SECTION 1

Anatomy, pathophysiology, and epidemiology of the biliary system

1

CHAPTER 1

Anatomy and physiology of the biliary tree and gallbladder

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OBJECTIVES

- Describe the anatomy of the liver and biliary tract
- Highlight the surgical anatomy of the liver and biliary tract
- Describe the physiology of bile formation
- Outline the mechanisms of gallstone formation
- Outline the normal motility of the biliary tract and abnormalities that are associated with clinical syndromes

The biliary tract is the conduit between the liver and the duodenum and is designed to store and transport bile, under control of neuronal and hormonal regulation. Bile is formed in the hepatocytes and steadily secreted into canaliculi, which transport it to the larger extrahepatic ducts. The sphincter of Oddi regulates the flow of bile into the duodenum or to the cystic duct and the gallbladder. When stimulated, the gallbladder contracts steadily, the sphincter relaxes and bile flow into the duodenum increases.

Liver anatomy

To understand the anatomy and physiology of the biliary tract and the production of bile, it is necessary to briefly outline the anatomy of the liver. The liver is divided macroscopically into the right and left lobe by the falciform ligament anteriorly (Fig. 1.1). Inferiorly, this corresponds to the round ligament and umbilical fissure. The right lobe is further divided by the gallbladder fossa into the right hemiliver to the right of the gallbladder and the quadrate lobe to the left. The fourth lobe (caudate) is posterior and surrounds the inferior vena cava. Hence, anatomically the liver is divided into two main lobes and two accessory lobes.

With improved understanding of liver function, the concept of functional anatomy has developed. This was initiated by Cantlie in 1898 and was enhanced by McIndoe in 1929, Ton That Tung in 1939, and Couinaud in 1957. In December 1998, the Scientific Committee of the International Hepato-Pancreato-Biliary Association created a terminology committee to deal with confusion in the nomenclature of hepatic anatomy and liver resections. This committee formulated a new terminology termed *The Brisbane 2000 Terminology of Liver Anatomy and Resections*. This is now internationally accepted. It is anatomically and surgically correct, consistent, self-explanatory, linguistically correct, precise and concise [1].

The liver was divided into three functional livers: the right, the left and the caudate [2]. The separation between the right and left hemiliver is at Cantlie's line, which is an oblique plane extending from the center of the gallbladder bed to the left border of the inferior vena cava. In this plane runs the middle hepatic vein, which is an important radiological landmark.

The right hemiliver is divided further into two sections by the right portal scissura (anterior and posterior sections), within which runs the right hepatic vein. Each section is then divided on the basis of their blood supply and bile drainage into two segments. The anterior section is divided into segment 5 (inferior) and segment 8 (superior) and the posterior section into segment 6 (inferior) and segment 7 (superior) (Tables 1.1, 1.2 and 1.3).

The left hemiliver is divided into three segments. Segment 4 (quadrate lobe) is known as the left medial section, which lies to the right of the falciform ligament and its right margin forms the right margin of the left hemiliver. Segment 3, which lies in the anterior part, and segment 2, which lies in the posterior part of the left hemiliver, form the left lateral section. The left lateral section lies on the left of the falciform ligament. Between segment 2 and segment 3 runs the left hepatic vein (Tables 1.1 and 1.2).

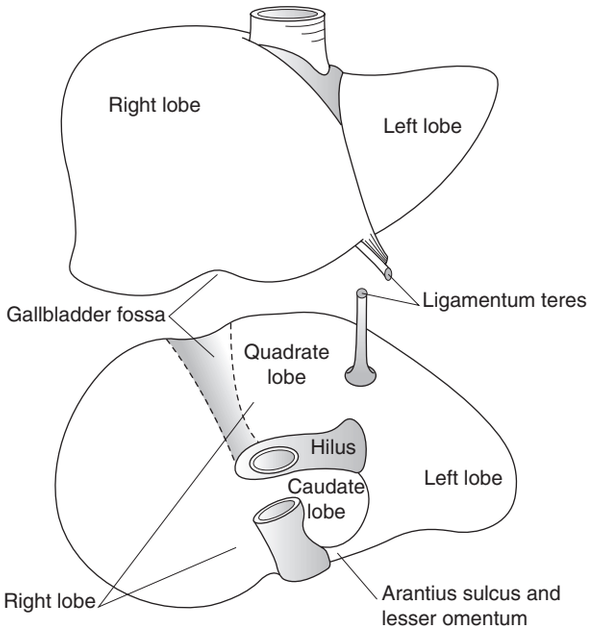


Figure 1.1 The classic anatomical division of the liver into two main lobes (right and left lobes) and two accessory lobes (quadrate and caudate lobes). (Redrawn from Nyhus LM, Baker RJ, Fisher JE, eds. Mastery of surgery, 3rd ed., p. 1004. Boston: Little Brown, 1997.)

The caudate hemiliver (segment 1) is considered separately because of its separate blood supply, and venous and bile drainage [2]. The importance of this will be illustrated later in the chapter.

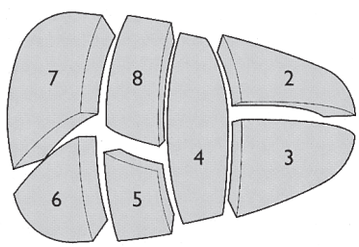
Blood supply and venous drainage

The arterial supply to the liver in early gestation life is from three main sources: the left hepatic artery from the left gastric artery; the middle hepatic artery (common hepatic artery) from the celiac trunk; and the right hepatic artery from the superior mesenteric artery. With further development, the blood supply assumes the adult pattern, with atrophy of both the right and left hepatic arteries and the common hepatic artery (middle hepatic) supplying the whole liver (Fig. 1.2) [3]. This adult pattern occurs in around 67% of individuals [4]. The common hepatic artery gives the right and left hepatic arteries, which supply the right and left hemilivers, respectively. In 90% of cases, segment 4 is supplied by a named branch (middle hepatic) from either the right or left hepatic artery (45% each) [4]. The other variations that occur are [5]:

- The common hepatic supplying the right liver and the left hepatic arising from the left gastric in 8%.
- The common hepatic supplying the left liver and the right hepatic arising from the superior mesenteric artery in 11%.
- Persistence of all three arteries in 3%.

Table 1.1 First-order division.

Schematic diagram of the segments for reference in the table ***(for purposes of clarity Sg1 is not shown)***



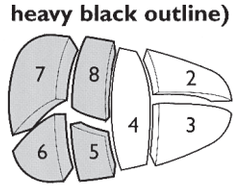
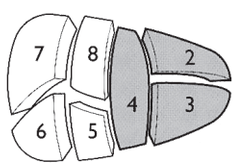
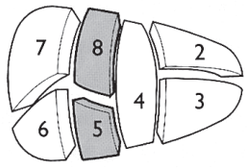
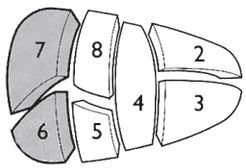
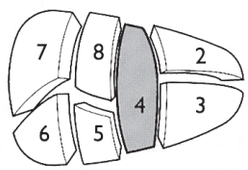
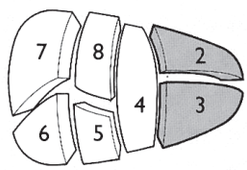
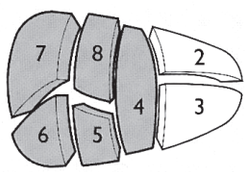
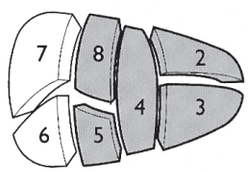
Anatomical term	Couinaud segments referred to	Term for surgical resection	Diagram (pertinent area is in heavy black outline)
Right hemiliver **OR** *Right liver*	Sg5–8(+/−Sg1)	*Right hepatectomy* **OR** *Right hemihepatectomy* (stipulate +/− segment 1)	
Left hemiliver **OR** *Left liver*	Sg2–4 (+/−Sg1)	*Left hepatectomy* **OR** *Left hemihepatectomy* (stipulate +/− segment 1)	

Table 1.2 Second-order division.

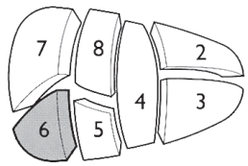
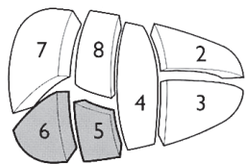
Anatomical term	Couinaud segments referred to	Term for surgical resection	Diagram
Right anterior section	Sg5,8	Add '-ectomy' to any of the anatomical terms as in *Right anterior sectionectomy*	
Right posterior section	Sg6,7	*Right posterior sectionectomy*	
Left medial section	Sg4	*Left medial sectionectomy* **OR** *Resection segment 4* **OR** *Segmentectomy 4*	
Left lateral section	Sg2,3	*Left lateral sectionectomy* **OR** *Bisegmentectomy 2,3*	
Right hemiliver plus left medial section	Sg4-8 (+/−Sg1)	*Right trisectionectomy* **or** *Extended right hepatectomy* **or** *Extended right hemihepatectomy*	
Left hemiliver plus right anterior section	Sg2,2–5,5,8 (+/−Sg1)	*Left trisectionectomy* **or** *Extended left hepatectomy* **or** *Extended left hemihepatectomy*	

• Atrophy of the common hepatic artery in 12%, with the liver supplied by the:
  —right hepatic in 9%
  —left hepatic in 1%
  —both right and left in 2%.

The left hepatic arising from the left gastric is usually easy to identify in the gastrohepatic ligament. When this artery is present, care should be taken not to damage it when performing a gastrectomy.

The right hepatic artery arising from the superior mesenteric artery, on the other hand, is more variable. It ascends behind the pancreas in relation to the portal vein, and in the portal pedicle it assumes a posterior location, usually slightly to the left of the portal vein.

Table 1.3 Third-order division.

Anatomical term	Couinaud segments referred to	Term for surgical resection	Diagram
Segments 1–9	Any one of Sg1 to Sg9	*Segmentectomy*	 (Segmentectomy 6)
2 *contiguous segments*	Any two of Sg1 to Sg9 in continuity	*Bisegmentectomy*	 (Bisegmentectomy 5,6)

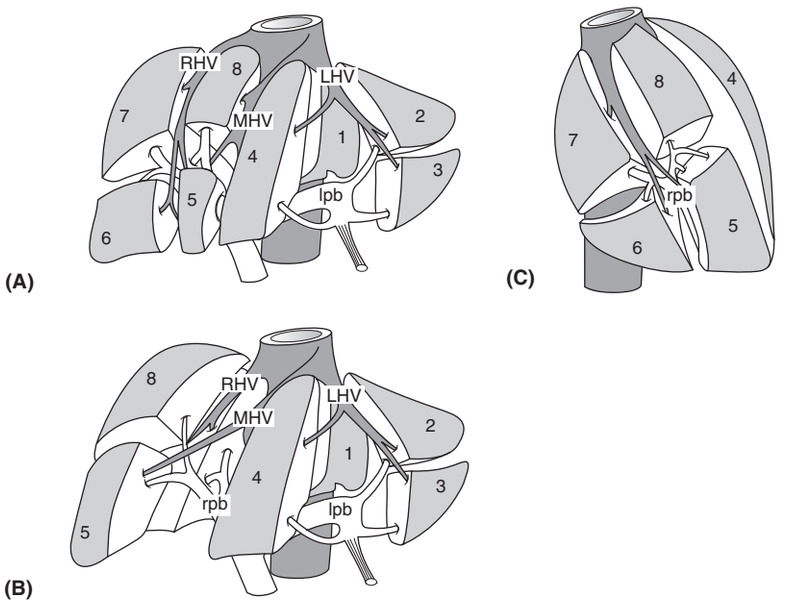


Figure 1.2 The functional division of the liver using Couinard's original drawings. **(A)** In the bench position. **(B)** The actual orientation in patient. **(C)** The right hepatic vein dividing the right liver into the anterior sector (segments 5 and 8) and the posterior sector (segments 6 and 7). RHV, right hepatic vein; MHV, middle hepatic vein; lpb, left portal branch; rpb, right portal branch; IVC, inferior vena cava. (Redrawn from Nyhus LM, Baker RJ, Fisher JE, eds. Mastery of surgery, 3rd ed., p. 1005. Boston: Little Brown, 1997.)

The venous drainage of the liver is into the inferior vena cava through the right, middle and left hepatic veins. The union of superior, middle and inferior branches usually forms the right vein, where the superior is the largest branch. The right hepatic vein trunk joins at the right margin of the vena cava at a point separate and slightly above the trunk that is formed by the middle and left vein. The middle hepatic vein forms from two veins arising from segment 4 and segment 5. The middle hepatic vein joins the left hepatic vein to form a common trunk before draining into the vena cava in 90% of people. The left hepatic vein is more variable and is usually formed by the union of the branches from segment 2, segment 3 and segment 4.

Intrahepatic bile ducts

There are more than 2 km of bile ductules and ducts in the adult human liver. These structures are far from being inert channels, and are capable of significantly modifying biliary flow and composition in response to hormonal secretion. Bile secretion starts at the level of the bile canaliculus, the smallest branch of the biliary tree [6]. They form a meshwork between hepatocytes with many anastomotic interconnec-

tions. Bile then enters the small terminal bile ductules (canals of Hering), which provide a conduit through which bile may traverse to enter the larger perilobular or interlobular bile ducts.

The interlobular bile ducts form a richly anastomosing network that closely surrounds the branches of the portal vein [7]. These ducts increase in caliber and possess smooth muscle fibers within their wall as they reach the hilus of the liver. Furthermore, as they become larger, the epithelium becomes increasingly thicker and contains many elastic fibers. These ducts anastomose to form the segmental branches (from segment 1 to segment 8) [8].

In 80 to 85% of individuals, these segmental branches anastomose to form the anterior (segment 5 and segment 8) and posterior sectorial bile ducts (segment 6 and segment 7) (as described in the previous section) in the right hemiliver. With the union of these two sectorial ducts, in 57% of individuals, the right hepatic duct is formed [1]. The right hepatic duct is usually short—approximately 9 mm in length [7]. In the left hemiliver the segmental branches 2 and 3 anastomose to form the left hepatic duct in the region of the umbilical fissure. The anastomosis of segment 4 to the left hepatic duct usually occurs as a single trunk to the right of the umbilical fissure in 67% of individuals [7]. The left hepatic duct is generally longer and more surgically accessible than the right hepatic duct. Variations of the sectorial and hepatic ducts will be discussed separately.

The caudate lobe (segment 1) is drained by both right and left hepatic ducts. Its arterial supply is also from both right and left portal vein and hepatic artery, with small venous branches draining directly to the inferior vena cava [7].

The anatomy of this third hemiliver is revealed in certain pathologic conditions, such as Budd–Chiari syndrome where the outflow of the three hepatic veins is obstructed, leading to diversion of blood to the caudate lobe resulting in hypertrophy [9].

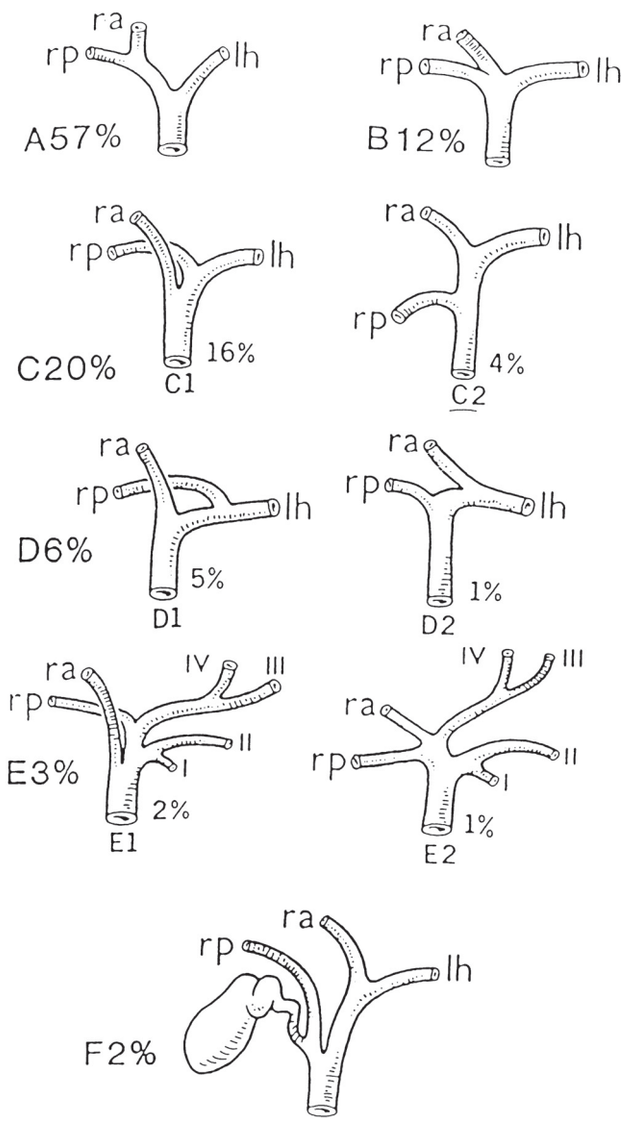


Figure 1.3 Variations in the confluence of sectorial and hepatic ducts. ra, right anterior; rp, right posterior; lh, left hepatic. (Reprinted from Blumgart LH, ed. Surgery of the liver and biliary tract, 3rd ed., p. 19. © 2000, with permission from Elsevier.)

Variation of the intrahepatic bile ducts

As illustrated previously, the incidence of the right anterior and posterior sectorial ducts joining to form the right hepatic duct occurs in only 57% of people (Fig. 1.3). In 12%, the right anterior and right posterior ducts join at the junction with the left hepatic duct without the existence of the right hepatic duct. In 20% of cases, drainage occurs directly into the common hepatic duct [2].

There has also been reported variation in the segmental anastomosis in the right liver. The main right segmental drainage was variable in 9% of segment 5, 14% in segment 6, and 29% in segment 8. Variation in segment 7 was not reported [7].

With regard to the left liver, 67% of individuals have the previously described anatomy. The main variation lies in the ectopic drainage of segment 4. It has been reported that 2% drain directly into the common hepatic duct, and 27% drain directly into segment 2 or segment 3 only. This should be taken into consideration when performing a left lobectomy to avoid compromising the drainage of segment 4 [7].

Another form of ectopic drainage of the intrahepatic ducts is the involvement of the cystic ducts and the gallbladder (Fig. 1.4). As illustrated, these variations are important to note during cholecystectomy [10].

Extrahepatic bile ducts

The joining of the right and left hepatic ducts forms the

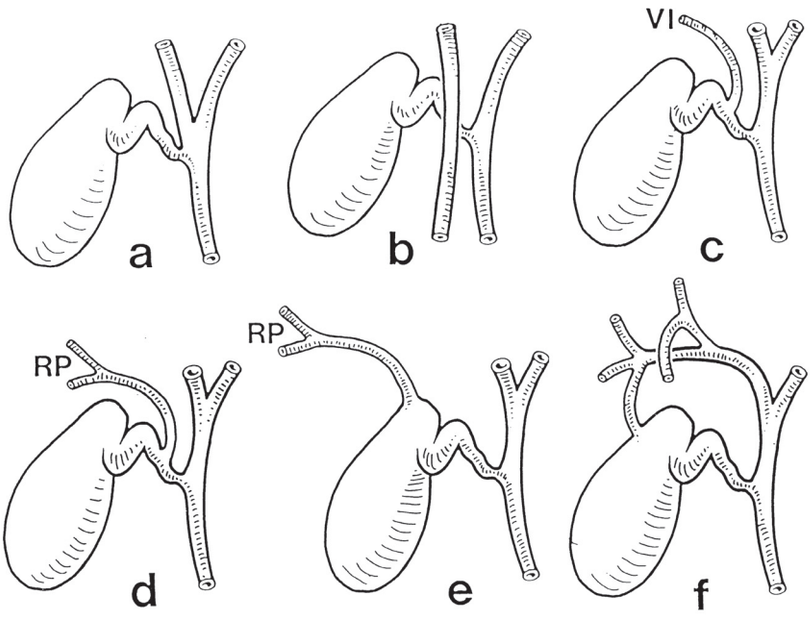


Figure 1.4 Variations in the drainage of the intrahepatic ducts into the cystic duct. RP, right posterior. (Reprinted from Blumgart LH, ed. Surgery of the liver and biliary tract, 3rd ed., p. 20. © 2000, with permission from Elsevier.)

common hepatic duct. The accessory biliary apparatus, composed of the gallbladder and cystic duct, joins the common hepatic duct to form the common bile duct that drains bile into the duodenum. This comprises the extrahepatic biliary system.

The confluence takes place at the right of the hilus of the liver, anterior to the portal venous bifurcation and overlying the origin of the right branch of the portal vein (Fig. 1.5). The biliary confluence is separated from the posterior aspect of segment 4 of the left liver by the hilar plate, which is the fusion of connective tissue enclosing the biliary and vascular structures with Glisson's capsule [11].

Gallbladder and cystic duct

The gallbladder is a reservoir of bile in the shape of a piriform sac partly contained in a fossa on the inferior surface of the right hepatic lobe. It extends from the right extremity of the porta hepatis to the inferior border of the liver. It is 7 to 10 cm long and 3 to 4 cm broad at its widest part, and can hold from 30 to 50 ml. The gallbladder is divided into a fundus, body, infundibulum and neck.

The fundus extends about 1 cm beyond the free edge of the liver. The body is the largest segment. The infundibulum is the transitional area between the body and the neck. Hartmann's pouch is a bulge on the inferior surface of the infundibulum. Gallstones may become impacted here and can cause obstruction of the cystic duct. The neck is the tapered segment of the infundibulum that is narrow and joins the cystic duct.

The cystic duct is 3 to 4 cm long and passes posteriorly inferior and to the left from the neck of the gallbladder to join the common hepatic duct to form the common bile duct (CBD). The mucosa of the cystic duct is arranged with spiral folds known as the valves of Heister [12].

Table 1.4 Anomalies of the gallbladder.

Congenital
Phyrygian cap
Duplication
Bilobed gallbladder
Diverticulum
Hypoplasia or absent
Abnormal position
Falciform ligament
Intrahepatic
Left sided
Abnormal mesentry

A number of anomalies occur in the gallbladder (Table 1.4). Furthermore, the cystic duct inserts into the bile duct at a variety of sites (Fig 1.4) [13,14].

The arterial supply to the gallbladder is from the cystic artery. Because the cystic artery is an end artery, the gallbladder is more susceptible to ischemic injury and necrosis as a result of inflammation or interruption of the artery. The cystic artery can originate from the right hepatic, left hepatic or the common hepatic artery, and it can be anterior or posterior to the common hepatic duct. Figure 1.6 illustrates some of these variations.

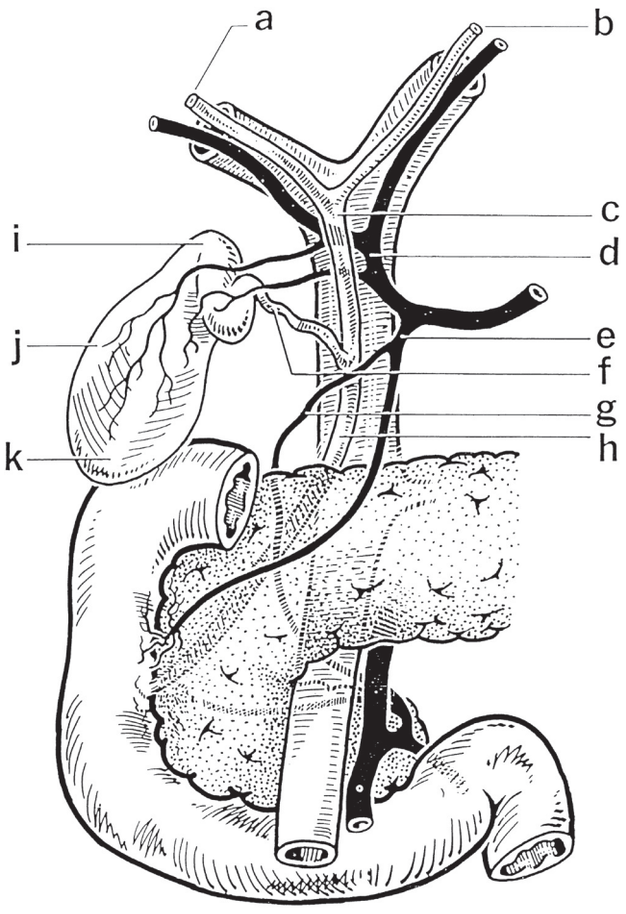


Figure 1.5 The anatomy of the extrahepatic biliary system: (a) right hepatic duct, (b) left hepatic duct, (c) common hepatic duct, (d) hepatic artery, (e) gastroduodenal artery, (f) cystic duct, (g) retroduodenal artery, (h) common bile duct, (i) neck of the gallbladder, (j) body of the gallbladder, (k) fundus of the gallbladder. (Reprinted from Blumgart LH, ed. Surgery of the liver and biliary tract, 3rd ed., p. 14. © 2000, with permission from Elsevier.)

The venous drainage is through the cystic vein, which drains into the portal vein. There are also some small veins that drain directly into the liver to the hepatic veins.

The lymphatic drainage of the gallbladder proceeds mainly by four routes, which form two pathways that drain in the thoracic duct (these will be discussed later with the common bile duct) [15].

1 Superior and external, drains the fundus (around 6% of cases).

2 Superior and medial, drains the medial aspect of the gallbladder (around 10% of cases).

3 Inferior and external, drains the body of the gallbladder (present in 82% of cases).

4 Inferior and medial, from the body of the gallbladder (constant).

All four routes drain to both pathways, except the inferior and external which drain only to the inferior pathway. This is important in cases of gallbladder cancer, which can spread to the liver; because of its extensive lymph drainage to both pathways, cure by radical surgery is difficult.

The gallbladder is innervated by the vagus nerve through its hepatic branch from the anterior vagal trunk. The gallbladder is also innervated by the sympathetic nervous system through the celiac plexus. Fibers in the right phrenic nerve may also be distributed to the gallbladder through the hepatic plexus.

The duct of Luschka

The duct of Luschka is a small bile duct, running in the bed of the gallbladder, outside the wall. It is present in 50% of individuals [16]. This duct is surgically significant because it may be injured during cholecystectomy and may result in bile fistula unless ligated. Recent reports demonstrated a 1.5 to 2.0% incidence of bile leak from the duct of Luschka after laparoscopic cholecystectomy. Ligation has no consequences as it is an end duct that drains an isolated segment.

Common bile duct

The common bile duct forms by the junction of the cystic duct with the common hepatic duct. Its course is divided into supraduodenal, retroduodenal, pancreatic and intraduodenal (joins the main pancreatic duct to form the sphincter of Oddi, which will be discussed separately).

The supraduodenal segment usually lies in the free border of the hepatoduodenal ligament. It runs to the right of the hepatic artery and anterior to the portal vein. The retroduodenal segment descends posterior to the first part of the duodenum and slightly obliquely from right to left. The pancreatic segment is related to the head of the pancreas; it can run entirely retropancreatic or travel through its parenchyma.

The diameter of the common bile duct is often used as an indication of biliary pathology. Its "normal" size varies depending on the modality used to measure it, and a range of 4 to 13 mm has been reported [16,17]. The most common modality to examine the common bile duct diameter is ultrasound, and a diameter up to 6 mm is considered normal. Some consider the equivalent in contrast radiology to be 10 mm; this depends on the magnification [18].

Sphincter of Oddi

The common bile duct enters the duodenum approximately 8 cm from the pylorus in the second part of the duodenum. The site entry is marked by a papilla (major papilla). Its position can be variable; in approximately 13% of individuals it can be located at the junction of the second and third part of the duodenum, or even more distally [19]. A transverse fold of mucosa usually covers the papilla. The papilla is

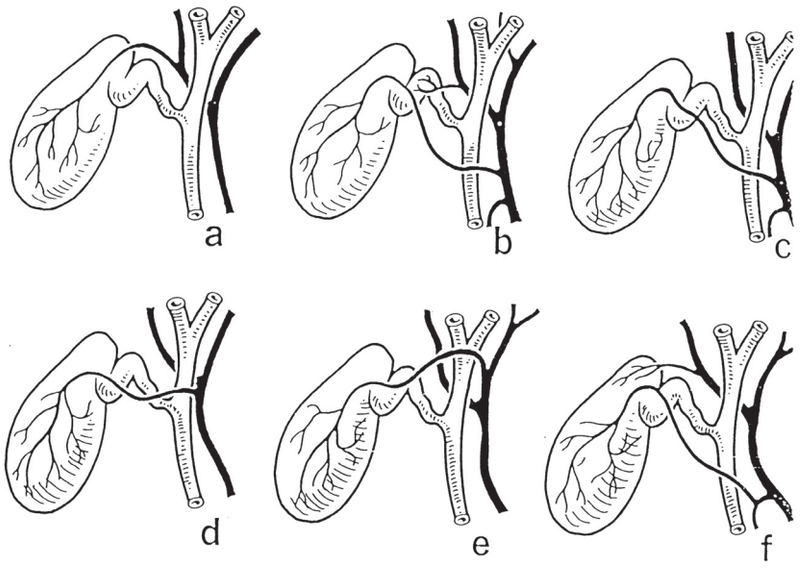


Figure 1.6 Variations of the blood supply (cystic artery) to the gallbladder. (Reprinted from Blumgart LH, ed. Surgery of the liver and biliary tract, 3rd ed., p. 17. © 2000, with permission from Elsevier.)

identified as a small nipple or pea-like structure in the lumen of the duodenum [20].

The main pancreatic duct of Wirsung joins the common bile duct and forms a common channel in approximately 85% of individuals. In 15%, they open either separately or as a V junction with the duodenal mucosa. In 4% of individuals, the body and tail of the pancreas drain via the duct of Santorini (pancreas divisum) to the minor papilla. In this instance, only the ventral aspect of the pancreas drains through the duct of Wirsung. The minor papilla is located proximal and slightly anterior to the major papilla.

The human sphincter of Oddi is generally a continuous smooth muscle structure that is subdivided into several parts that largely reflect the arrangements found in other animal species [8] (Fig. 1.7).

1 Sphincter choledochus consists of circular muscle that surrounds the common bile duct.

2 Pancreatic sphincter surrounds the intraduodenal portion of the pancreatic duct before its juncture with the ampulla.

3 Fasciculi longitudinales are composed of longitudinal muscle fibers between the pancreatic and bile ducts.

4 Sphincter ampullae are composed of longitudinal muscle fibers that surround the papilla.

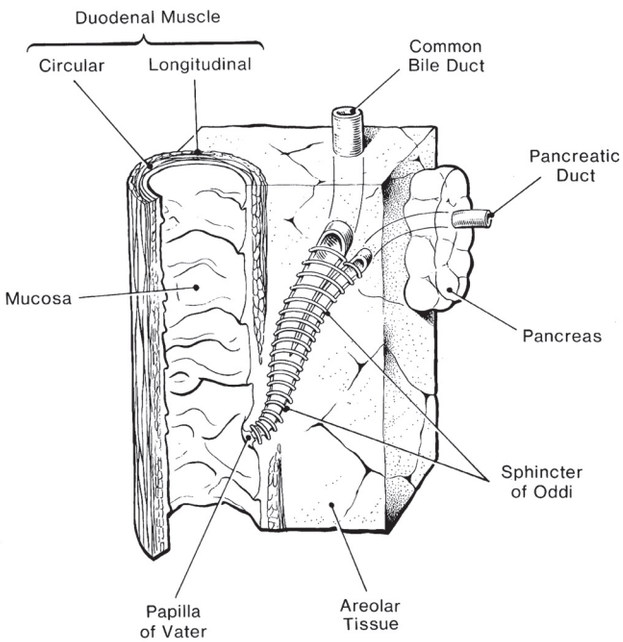


Figure 1.7 The choledochoduodenal junction. The sphincter muscle is predominantly circular in orientation, and extends beyond the wall of the duodenum. There is a small extension along the pancreatic duct.

Blood supply

The blood supply to the common bile duct is also divided into three segments (Fig. 1.8) [5]. The supraduodenal segment of the duct essentially has an axial blood supply. The blood supply originates from the retroduodenal artery, right hepatic artery, cystic artery, gastroduodenal artery and the retroportal artery. On average there are eight small arteries with the main two running along the side of the common bile duct at 3 and 9 o'clock. Sixty percent of the arterial blood supply occurs from the duodenal end of the duct, and 38% is from the hepatic end. Only 2% of the arterial supply is nonaxial, arising directly from the main hepatic trunk. The second segment is the retropancreatic part of the duct, which is supplied by the retroduodenal artery. It provides blood to the multiple

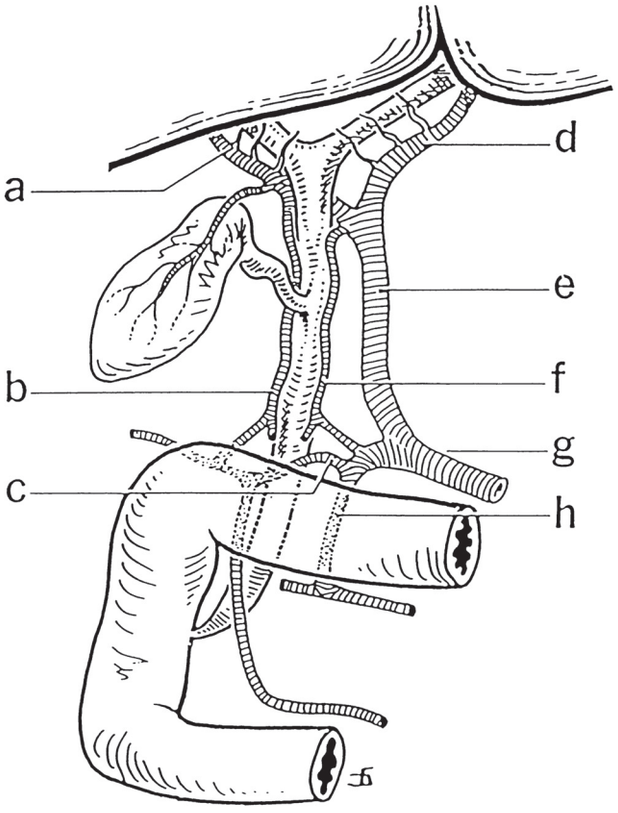


Figure 1.8 Blood supply to the extrahepatic bile ducts: (a) right hepatic artery, (b) 9 o'clock artery, (c) retroduodenal artery, (d) left hepatic artery, (e) hepatic artery, (f) 3 o'clock artery, (g) common hepatic artery, (h) gastroduodenal artery. (Reprinted from Blumgart LH, ed. Surgery of the liver and biliary tract, 3rd ed., p. 21. © 2000, with permission from Elsevier.)

small vessels running around the duct to form a mural plexus. The third segment is the hilar duct, which receives its blood supply from the surrounding blood vessels, forming a rich network.

The veins draining the bile duct correspond to the described arteries. They drain into veins at 3 and 9 o'clock on the side of the common bile duct.

Lymphatic drainage

The lymph drainage of the extrahepatic biliary system is through two pathways [15]:

1 The superior pathway of nodes along the cystic duct, the hepatic duct, the anterior and medial aspect of the portal vein, and the celiac axis.

2 The inferior pathway of nodes along the cystic duct, anterior and lateral aspect of the portal vein, the posterior aspect of the pancreas, between the aorta and the inferior vena cava, and the left aspect of the aorta under the left renal vein.

Lymph drainage of the common bile duct is by lymph nodes along the duct to both the inferior and superior pathway.

Nerves of the common bile duct and sphincter of Oddi

The nerve supply to the extrahepatic bile duct is from extrinsic and intrinsic nerves. The extrinsic nerves are mainly from the hepatic plexus. The posterior hepatic plexus contains preganglionic parasympathetic fibers from branches of the vagus nerve and postganglionic sympathetic fibers that arise from the right celiac plexus. The anterior hepatic plexus contains postganglionic fibers from the left celiac and preganglionic fibers from the left vagus. The intrinsic nerve supply is mainly from neural connection from surrounding organs such as the duodenum, stomach and gallbladder. This complex neural supply is important in controlling sphincter motility.

Calot's triangle

Calot's triangle is an anatomical region bounded medially by the common hepatic duct, inferiorly by the cystic duct and superiorly by the inferior surface of the liver. The cystic artery runs within this triangle. Two anomalies may be encountered in Calot's triangle. Firstly, an aberrant right hepatic artery which arises from the superior mesenteric artery, it is seen in 16% of individuals. It can be located in the medial border of Calot's triangle in 90% of these patients. Secondly, the right posterior or anterior sectoral ducts may run through Calot's triangle and may be mistaken for the cystic duct.

It has been well demonstrated that, during cholecystectomy, the cystic artery can safely and easily be identified at the junction of the gallbladder neck and the cystic duct by defining the cystic lymph node. The node may be swept in the direction of the common bile duct, facilitating the recognition of the cystic duct and the cystic artery [21].

Physiology of the biliary tract

Bile production

Bile fulfils two major functions. It participates in the absorption of fat and forms the vehicle for excretion of cholesterol bilirubin, iron and copper. Bile acids are the main active component of biliary secretion. They are secreted into the duodenum and efficiently reabsorbed from the terminal ileum by the portal venous system [22].

Bile secretion

Bile is secreted by the hepatocytes through the canalicular membrane into the canalicular space. The secretory process is both active and passive and the active process generates bile flow. The products of active secretion are known as primary solutes and these are made up of conjugated bile acids, conjugated bilirubin, glutathione, conjugates of steroid hormones and leukotrienes. Filtrable solutes are generated by passive secretion induced by osmotic pressure and are called second-

ary solutes. These are mainly plasma, glucose, electrolytes, low-molecular-weight organic acids and calcium.

The maximum secretory pressure developed by the liver is 30 cm. In the fasting state, the sphincter of Oddi has an average resting pressure of 12 to 15 cm H_2O. Because the opening pressure of the cystic duct is 8 cm H_2O and the gallbladder is 10 cm H_2O, the pressure gradient favors the entry of bile into the gallbladder [23]. Therefore, during fasting, most of the bile is diverted into the gallbladder where it is concentrated.

Bile is produced by hepatocytes and cells of the intrahepatic ducts at a rate of 600 mL/day. The hepatic bile entering the gallbladder during fasting consists of approximately 97% water and 1 to 2% bile acids. Phospholipids, cholesterol, bile pigment and electrolytes make up the remainder [24,25]. Hepatic bile is iso-osmolar with plasma. Sodium, chloride and bicarbonate ions, with nearly an isotonic amount of water, are absorbed from the bile. The gallbladder is able to remove 90% of the water from hepatic bile [26]. In monkeys the volume of water absorption is 30% of the gallbladder bile volume per hour [27]. The gallbladder concentration of bile salts, bilirubin and cholesterol may rise 10-fold or more, relative to hepatic bile levels.

The gallbladder partially empties during fasting in conjunction with the phases of the interdigestive cycle. After a meal, the gallbladder contracts and the sphincter of Oddi relaxes, leading to the delivery of bile to the duodenum. The gallbladder empties around 75% of its content. At the same time, hepatic bile bypasses the gallbladder and empties into the duodenum. At the end of the meal, the gallbladder relaxes and the sphincter of Oddi contracts, leading to the diversion of hepatic bile into the gallbladder once again for storage until the next meal.

In individuals who have undergone a cholecystectomy, bile acids are stored in the proximal small intestine [28]. After meal ingestion, the acids get transported to the distal ileum for absorption and maintenance of the enterohepatic circulation.

Bile reabsorption

The reabsorption of bile acids is through the enterohepatic circulation. Bile acids are absorbed from the terminal ileum and transported back to the liver by the portal system. This is achieved by passive and active transcellular absorption. The most important mechanism is a sodium-coupled transport system that is present in the apical membrane of the enterocytes; it is known as the ileal bile acid transporter (IBAT) [29].

In the distal ileum and large intestine, intestinal bacteria deconjugate bile acids, which are absorbed passively in solution [30]. A small amount of the bile acid is lost from the body in feces. This fecal loss is compensated by synthesis of new bile acids. In healthy adults, less than 3% of bile acids present in hepatic bile are newly synthesized.

In the portal system, bile acids are bound to albumin. The ability of the albumin binding depends on the nuclear substitutes. For trihydroxy bile acids, this is around 75%, whereas it is 98% for dihydroxy bile acids. On the first pass, the hepatic circulation extraction is between 50 and 90%; the level of bile acids in the systemic circulation is directly proportional to the load presented to the liver, and it increases after meals [28]. The plasma level of total bile acids is 3 to 4 μmol/L in the fasting state and increases twofold to threefold after digestion.

Abnormality in secretion and gallstone formation

Cholesterol is insoluble in water but is made soluble in bile with the aid of bile salts and phospholipids. Thus, in simple terms, gallstones form when the cholesterol concentration in the bile exceeds the ability of the bile to hold it in soluble form. This occurs either by an increase in cholesterol secretion by the liver or a decrease in bile salts or phospholipids through a decrease in synthesis or interruption of the enterohepatic circulation. The result is crystals that grow into gallstones.

Bile cholesterol is normally derived from three main sources: synthesis in the hepatocytes from acetate, low-density lipoproteins that carry cholesterol from extrahepatic tissue to the liver, and chylomicrons that transport dietary cholesterol to the liver [31].

The main source of cholesterol is the synthesis by the liver. This process is through a sequence of enzymatic steps with 3-hydroxy-3-methyl-glutarylcoenzyme (HMG-CoA) reductase being the rate-limiting reaction [32]. It is thought that obese people have an increase in the activity of this enzyme. When cholesterol is secreted into the bile, it forms mixed micelles and vesicles via the aid of bile salts and phospholipids [33,34]. The micelles are lipid aggregates that have the polar group directed out toward the aqueous side, and the nonpolar group directed inward. As cholesterol saturation increases in bile, more cholesterol is carried in the vesicle form [35]. The cholesterol saturation index is determined by the ratio of the measured concentration of bile salts and phospholipids compared to the concentration of cholesterol. If this ratio is greater than 1, bile is saturated with respect to cholesterol, thus producing the environment for the precipitation of cholesterol to form vesicles. Vesicles are 10 times bigger than micelles and have phospholipid bilayers, but contain no bile salts. With the increase in the cholesterol saturation index, more complex and unstable vesicles form [36]. Compared with normal individuals, patients with gallstones secrete vesicles that are 33% more enriched with cholesterol [37], which are more prone to aggregate as well as crystallize [38]. So a decrease in bile salts can increase the cholesterol saturation index without an increase in cholesterol concentration. However, bile salt hyposecretion is not usually present [39]. Once the unstable vesicles are present, they aggregate together in the supersaturated bile [40]. Crystallization occurs,

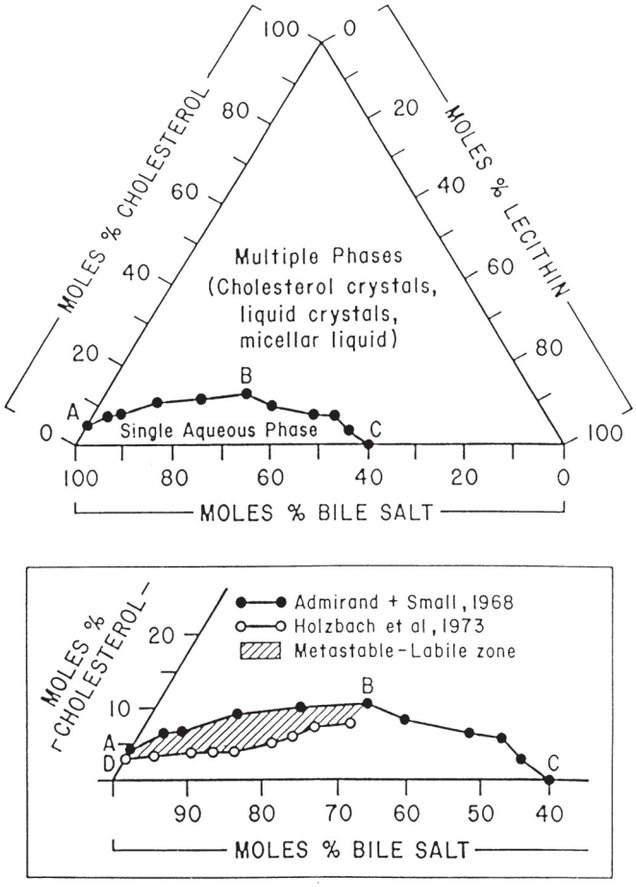


Figure 1.9 Triangle diagram demonstrating the molar co-ordination of cholesterol, bile salt and lecithin. If the point of bile analysis is above the line ABC, cholesterol is supersaturated; if it lies below the line DBC, cholesterol is completely soluble; in between the two lines is a metastable–labile zone in which stones may form if specific nucleating factors are present. (Reprinted from Sabiston DC, Jr, ed., Textbook of surgery: the biological basis of modern surgical practice, 14th ed., p. 1058. © 1991, with permission from Elsevier.)

resulting in cholesterol monohydrate crystals that can agglomerate to form macroscopic gallstones [41].

During the normal interdigestive period the gallbladder partially contracts, thus potentially evacuating any small crystals that might have formed. This cleansing function of the gallbladder should in theory prevent bile stasis and prevent crystals from growing into stones.

Motility of the biliary tract

Normal flow of bile occurs following contraction of the gallbladder and relaxation of the sphincter of Oddi. Control of these motor events is complex and involves both nerves and hormones. Disturbance of any of these controlling factors may lead to dysmotility and result in clinical disorders.

Gallbladder motility

The normal motility of the gallbladder regulates the flow of bile during fasting and after meals. Gallbladder filling is determined by the rate of bile secretion from the liver, the active relaxation of the gallbladder, and the resistance to flow through the lower end of the bile duct produced by the sphincter of Oddi. In the fasting state the gallbladder progressively fills with bile. This is accomplished without large pressure gradients in the biliary system. As the gallbladder accommodates filling, significant changes in volume occur with little change in its intraluminal pressure [42].

The gallbladder does not remain dormant during the fasting periods (interdigestive phase); it has its own motility cycle that is correlated with the migratory motor complex (MMC) of the gut. It was first observed in dogs [43] and then in humans [44] during cholecystographic studies. The gallbladder volume changes during the interdigestive phase [45], decreasing by 30 to 35% of maximal contractile capacity at the end of phase two and continuing to empty during phase three of the MMC. During phase one and early in phase two, the gallbladder refills and the cycle repeats [46–48]. This process of partial emptying and refilling during fasting may promote bile mixing and prevent sludge and microcalculi formation [49].

When an individual feeds, a cephalic response occurs. Gallbladder contraction in humans in response to the smell of fried meats has been observed [44], and similar findings have also been reported in dogs [50]. The release of cholecystokinin (CCK), the main gallbladder-contracting hormone, by the duodenum after the ingestion of food (mainly fat, intraluminal acid and amino acid) [51] causes an increase in hepatic bile flow and gallbladder contraction, and a reduction in the resting pressure of the sphincter of Oddi. These events promote the flow of gallbladder bile into the duodenum [52], with more than 75% of resting gallbladder volume ejected during endogenous CCK stimulation [53]. During this process the gallbladder tone remains constant over short periods of time [54]. This allows rapid, passive refilling of the gallbladder (active refilling) in the postprandial period, thus helping to maintain a pool of bile salts continuously in the gallbladder to preserve the enterohepatic circulation of bile salts [55].

Control of gallbladder motility Motility of the gallbladder is controlled by a number of mechanisms involving gut hormones (mainly CCK), bioactive peptides, nerves (sympathetic, parasympathetic and intrinsic), and other hormones (progesterone).

Gut hormones and peptides CCK is the major hormone controlling gallbladder motility, as first described by Ivy and Oldberg in 1928 [56]. This hormone is composed of 33 amino acids and is produced by the I cell in the duodenum. The action of CCK on the gallbladder is mediated by direct binding to a spe-

Table 1.5 The action of hormones and peptides on the human biliary tract.

Hormones/peptides	Gallbladder	Sphincter of Oddi
CCX	E	R
Gastrin/pentagastrin	E	E
Glucagon		NE
Motilin	E	E
Secretin		E followed by R
Octreotide	R	E
Enkephalin	R	R
Gastrin-releasing peptide	E	
Vasoactive intestinal peptide		R

E = excitatory; R = relaxation; NE = no effect.

cific receptor in the gallbladder smooth muscle [57]. Blockade of the receptor by a specific antagonist, loxiglumide, completely prevents CCK-mediated gallbladder contractions [58]. CCK-induced contraction is not significantly altered by cholinergic [59] or adrenergic [60] blockade. CCK may act as a parasympathetic neurotransmitter within vagal neurons in the gallbladder intramural plexus, where it has been identified [61]. Parasympathetic postsynaptic transmission enhancement has also been demonstrated by CCK, which promotes gallbladder contraction [62].

Other gut hormones and peptides, such as secretin, gastrin and motilin, also have been identified that affect the gallbladder motility (Table 1.5).

Neuronal control The neuronal control of gallbladder motility is not yet clearly understood. As discussed in the anatomy section, the gallbladder is innervated by the vagus, the celiac plexus, and the phrenic nerve and intrinsic nerves.

The cholinergic input from the vagus nerve plays a major role in the interdigestive, cephalic, and gastric phases of gallbladder motility. Gallbladder interdigestive motility in humans and dogs is lost following atropine treatment [63,64]. It has also been noted that patients develop a larger fasting gallbladder volume after truncal vagotomy [65,66].

In the cephalic and gastric phases, sham feeding causes gallbladder contraction without an increase in CCK blood levels [67,68]. This action is blocked by atropine and truncal vagotomy [69], indicating a cholingergic vagal innervation involving muscarinic receptors.

In the interstitial phase, multiple studies have shown that atropine causes relaxation of the CCK-stimulated gallbladder in humans [70,71], dogs [72] and opossums [73]. This response is mainly through M1 receptors. The M1 receptor antagonist (telenzepine) causes an inhibitory effect [74]. The cholinergic fibers mediating in this action are thought to run in the vagus nerve, because the gallbladder response to intraduodenal nutrients is inhibited in humans [75], dogs [71] and opossums [76] following truncal vagotomy. However, direct electrical stimulation of the vagus nerve does not increase gallbladder contraction or enhance subthreshold levels of CCK [77]. This indicates that the vagus nerve plays only a minor role in gallbladder motility.

The effect of sympathetic nerve input on gallbladder motility has been inconsistent. It is generally accepted that sympathetic stimulation causes gallbladder relaxation. Norepinephrine and isoprenaline relaxed the stimulated gallbladder in the guinea pig [78,79], whereas direct stimulation of the sympathetic nerves did not affect gallbladder pressure in the cat [80] and norepinephrine and isoprenaline did not produce any effect at physiologic doses [54]. It was demonstrated that the gallbladder has both α-adrenergic and β-adrenergic receptors [81]. Subsequent studies demonstrated that the gallbladder has mainly β-adrenergic receptors that mediate gallbladder relaxation and that the α-adrenergic receptors (mainly excitatory) do not act except after blocking the β-adrenergic receptors [82,83].

There is accumulating evidence for the involvement of nonadrenergic noncholinergic nerves in the regulation of gallbladder motility and inhibition of nitric oxide (NO) synthase-enhanced gallbladder responses to CCK [84]. In the prairie dog, the gallbladder was found to contain NO synthase in nerves, causing relaxation of the gallbladder that was precontracted by CCK [85]. Cullen et al. concluded that superoxide increases gallbladder motility by affecting NO synthase, and the presence of superoxide scavenging enzyme in the gallbladder may regulate gallbladder motility by clearing endogenous superoxide [86].

Other factors in the control of gallbladder motility Although both estrogen and progesterone receptors have been identified in the gallbladder's smooth muscle [87], multiple studies have shown that estrogen has no effect on gallbladder motility. However, clinical observation has suggested that these hormones have considerable effect on gallbladder motility, probably via progesterone. Multiple studies testing progesterone's effect on the gallbladder motility have shown inhibition [42,88], and the contractile effect of a cholecystokinin octapeptide CCK-8) was reduced when the tissue was pretreated with progesterone [88]. Two studies in the guinea pig demonstrated progesterone-impaired gallbladder emptying in response to CCK; also, progesterone might cause a down regulation of the contractile G-protein and an upregulation of the G-alphas that mediate relaxation [89,90]. Although the action of the female sex hormone on gallbladder motility is evident, there is no clear documentation on its role in the normal physiology of gallbladder motility.

Prostaglandins have also been suggested to play a role in gallbladder motility. Arachidonic acid (AA) produces contraction of the guinea pig gallbladder in vitro that was blocked by indomethacin, a potent inhibitor of prostanglandins [91,92]. In humans, a close-dependent gallbladder contraction was demonstrated in vitro with the use of several different prostaglandins [93]. Another study suggested that the inhibitory effect of indomethacin is related to the inhibition of prostaglandin synthesis [94], and it was effective in relieving pain in patients with biliary colic [95].

Although one study demonstrated that CCK may increase the release of AA [96], aspirin had no effect on stone formation nor did it prevent the decrease in contractility despite a profound decrease in endogenous gallbladder prostaglandin synthesis [97].

Sphincter of Oddi motility

The sphincter of Oddi has three main functions: the regulation of flow into the duodenum, prevention of reflux from the duodenum to the bile and pancreatic duct, and the filling of the gallbladder. Manometric studies in humans have shown that the sphincter of Oddi has a basal pressure of 10 mmHg over which are superimposed contractions with a frequency of 2 to 6 per minute and amplitude of 50 to 140 mmHg above duodenal pressure. These contractions are mainly in an antegrade direction (Fig. 1.10). Bile flow occurs mainly in between contractions [98] when the pressure in the bile duct overcomes the low basal pressure. The phasic contractions expel small volumes of bile and thus keep the opening of the bile duct free of crystals or debris. Furthermore, this prevents any reflux of duodenal content into the bile or pancreatic ducts. Modulation of the sphincter of Oddi basal pressure causes filling of the gallbladder and decrease in pressure causes flow of bile and pancreatic juice into the duodenum.

During fasting, the sphincter of Oddi exhibits a cyclical activity pattern that is distinct from, but coincident with, duodenal interdigestive activity. The sphincter of Oddi contracts throughout all phases of the interdigestive cycle. The frequency increases just prior to phase three of the duodenal activity, thus increasing the resistance of reflux of duodenal contents into the ducts. Feeding enhances the flow of bile through the sphincter with an overall decrease in sphincteric pressure. In humans, this is characterized by a decrease in basal pressure and a fall in contraction amplitude [98]. These changes produce a decrease in resistance and facilitate flow from the ducts into the duodenum.

Control of sphincter of Oddi motility Like the gallbladder, control of the sphincter of Oddi's motility is complex and involves neural and hormonal pathways.

Gut hormones and peptides Cholecystokinin produces inhibition of the phasic contraction and a decrease in basal pressure. The mechanism of its action appears to be via a stimulation of nonadrenergic, noncholinergic inhibitory neurons. Secretin decreases the activity of the sphincter in most species, such as rabbits and cats, with no effect. In humans it causes an initial excitation followed by relaxation. Other hormones and peptides, such as gastrin, motilin and octreotide, have been reported to alter the contraction of the sphincter of Oddi (Table 1.5).

Neuronal control Parasympathetic innervation is the main extrinsic innervation of the sphincter. Vagotomy experi-

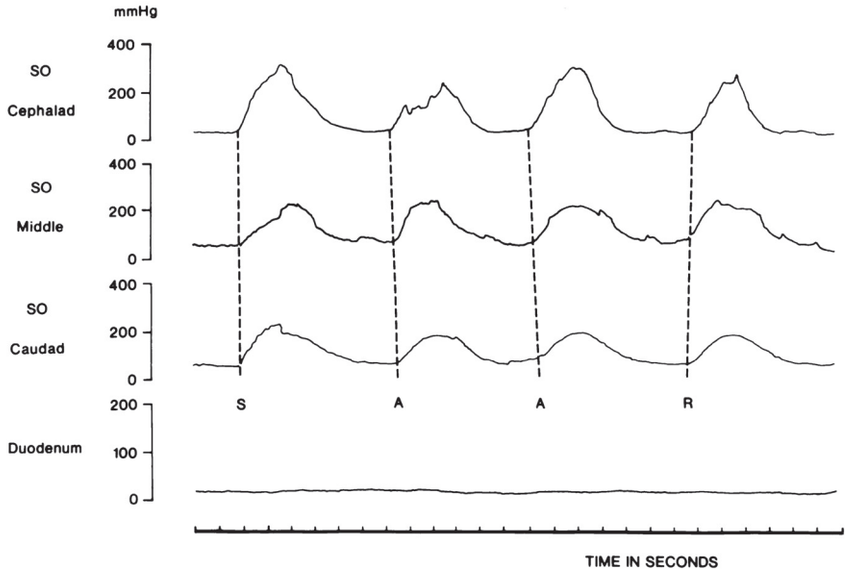


Figure 1.10 Manometric recording from the human sphincter of Oddi using a triple-lumen catheter. Prominent phasic contractions are superimposed on a modest basal pressure. The contractions may be antegrade (A), simultaneous (S), or retrograde (R). They are independent of duodenal pressure changes.

ments in animals have shown mixed results, with both excitatory and inhibitory effects [99]. Vagal stimulation induces sphincter contraction. After administration of sympathetic blockers and atropine, vagal stimulation relaxes the sphincter, which suggests a noncholinergic nonadrenergic effect. These results indicate that vagal innervation to the sphincter is mainly excitatory; however, there exists an underlying inhibitory action via noncholinergic, nonadrenergic nerves. Sympathetic blockade on its own does not influence sphincter of Oddi activity, suggesting that the sympathetic system does not have a major regulatory role under normal circumstances. Intrinsic nerves have a prominent role in controlling sphincter of Oddi activity.

Recent studies have identified a role for NO as the major noncholindergic nonadrenergic inhibitory transmitter acting on the sphincter of Oddi. NO donors, such as sodium nitroprusside, induce relaxation of the opossum sphincter, whereas inhibition of NO synthase with L-arginine analogues reduces the relaxation induced by transmural electrical stimulation.

Electrical stimulation of the gallbladder produces a fall in sphincter of Oddi pressure in dogs [100]. Subsequent studies in humans demonstrated that distention of the gallbladder decreased resistance to flow by reducing the amplitude and decreasing the basal pressure, thus promoting the flow of bile [101]. This response of the sphincter of Oddi to gallbladder distention, a cholecystic–sphincter of Oddi reflex, is mediated via neural connections between the gallbladder and the sphincter. This connection was abolished by application of local anesthetic to the common bile duct.

Distention of the stomach causes sphincter of Oddi contraction, thus producing a resistance to reflux of duodenal contents through the sphincter of Oddi. It has been identified as the pyloro-sphincter reflex. This response is abolished by atropine, which suggests it is mediated by cholinergic nerves.

Distention or the installation of dilute hydrochloric acid into the duodenum of humans results in sphincter spasm. This enterosphincter reflex is abolished by atropine.

Other factors in the control of sphincter of Oddi

• **Prostaglandin.** Prostaglandin E_1 inhibits sphincter of Oddi activity by suppressing its membrane activity. In addition, prostaglandin E_2 has an inhibitory action.

• **Sex hormones.** Recent reports suggest that sex hormones and pregnancy affect the motility of the sphincter of Oddi. This action is demonstrated by differences in the response to cholecystokinin stimulation of male and female prairie dogs. In a separate study, sphincter motility was significantly reduced during high-dose estrogen infusion (primarily due to decreased phasic wave frequency), and it remained low for at least 20 minutes following the infusion.

• **Hymecromone glucuronides.** These antispastic drugs, given intravenously, as well as lignocaine given via T-tube in the bile duct, were effective in reducing sphincter of Oddi activity in patients.

Dysmotility of the biliary tract

Dysmotility of the gallbladder has been documented in several studies and is thought to play a role in gallstone formation. Impaired gallbladder-emptying in response to exogenous CCK or meal stimulus has been well documented in gallstone patients. Increased fasting and residual gallbladder volumes mainly characterize the motility defect. In a study of patients on total parenteral nutrition, their gallbladder motility was shown to be defective, promoting sludge and microcrystal formation. It may be that crystals are continually formed, but the ability to eject them is what prevents gallstone formation. Consequently, formation of gallstones may require dysmotility of the gallbladder.

Sphincter of Oddi dysmotility results in either biliary sphincter of Oddi dysfunction or episodes of recurrent pancreatitis [102]. Both of these clinical entities are associated with abnormally elevated sphincter of Oddi basal pressure and are treatable by division of the sphincter of Oddi [102,103].

Questions

1. The Cantlie's line is an oblique plane extending from the
a. center of the gallbladder bed to the right border of the inferior vena cava
b. center of the gallbladder bed to the left border of the inferior vena cava
c. center of the gallbladder bed to the right border of the middle hepatic vein
d. center of the gallbladder bed to the left border of the portal vein
e. falciform ligament to the left border of the inferior vena cava

2. The right hemiliver comprises
a. segments 2, 3, 4
b. segments 4, 5, 8
c. segments 5, 6, 7, 8
d. segments 6, 7
e. segments 4, 5, 6, 7, 8

3. The left medial section is Couinaud's segment
a. 2 and 3
b. 4
c. 3 and 4
d. 5 and 8
e. 1

4. The superior border of Calot's triangle is formed by the
a. cystic artery
b. common bile duct
c. cystic duct

d. inferior surface of the liver
e. common hepatic duct

5. Cholesterol stone formation can be due to
a. increase in cholesterol secretion by the liver
b. decrease in synthesis of bile salts
c. decrease in synthesis of phospholipids
d. all the above

6. Liver receives 75% of blood flow from the
a. common hepatic artery
b. superior mesenteric artery
c. portal vein
d. right hepatic artery
e. cystic artery

7. The valves of Heister are mucosal folds in the
a. cystic duct
b. common hepatic duct
c. common bile duct
d. duct Luschka
e. sphincter of Oddi

8. Bile acids are reabsorbed from the
a. distal jejunum
b. terminal ileum
c. proximal colon
d. sigmoid colon
e. not absorbed at all

9. Which of the following is not true?
a. CCK affects gallbladder motility
b. gallbladder volume decreases following truncal vagatomy
c. sympathetic stimulation causes gallbladder relaxation
d. patients on total parenteral nutrition may have defective gallbladder motility
e. gallbladder motility can be correlated with migratory motor complex of the gut during the interdigestive period

10. The cystic artery usually arises from the
a. common hepatic artery
b. right hepatic artery
c. left hepatic artery
d. celiac trunk
e. superior mesenteric artery

Suggested readings

Corazziari E, Shaffer EA, Hogan WJ, Sherman S, Toouli J. Functional disorders of the biliary tract and pancreas. Gut 1999;45(suppl 2):48–54.
This is a review article derived from a consensus working party report as part of the Rome criteria for the diagnosis and management of gastrointestinal motility disorders. It is an excellent overview by the world experts in the field.

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