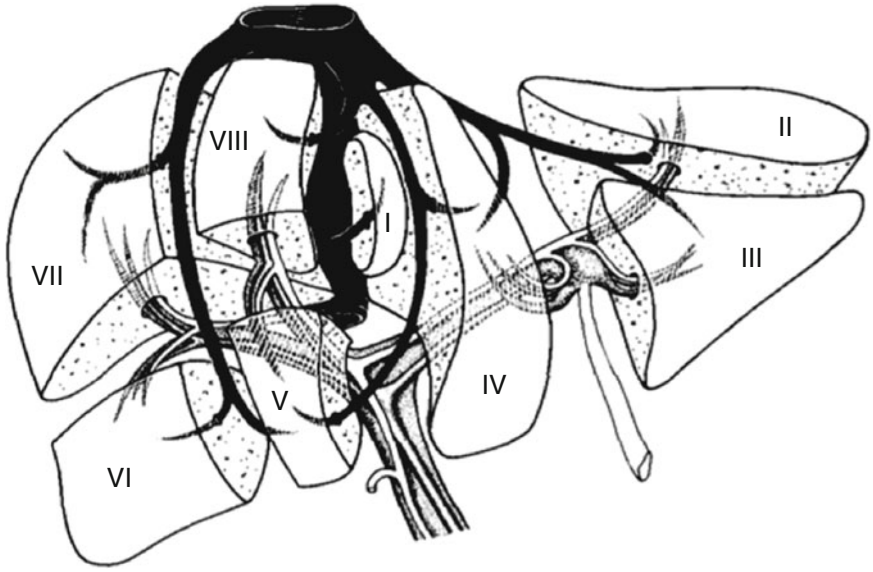

Fig. 1.4 Internal anatomy. With kind permission from Springer Science + Business Media [7]

Histology

Cellular Classification

The liver is composed of a rich population of specialized cells that permit it to carry out its complex functions, grossly characterized as "parenchymal" cells: the hepatocytes, and "nonparenchymal cells": all others. The nonparenchymal cells include stellate cells, sinusoidal endothelial cells, kupffer cells, dendritic cells, and lymphocytes (Fig. 1.5, Table 1.2). The hepatocytes or parenchymal cells make up 60–80% of liver cells [8] and carry out the liver's metabolic, detoxification, and synthetic functions. The hepatocytes have a unique relationship with the sinusoidal endothelium that carefully regulates the exposure of the hepatocytes to the metabolic substrate arriving in the portal blood through fenestrations. The baso-lateral membrane of the hepatocyte absorbs nutrients from the sinusoids, which are then processed with excretion of the metabolic products through the apical cell membrane into the bile duct. Hepatocytes divide under stress and cytokine stimulation and are the principal components of mass restoration during regeneration. In vitro, hepatic mitotic activity is stimulated by hepatocyte growth factor (HGF), cytokines, and tumor necrosis factor alpha (TNF) clinically observed after hepatectomy, toxic cell necrosis, or trauma [9].

Hepatic stellate or Ito cells are vitamin A and fat storing cells located in the perisinusoidal space of Disse, described by Toshio Ito in 1951 [10, 11] and are of tremendous importance and scientific interest as critical regulators of hepatic function and prime suspects in the pathogenesis of cirrhosis. In the normal liver, stellate cells are quiescent but can become activated by injury and transform into collagen secreting myofibroblasts with contractile properties. This fibroblast-like cellular activity of hepatic stellate cells has a protective function in the generation of scar tissue, promotion of wound healing, and remodeling of the extracellular matrix [12]. Excessive collagen deposition is the underlying mechanism of fibrosis and cirrhosis [13]. Hepatic stellate cell secretion of collagen in the perisinusoidal space of Disse narrows the sinusoidal lumen, thereby increasing hepatic vascular resistance and contributing to portal hypertension [10]. The impact of this dis-

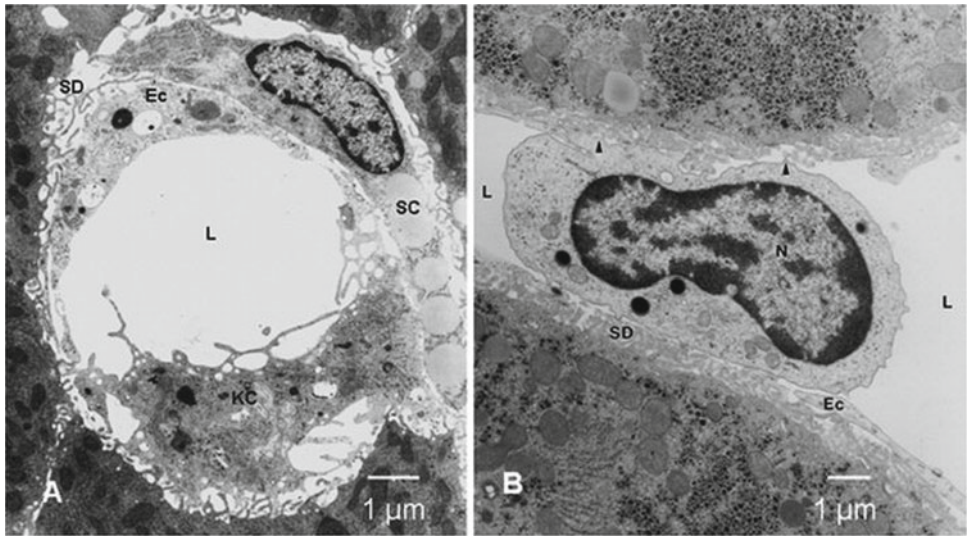

Fig. 1.5 Transmission electron micrographs of (**a**) sinusoidal endothelium (Ec) with attached Kupffer cell (KC) encasing the sinusoid lumen (L), and perisinusoidal stellate cell (SC) containing fat droplets in space of Disse (SD); and (**b**) Pit cell with typical dense granules. This pit cell is in close contact with the endothelial lining and is seen to contact microvilli of the parenchymal cells (*arrowheads*). *Ec* endothelial cell; *f* fenestrae; *L* sinusoidal lumen; *N* nucleus; *SD* space of Disse (with kind permission from McCuskey [20], Figure 5 slide A, Figure 6 slide B)

turbance on sinusoidal perfusion creates a secondary ischemic injury, potentially accelerating the destructive impact of an initially limited injury [12]. Stellate cells also have intrinsic contractile function important in the regulation of blood flow and the pathogenesis of portal hypertension. Vasopressin, endothelin-1, and angiotensin II bind to receptors on stellate cells, activating a rho-mediated signal transduction pathway and myosin II contraction [10, 13]. Endothelin-1, angiotensin II, vasopressin, and their receptors have been studied as therapeutic targets for the treatment of portal hypertension and the management of variceal bleeding [14–18].

Hepatic endothelial cells are fenestrated cells that line the sinusoids and also play an important role in the regulation of intrahepatic resistance to blood flow through expression endothelial nitric oxide synthase (eNOS) and release of nitric oxide (NO), a potent vasodilator [19, 20] (Fig. 1.6a). Disruption of sinusoidal endothelial cells in cirrhosis results in a concomitant decrease in the production of NO [21]. This is in contrast to the mesenteric vascular bed that has an increased NO production in portal hypertension [21]. NO-mediated increase of splanchnic flow is consistent with the *forward flow theory* of portal hypertension that states that portal hypertension is not only due to an increase in hepatic vascular resistance but also due to splanchnic hyperemia [22]. Neoangiogenesis mediated by vascular endothelial-derived growth factor (VEGF) also contributes to splanchnic hyperemia and the hyperdynamic state of end stage liver disease [23, 24].

The kupffer cells are macrophages that reside in the hepatic sinusoids and constitute 80–90% of the macrophages in the human body [25] (Fig. 1.6b). These cells are specialized due to their exposure to high concentrations of endotoxin and oxidative stress in the sinusoids and are critical protectors of the systemic circulation from toxic exposure. They are part of the innate immune system, which is the intrinsic host defense system that allows nonspecific targeting of foreign antigens in contrast to the adaptive immune system that allows specific targeting of foreign antigens. There is a close relationship between the regulation of blood flow and kupffer

Table 1.2 Cellular microanatomy

	Function	Derivation	Percentage of liver cells
Hepatocytes	Hepatic regeneration Xenobiotic metabolism Protein synthesis and metabolism Lipid synthesis and metabolism APCs—innate immunity	Anterior portion of definitive endoderm	60–80
Stellate/Ito cells	Vitamin A and fat storage Collagen secreting myofibroblasts Scar tissue and wound healing Fibrosis and cirrhosis Contractile cells Regulate vascular resistance APCs—innate immunity	Endoderm or septum transversum mesenchyme	5–15
Liver sinusoidal endothelial cells	Fenestrated endothelial cells Release of nitric oxide (NO) Regulate vascular resistance APCs—innate immunity	Angiogenesis of existing vessels from septum transversum mesenchyme	15–20
Kupffer cells	Macrophages APCs—innate immunity NO, TNF alpha, cytokines Ischemia reperfusion injury Downregulation of APC and T cell activation mediating tolerance	Bone marrow	15
Dendritic cells	APCs—innate immunity	Bone marrow	<1
Lymphocytes			
NK	Nonspecific targeting of tumor and viruses—innate immunity	Bone marrow	5–10
NKT	Target lipid antigens—innate and adaptive immunity	Thymus	
T cells	Cell-mediated adaptive immunity	Thymus	
B cells	Humoral-mediated adaptive immunity	Bone marrow	
Cholangiocyte	Bile duct cells	Hepatoblasts-→ intrahepatic biliary tree Ventral endoderm-→ extrahepatic biliary tree	<1

Table created from the following publications [8, 10, 12, 92, 93]. *APCs* antigen presenting cells; *NO* nitric oxide

cell macrophage function based on the NO pathway [26] resulting in consistent overlap between ischemic and inflammatory injury to the liver.

Hepatic dendritic cells are antigen presenting cells (APCs) synthesized in the bone marrow that can migrate from the liver to lymphoid tissue, though they are often localized near the central vein [27]. They serve a critical role in antigen presentation and activation of T lymphocytes when encountering an antigen. A subpopulation of dendritic cells become resident in the liver and functions in this unique environment as key initiators of innate immunity modulating or in other cases activating acute inflammatory responses [28].

Though small in number relative to other cell populations in the liver, hepatic lymphocytes include natural killer cells, NKT cells, T lymphocytes, and B lymphocytes. Natural killer (NK) cells are part of the innate immune system and are known for their nonspecific targeting of tumor

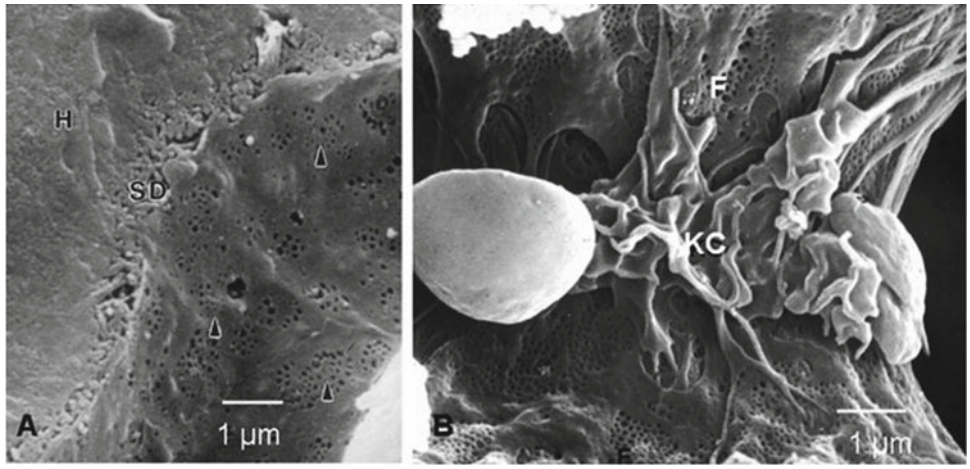

Fig. 1.6 Electron micrographs of sinusoidal endothelial cell, hepatic stellate cell, and Kupffer cell. (**a**) Scanning electron micrographs of sinusoid illustrating fenestrae organized in clusters as "sieve" plates (*arrowheads*). *SD* space of Disse; *H* hepatic parenchymal cell. (**b**) Kupffer cell (KC) attached to luminal surface of sinusoidal endothelium by processes that penetrate fenestrae (with kind permission from McCuskey [20], Figure 5 slide A, Figure 6 slide B)

cells and viruses. NKT cells link the innate and adaptive immune systems. They are a subpopulation of lymphocytes with T cell markers and NK cell surface receptors. Conventional T and B lymphocytes are part of the adaptive immune system and play a role in epitope specific cell and antibody mediated destruction of foreign antigens.

Anatomic Lobules and Metabolic Zones

The microscopic anatomy of the liver can be conceptualized either morphologically as anatomic hepatic lobules or functionally as precise metabolic zones. The hexagonal hepatic lobule is centered around the central vein with the portal triad (hepatic artery, portal vein, and common bile duct) at each corner of the hexagon. These microscopic-ordered aggregations of liver cells are complete and independent units of metabolic capacity that recapitulate on a tiny scale the entire liver. The hepatic artery and portal vein travel together, and transport blood containing oxygen and splanchnic metabolites to the liver, that the functional hepatocytes in the hepatic lobule then process and drain into a common central vein. Bile from each hepatocyte drains into canaculi. These canaculi join to form the ductules that aggregate to form the inter-lobular bile ducts and eventually the macroscopic segmental ducts. Segmental ducts bring bile to the common bile duct that drains into the gallbladder and duodenum. A more functional histologic classification of the liver defines metabolic zones that form the hepatic acinus [29, 30]. Zone I is known as the periportal zone and is centered around the portal triad, making it oxygen rich given its proximity to the hepatic artery. This periportal zone is the most resilient to hemodynamic stressors, least susceptible to necrosis and the first to regenerate. The cells in zone I also have distinct metabolic capacity and focus on aerobic functions of the liver such as gluconeogenesis and glycogenolysis, generating a fuel source for the body's extrahepatic work [30–32]. Zone I also is the site of cholesterol synthesis and beta-oxidation of fatty acids. It is active in the degradation of amino acids in the urea cycle, which is responsible for the majority of ammonia metabolism in the body [30, 31]. While enzymes involved in this periportal zone are expressed throughout the acinus, they are metabolically most active in zone I. Zone II is the intermediate zone between zones I and III. Zone III is the pericentral or perivenous zone and is in close proximity to the central vein. This zone has the lowest oxygen tension (PaO_2), is the most

susceptible to hemodynamic stressors, and the last to regenerate. Zone III is involved in ketogenesis, which generates ketone bodies for the extrahepatic tissues during fasting states. Zone III is also the site of drug detoxification, or phase I and II metabolism [31].

Immunological Function of the Liver

Innate and Adaptive Immunity

The liver is an integral part of both the innate and adaptive immune systems. The innate immune system is the intrinsic host defense system that allows nonspecific targeting of foreign antigens. Of the nonparenchymal cells in the liver, there are four types of APCs that function as immunologic gatekeepers, engulfing bacteria that enter the portal system from the splanchnic circulation, presenting antigenic epitopes to effector T and B lymphocytes, and preventing bacterial entry into the systemic circulation. These four APCs, kupffer cells, dendritic cells, stellate cells, and sinusoidal endothelial cells are all part of the innate immune system.

The innate immune system also includes natural killer (NK) cells and natural killer T (NKT) cells. NK cells play a role in destruction of tumor, bacteria, viruses, and parasites by killing cells that lack "self" major histocompatibility complex I (MHC I) markers [25]. They release granules with perforin that punctures cell membranes and granzymes that lyse internal cellular contents, thereby inducing apoptosis of the target cell. The number of NK cells may comprise up to 90% of total lymphocytes in patients with hepatocellular carcinoma, and diminished function of NK cells has been associated with increased tumor burden [25]. NKT cells link the innate and adaptive immune systems. They are a subpopulation of lymphocytes with NK cell surface receptors and T cell markers [25]. NKT cells target lipid antigens such as glycolipids of mycobacterial cell walls [33].

The adaptive immune system is the acquired host defense system that allows epitope-specific cell and antibody-mediated destruction of foreign antigens, utilizing memory for fighting subsequent infections. Members of the liver's adaptive immune system include conventional T and B lymphocytes involved in cell-mediated/cytotoxic and antibody-mediated/humoral immunity respectively. In contrast to the cellular composition in the peripheral circulation, the hepatic circulation has a predominance of nonspecific innate immune cells, which is fitting considering its function as immunologic gatekeeper, regulating the passage of antigens from the splanchnic to portal to systemic circulation [34].

Oral and Allograft Tolerance

The liver strikes a balance between immunity to infection and tolerance of commensal bacteria and orally consumed antigens, a concept known as oral or systemic tolerance [35]. This immunologic adaptation may underlie the physiologic mechanism of allograft tolerance, the transplantation of organs between the same species of varying genotypes. In 1960 Peter Medawar won the Nobel Prize in Physiology or Medicine for describing the tolerance of skin grafts between dizygotic twin cattle [36, 37]. This observation was thought to be due to the in utero exposure of each twin to erythrocytes of the other [38]. Animal models of porcine allogenic transplantation illustrate the ability to transplant livers though not kidneys, between unrelated pigs [39]. Pigs, mice, and rats will accept unrelated livers without immunosuppressive therapy and human liver recipients can wean their immunosuppressive regimen over time [28].

This concept of tolerance describes the liver's ability to downregulate T cell activation or "tolerate" antigens that present no harm. Tolerance is mediated by cytokines such as TNF alpha and interleukin 10 (IL-10). Kupffer cells release these cytokines, which in turn downregulate the activity of antigen presenting dendritic and sinusoidal epithelial cells, thereby decreasing T cell activation [8]. Tolerogenicity is important in liver transplantation and may explain why donor leukocytes can improve hepatic allograft survival [40].

The mechanism underlying enteric tolerance associated with the liver may be mediated by lipopolysaccharide (LPS) endotoxin, a cell wall component of gram-negative bacteria [41]. The portal vein delivers antigens to the liver often in the form of LPS, which complexes with toll-like receptor 4 (TLR 4) and its coreceptors MD 2 and CD14 on APCs. The constitutive exposure of LPS to these APCs is thought to result in a dampening of the immune response or tolerance [41].

Hepatic Blood Flow

Normal Venous Pressure Gradients

The liver receives approximately 1,500 mL of blood per minute or 20–25% of cardiac output, of which three fourths is from the portal vein and one fourth from the hepatic artery [10, 34, 42]. The liver acts as a low resistance reservoir for storage of blood during times of hypervolemia and a source of blood during times of hypovolemia [43, 44]. In a healthy liver blood flows from the portal vein through this low resistance system to the hepatic sinusoids, hepatic veins, vena cava, to the right atrium. The pressure is highest in the portal vein and lowest in the right atrium favoring forward flow to the heart. Directly measuring portal venous pressure is technically challenging and studies have found that in a cirrhotic liver, the wedged hepatic venous pressure (WHVP) is a reliable estimate of portal pressure [45]. In a patient with a healthy liver, however, WHVP is actually a measurement of hepatic sinusoidal pressure. The occlusion of blood flow by a balloon in the hepatic vein transduces the pressure in a static column of fluid from the adjacent vessel [46, 47]. The hepatic venous pressure gradient (HVPG) is the difference between portal vein and hepatic vein pressures, normally 1–5 mmHg and greater than 10–12 mmHg in portal hypertension [47]. This gradient is important in determining the degree of portosystemic shunting and the likelihood of its complications such as variceal bleeding and hepatic encephalopathy [47].

Hepatic Arterial Buffer Response

While hepatic outflow may vary, maintaining constant inflow is crucial for optimal drug metabolism and the synthetic functions of the liver. This regulation of hepatic blood flow is achieved by the *hepatic arterial buffer response*. When portal venous flow rises, hepatic arterial flow falls, and when portal venous flow falls, hepatic arterial flow rises thereby maintaining total hepatic inflow constant [42]. This inverse relationship is called the hepatic arterial buffer response since the hepatic artery "buffers" changes in portal venous flow to maintain a steady state [48]. While changes in portal flow affect hepatic arterial tone, the reverse is not true. Hepatic arterial tone does not affect portal venous flow therefore the relationship is not one of reciprocity [48].

In organs such as the brain, vascular tone is determined primarily by oxygen and carbon dioxide tension (pO_2 and pCO_2), however, these factors do not seem to affect hepatic arterial tone. Hypoxia and hemodilution do not cause hepatic artery vasodilation rather hepatic artery tone is modulated by portal venous inflow. Experiments that induce hypermetabolic states have found that the liver responds to increased oxygen demand by increasing hepatic oxygen uptake and reducing portal and hepatic venous oxygen content without dilatation of the hepatic artery [49]. This observation is possibly the explanation for necrosis or cell death associated with alcohol intoxication or thyrotoxicosis, in which the liver is unable to respond to increased oxygen demand by hepatic artery vasodilation [49]. Carbon dioxide tension (pCO_2), seems to be unaffected [49].

Adenosine, a potent vasodilator, modulates this physiologic response. Adenosine is produced in smooth muscle and tissues is the space of Mall surrounding the hepatic vasculature and is able to diffuse locally to exert its effect [42]. When injected into the portal vein, adenosine causes significant hepatic arterial dilation [50]. Elevations in portal venous flow "wash out" locally produced adenosine, thereby decreasing hepatic arterial flow. Conversely, low portal flow causes

an accumulation of adenosine and hepatic arterial dilatation [50]. This concept is described as the *adenosine washout hypothesis* [50, 51].

Small for Size Syndrome

This peculiar situation occurs after massive hepatic resection or in transplantation when extremely small livers are used either from liver donors or whole organ donors much smaller than the recipient. In brief, the hepatic mass is not sufficient for the needs of the host. The study of this complication arose in the early work with living donor liver transplantation and raised some fundamental physiologic questions about the limits of adaptation of the liver and the extent of regeneration in the clinical setting [52]. Small for size syndrome is characterized by coagulopathy, cholestasis, hyperbilirubinemia, and ascites that results from transplantation with a donor graft to recipient weight ratio of less than 0.8–1% [53]. The adenosine-mediated regulation of hepatic inflow as described by the hepatic arterial buffer response has implications in the pathogenesis of small for size syndrome. Portal hyperperfusion of the relatively small-sized recipient results in graft dysfunction. Sinusoidal congestion, endothelial damage, obliteration of the space of Disse, and hepatocyte apoptosis are the histologic markers of this syndrome [54]. High portal venous pressures in the first week following living donor liver transplantation in small for size grafts result in increased patient morbidity and mortality [55]. Furthermore, elevation of portal venous pressure is associated with a decrease in hepatic arterial flow, more pronounced in split liver transplantation of left compared to right liver grafts. The lower the graft to recipient volume ratio (left lobe ratio lower than right lobe ratio), the higher the portal vein flow and pressure and therefore the lower the hepatic arterial flow [56]. The hepatic arterial buffer response, as measured by hepatic artery flow in response to portal vein occlusion remains intact in split liver grafts shortly after reperfusion, however, the hepatic arterial flow is much less in split liver grafts compared to whole grafts [56]. Evidence in animal models suggests that while the hepatic arterial buffer response may be preserved immediately after reperfusion, postoperative normalization of portal venous blood flow is not accompanied by a concomitant elevation or normalization of hepatic arterial flow [57]. An impaired hepatic arterial buffer response characterized by hepatic arterial vasospasm is important in the pathogenesis of small for size syndrome. Clinically, a sustained postoperative reduction in hepatic arterial flow can result in centrilobular tissue necrosis, biliary ischemia, and hepatic artery thrombosis. In the porcine model, intra arterial injection of adenosine can reverse these histopathologic findings and improve graft survival [57].

Hepatic Drug Metabolism

First Past Metabolism

Drugs administered intravenously have 100% bioavailability because the original form of the drug reaches the systemic circulation unchanged. Drugs ingested orally, however, undergo first pass metabolism. The intestines and liver absorb and process drugs thereby decreasing the effective dose that enters systemic circulation. Drugs with a high bioavailability are minimally metabolized by enzymes of the enterohepatic system. In contrast, drugs with a low bioavailability are extensively metabolized by enterohepatic enzymes. Drugs that undergo extensive first pass metabolism are particularly susceptible to fluctuations in blood levels if their enzymatic metabolism is altered by co-ingestants [58].

Phase I and II Reactions

The enzymes involved in drug metabolism in the liver are part of the P450 cytochrome family, located in metabolic zone III. Cytochrome P450s catalyze phase I reactions. Phase I reactions are oxidation, reduction, and hydrolysis reactions that increase the polarity of substances for excretion or for further metabolism by phase II enzymes [59]. Phase II enzymes, such as uridine diphosphate

glucuronosyl transferases (UGTs), sulfotransferases, and glutathione-S-transferases, conjugate phase I metabolites to substances such as glucuronate, sulfate, and glutathione [59]. These conjugation reactions transform drugs into hydrophilic substances, thereby increasing their solubility in bile and blood for excretion. Absence or dysfunction of these phase I or II enzymes can result in hyperbilirubinemia and encephalopathy.

In Gilbert's syndrome, there is a mutation in the promoter region of bilirubin-UGT that leads to decreased levels of normally functioning enzyme, reduced conjugation of bilirubin with glucoronide, and an unconjugated hyperbilirubinemia. In Crigler-Najjar syndrome, there is a mutation in the coding region of bilirubin-UGT that results in absent or defective bilirubin-UGT, unconjugated hyperbilirubinemia, and in some cases kernicterus [60].

Similarly, depletion of molecules involved in these conjugation reactions can result in liver injury. Acetaminophen toxicity for example occurs because of the relative depletion of glutathione and the accumulation of *N*-acetyl-*p*-benzoquinone-imine (NAPQI), the unconjugated toxic acetaminophen byproduct. The accumulation of NAPQI leads to zone III or centrilobular necrosis. *N*-acetylcysteine, a precursor to glutathione and a free radical scavenger, may be of benefit in the treatment of acetaminophen toxicity [61]. Some studies have also suggested its use in decreasing ischemia reperfusion injury, primary graft dysfunction, and acute kidney injury in liver transplantation [62, 63]. These findings, however, are controversial and not all studies have proven definitive benefit of *N*-acetylcysteine in the perioperative transplant setting [64].

Substrates, Inducers, Inhibitors of P450 System: Implications for Toxicity and Therapeutic Failure

Many commonly used drugs in the clinical setting interact with P450 enzyme substrates either as inhibitors or inducers. Inhibitors slow down P450 enzyme activity, thereby increasing the substrate bioavailability. This can result in drug toxicity, which has profound implications for medications with a narrow therapeutic index, such as the P450 substrate warfarin. Initiating treatment with inhibitors such as azoles, macrolides, beta blockers, calcium channel blockers, and proton pump inhibitors may lead to a supratherapeutic INR and clinically significant bleeding. Conversely, initiating treatment with a P450 inducer such as phenobarbital, phenytoin, rifampin, or dexamethasone may cause therapeutic failure.

Substrate competition can also lead to therapeutic failure as demonstrated by the interaction between clopidogrel and proton pump inhibitors. Recent studies have suggested that the use of proton pump inhibitors may decrease the efficacy of clopidogrel resulting in an increased incidence of hospitalization for recurrent myocardial infarction or percutaneous coronary intervention (PCI) [65, 66]. Cytochrome 2C19 (CYP 2C19) is the enzyme that activates the prodrug of clopidogrel and the enzyme that metabolizes proton pump inhibitors [67]. Competition for this enzyme causes a decreased activation of clopidogrel and an increased risk of acute coronary syndrome. There are over 50 P450 enzymes and numerous drug interactions. A knowledge of clinically relevant substrates, inducers, and inhibitors is useful in predicting these types of enzyme interactions [68–71].

Hepatic Glucose, Amino Acid, and Lipid Metabolism

Glucose Homeostasis

The liver has the ability to produce glucose during fasting states to preserve euglycemia. It is the main site of gluconeogenesis, the synthesis of glucose from pyruvate, lactate, glycerol, and amino acids. The liver also stores glucose in the form of glycogen which can be converted back to glucose during fasting states in the glycogenolysis pathway. Epinephrine stimulates glycogenolysis during states of stress. Both gluconeogenesis and glycogenolysis take part in the periportal metabolic zone I of the liver, the zone closest to the portal triad.

During nonfasting states the liver is able to store glucose by glycogenesis or convert glucose to pyruvic acid and ATP by glycolysis. These processes take place in metabolic zone III, or the pericentral zone. This zonal heterogeneity or differential expression of metabolic enzymes prioritizes crucial metabolic functions that provide energy or glucose to the body during fasting states by placing them in close proximity to the oxygen and nutrient rich environment of the portal triad [30]. The minute to minute regulation of glucose homeostasis is clinically relevant in that hypoglycemia is the most dramatic manifestation of liver failure and generally implies a terminal state of hepatic failure.

Protein Metabolism and Hepatic Encephalopathy

When the body has sufficient protein stores, the liver transforms additional amino acids to ammonia in the urea cycle. Ammonia detoxification involves the degradation of proteins to their amino acid components, the breakdown of amino acids to alpha ketoacids and ammonia, and the generation of urea. This process occurs in the oxygen rich periportal zone I. The enzyme glutamine synthetase located in the perivenous zone III, then transforms ammonia and glutamate to glutamine. Liver dysfunction of any etiology results in hyperammonemia from both a decreased ability to produce urea and glutamine, and diminished first pass metabolism from portosystemic shunts [72]. Ammonia is neurotoxic, as is the excitatory neurotransmitter glutamate when present in excess [72]. Ammonia diffuses into brain astrocytes, causing edema and hepatic encephalopathy. Cerebral astrocytes can convert some ammonia to glutamine but supraphysiologic levels of glutamine result in an osmotic intracellular gradient and subsequent edema, elevated intracranial pressure, and at its worst herniation [72]. This is the basis of the ammonia-glutamine hypothesis of intracranial hyptertension in fulminant hepatic failure.

There are two types of cerebral edema: cytotoxic edema that results from cellular swelling due to an increase in osmotic load and intracellular water absorption, and vasogenic edema from the increased permeability of solutes and solvents through a disrupted blood brain barrier [73]. Cerebral edema due to fulminant hepatic failure is predominantly cytotoxic with a preserved blood brain barrier and responds to osmotic diuretics such as mannitol and hypertonic saline [73, 74]. Intracranial hypertension is less common in chronic liver failure due to a compensatory intracellular increase in solute load.

Lipid Metabolism and Nonalcoholic Fatty Liver Disease

The liver is the principal site of lipid metabolism, both in absorption of dietary fats and their de novo synthesis. Dietary fats are emulsified by bile salts and absorbed in the form of micelles by the intestine and delivered to the liver via enterohepatic circulation. Fatty acids can be hydrolyzed by beta-oxidation to generate energy or ATP for the body's extrahepatic metabolism. During fasting states, starvation, or diabetic keto-acidosis (DKA) when glucose is not available to the body, the liver can generate ketone bodies (acetoacetic acid, beta hydroxybutyric acid, and acetone) from fatty acids that can be used by organs such as the brain [75]. Conversely, in nonalcoholic fatty liver disease (NAFLD) when hepatic lipid content or steatosis constitutes 5% of liver weight, there is an increase in triglyceride synthesis and defective insulin-mediated inhibition of lipolysis [76, 77]. Metabolic syndrome, defined as visceral obesity associated with hypertension, dyslipidemia, and hyperglycemia may also be associated with NAFLD by a similarly impaired insulin-mediated inhibition of lipolysis [78, 79]. This metabolic derangement of lipid metabolism has striking clinical implications since NAFLD is the most prevalent liver disease and can progress to nonalcoholic steatohepatitis (NASH) [77]. Close to half of patients with NASH develop fibrosis and one sixth develop cirrhosis, which may eventually lead to liver failure requiring transplantation [80].

Liver Coagulation and Fibrinolysis

The liver is a major organ involved in hemostasis since it is the primary synthetic site of procoagulants, anticoagulants, fibrinolytics, and antifibrinolytics [81]. While extrahepatic sites such as the endothelium contribute to synthesis of some coagulation factors such as factor VIII and von Willebrand factor (vWF), the liver remains the principal synthetic site of coagulation cascade components. Primary and secondary hemostasis requires the formation of a platelet plug and fibrin clot, triggered by tissue trauma or endothelial damage [82]. While platelets are made in the bone marrow, they are often sequestered in the spleen of patients with portal hypertension and splenomegaly [83]. This platelet sequestration contributes to thrombocytopenia and bleeding in those with end stage liver disease. The liver synthesizes fibrinogen (factor I), prothrombin (factor II), factor V, and factors VII–XIII. It also synthesizes anticoagulants such as antithrombin III, protein C, protein S, selected fibrinolytics such as plasminogen, and antifibrinolytics such as alpha 2-antiplasmin and thrombin activatable fibrinolysis inhibitor (TAFI) [81]. The balance between procoagulants and anticoagulants in liver failure determines the risk of bleeding or thrombosis. In end stage liver disease, the balance may be tipped towards anticoagulant and fibrinolytic factors predisposing patients to bleeding, though cases of venous thrombosis can occur secondary to venous stasis or hepatocellular carcinoma [84]. Traditional laboratory makers of coagulopathy such as prothrombin time (PT) and partial thromboplastin time (PTT) may not accurately portray the balance between procoagulant and anticoagulant factors in liver disease. PT and PTT reflect the degree to which pro-coagulants factors are depressed but not whether anticoagulants such as protein C can offset this deficiency since reagents used in these laboratory assays do not contain enough thrombomodulin to activate protein C [85].

Hyperfibrinolysis has traditionally been associated with chronic liver disease as demonstrated by elevated levels of tissue plasminogen activator (tPA) and plasmin, both involved in the degradation of fibrin clots, as well as decreased levels of alpha 2 plasminogen inhibitor and thrombin activatable fibrinolysis inhibitor (TAFI) [82]. Whether or not these markers of fibrinolysis correlate with a clinical bleeding risk remains unclear [86, 87].

Other factors that can contribute to clinically significant bleeding include renal failure with platelet dysfunction, portal hypertension, endotoxemia with fibrinolysis, and disseminated intravascular coagulation [86, 87]. Patients with isolated hepatic coagulopathy usually have normal to elevated levels of factor VIII and vWF in contrast to patients with DIC, though both conditions may coexist [82]. Endotoxemia is associated with both fibrinolysis and a procoagulant state. Sepsis-induced hypercoagulability occurs by the inhibition of activated protein C and S, as well as by increased tissue factor expression [88]. This is the basis of therapeutic use of activated protein C in sepsis [89].

Hepatic Endocrine Function

The liver acts as an endocrine organ, producing hormones such as insulin like growth factor (IGF-1), thrombopoietin, angiotensinogen, and steroid hormones. The liver produces 75% of IGF-1, which is a peptide hormone, mediating the effects of human growth hormone (GH). Growth hormone activates the release of IGF-1, which stimulates tissue growth. Levels rise during puberty, are abnormally high in conditions such as acromegaly and may be low in patients with short stature.

Thrombopoietin is a peptide hormone produced in the liver that stimulates megakaryocytes and platelet production. Low levels of thrombopoietin in liver failure may contribute to thrombocytopenia since these levels as well as platelet counts are restored with orthotopic liver transplantation [90, 91].

Angiotensinogen, the precursor of angiotensin, is produced in the liver as well. This precursor peptide hormone is activated by renin in the renin-angiotensin-aldosterone pathway, the target of antihypertensives such as ACE inhibitors, angiotensin receptor blockers (ARBs), and

diuretics such as spironolactone, which antagonizes aldosterone, and is used to manage ascites in liver disease.

Lastly, the liver is the site of cholesterol synthesis therefore crucial in the genesis of endogenous steroid hormones such as cortisol, aldosterone, and testosterone. While these hormones are synthesized in the adrenal gland, their precursors are hepatic in origin.

Conclusion

This chapter is broad in its scope though we have attempted to provide relevant anatomic and functional information to enhance the management of patients with liver disease undergoing major surgical and anesthetic challenges. This chapter is not meant as an exhaustive review of liver disorders, portal hypertension, and functional hepatic impairment associated with extreme liver resections or the limits of transplantation in the ability of the liver to compensate under stress. However it provides the basis for understanding specific disease conditions and therapies presented in detail later in this volume.

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