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Cholangiography Using 64-Multi-Detector Row Computed Tomography in the Normal Dog

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Cholangiography using 64-multi-detector row computed tomography in the normal dog

By

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Cholangiography using 64-multi-detector row computed tomography in the normal dog

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Hepatobiliary disease can sometimes be difficult to diagnosis due to non-specific clinical signs, and diagnostic imaging is a vital tool in diagnosing these diseases. Multi-slice computed tomographic cholangiography (MSCTC) is a non-invasive way to obtain high quality images of the hepatobiliary system. Our objectives were to determine the best technique for performing MSCTC in normal dogs with regards to contrast agent, dose, and optimal time to imaging. Our test subjects included eight normal adult hounds. Four dogs were administered Cholografin and the other four Biliscopin. Two dose groups were established with four dogs receiving 0.5mL/kg and four receiving 1 mL/kg. Our results demonstrated that MSCTC is feasible in normal dogs and produces high quality images of the hepatobiliary system. The contrast agent Biliscopin at the higher dose subjectively produced the best quality images. The optimal time to image patients following contrast administration varied between contrast agents (15-60 minutes).

DEDICATION

I would like to dedicate this research to my husband, Nicholas Miller, who gave me the love, support, and encouragement I needed to come back to school to pursue a residency in something I felt passionate about and endured me being away from home for most of it. You are my rock. I would also like to dedicate this to my parents, Joe and Laura Wooley, who have loved and supported me throughout my lifetime and always encouraged me to go after my dreams no matter how big or small. This is for you mom. I would also like to dedicate this to my entire family and my friends who have kept me sane throughout this process and have loved and supported me through the hard times.

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CHAPTER I

INTRODUCTION

Background Information and Project Significance

Hepatobiliary diseases are being diagnosed more commonly in small animals due
to newer imaging modalities and techniques becoming more widely available. Imaging is
a critical tool in the diagnosis of these diseases. Many animals with hepatobiliary disease
go undiagnosed until their disease has progressed to the late stages due to the non-
specific clinical signs associated with hepatobiliary disease. Hepatobiliary disease can
also sometimes be mistaken for other intra-abdominal diseases due to similar clinical
signs. There is a need for a better way to obtain high quality cross-sectional and three-
dimensional images of the hepatobiliary system non-invasively in small animals.

Current modalities available for hepatobiliary imaging in small animals include
radiography, ultrasound, computed tomography, nuclear scintigraphy, intravenous
cholangiography combined with radiography, magnetic resonance
cholangiopancreatography, endoscopic retrograde cholangiography, and percutaneous
transhepatic cholangiography.[1-4] Abdominal radiography is widely available and is
recommended as an initial diagnostic step in dogs suspected of having hepatobiliary
disease. Unfortunately, it is often an insensitive method for diagnosing hepatobiliary
disease. Ultrasonography is a non-invasive technique that is readily available, but it is
operator dependent. While it often allows for better detail of biliary structures than

radiography, it provides inferior images of peripheral intrahepatic bile ducts when compared with other modalities.[1, 2, 4, 5] Gas in the gastrointestinal tract can also limit ultrasonographic evaluation of biliary structures in some dogs. Nuclear scintigraphy is used in dogs to diagnose biliary obstructions. It is non-invasive, but requires the use of radioisotopes and has limited availability. Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiography, which are considered the gold standard in hepatobiliary imaging in humans, are techniques that provide excellent visualization of the bile ducts.[4-6] These techniques have also been shown to produce high quality images of the hepatobiliary tract in small animals.[1-3, 5, 7] However, they are invasive, costly, can be technically demanding, and carry significant risk to the patient.[1-3] Magnetic resonance cholangiopancreatography is non-invasive but can be prone to artifact, provides little functional information, has limited availability, and is costly.[5, 6, 8]

Multi-slice computed tomography (MSCT) has been shown in humans to have a high diagnostic accuracy in the fields of abdominal, thoracic, and cardiovascular imaging.[9] In veterinary medicine, MSCT has also been shown to be valuable in imaging multiple body systems, including the adrenal glands, the hepatic portal vasculature, and the intestines.[10] MSCT allows for large volumes of data to be acquired rapidly and be reconstructed into detailed two-dimensional and three-dimensional images.[5, 9] Multi-slice computed tomographic cholangiography (MSCTC) combines the use of MSCT with an intravenous iodinated contrast agent that is excreted specifically through the biliary system. It has been shown in multiple studies performed in humans to be non-invasive and produce diagnostic quality studies of the biliary tract beyond just that obtained with MSCT, including information regarding biliary kinetics and function.[5, 6, 8, 9, 11, 12]

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MSCTC has been performed successfully for the description of normal biliary anatomy in porcine subjects.[6] MSCTC using a 64-slice multi-detector row scanner has not yet been described in dogs.

Indications for performing MSCTC in humans include but are not limited to cholelithiasis/choledocholithiasis, anomalous conditions of the bile ducts, unexplained upper abdominal pain, dilation of biliary ducts noted on ultrasound, neoplasia of the liver, biliary tract, and associated structures, biliary tract rupture and stricture, and pre-and post-surgical planning .[5, 6, 8, 11, 13] Indications for imaging the canine biliary tract are similar and include but are not limited to cholelithiasis/choledocholithiasis, cholecystitis, gallbladder mucoceles, neoplasia of the liver and biliary tract, or extra-hepatic biliary tract rupture or obstruction.[1-4]

Research Objectives

The purpose of our study was to describe the normal cross-sectional and three-dimensional biliary anatomy of the normal dog by developing a technique for performing MSCTC. With regards to technique, we also wanted to determine the optimal time for imaging following contrast injection, the optimal contrast media, and contrast dose.

We hypothesized that cholangiography using multi-slice computed tomography would be feasible in the normal dog and would produce high quality images of the biliary system. We also hypothesized that we would be able to reconstruct our raw data using multiple reconstruction formats to generate detailed two and three-dimensional images. With regards to contrast dose, we hypothesized that the higher dose of contrast would produce better quality images. We also hypothesized there would not be a difference in the image quality between the two different contrast agents available for evaluation.

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CHAPTER II

LITERATURE REVIEW

Normal Biliary Anatomy and Physiology

Bile is produced by the hepatocytes and excreted into the bile canaliculi, which lie

in between the cells.[1, 14] The canaliculi all unite and form biliary ductules which then

turn into interlobular ductules.[14] Larger interlobular ducts form from the anastomosis of

small interlobular ductules.[14] Lobar intrahepatic ducts are then formed from interlobular

ducts uniting.[14] The extrahepatic ducts arise from the intrahepatic ducts and consist of

the hepatic ducts.[14] Variations in the number of hepatic ducts and their terminal location

are commonly seen.[14, 15]

The cystic duct, which drains the neck of the gallbladder, merges with the

gallbladder and two or more hepatic ducts to form the bile duct.[1, 14] (Figure 2.1) The bile

duct exits the porta hepatis ventral to the portal vein and terminates in the lumen of the

duodenum at the major duodenal papilla near the pancreatic duct.[1] (Figure 2.2) The distal

portion of the bile duct that travels through the lesser omentum along the hepatoduodenal

ligament is typically 5cm in length and 2.5mm in diameter.[14, 16] The intramural portion

of the bile duct is approximately 1.5 to 2 cm in length.[14, 16] (Figure 2.3 A) The intramural

portion of the bile duct is surrounded by a double layer of smooth muscle.[14] The outer

layer consists of the *tunica muscularis* portion of the duodenum and the inner layer is

formed by the *musculus proprius* of the bile duct.[14] (Figure 2.3 B) The inner layer forms

the *musculus sphincter ampullae hepatopancreaticae* and the *musculus sphincter ductus choledochi* which cause the excretion of bile to be largely dependent upon duodenal activity.[14] Bile flows from the bile canaliculi into the interlobular ducts and then into the lobar ducts before exiting the liver.[14, 16] The lobar ducts then drain into the hepatic ducts and pass bile into the bile duct.[14, 16]
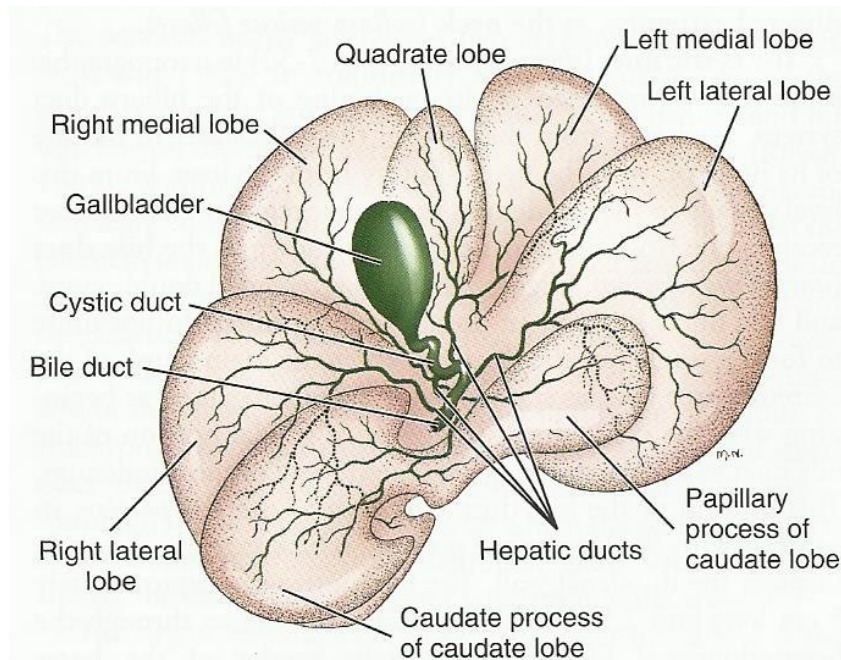
Figure 2.1   Schematic of gallbladder and hepatic ducts, visceral aspect
Miller's Anatomy of the Dog[14]
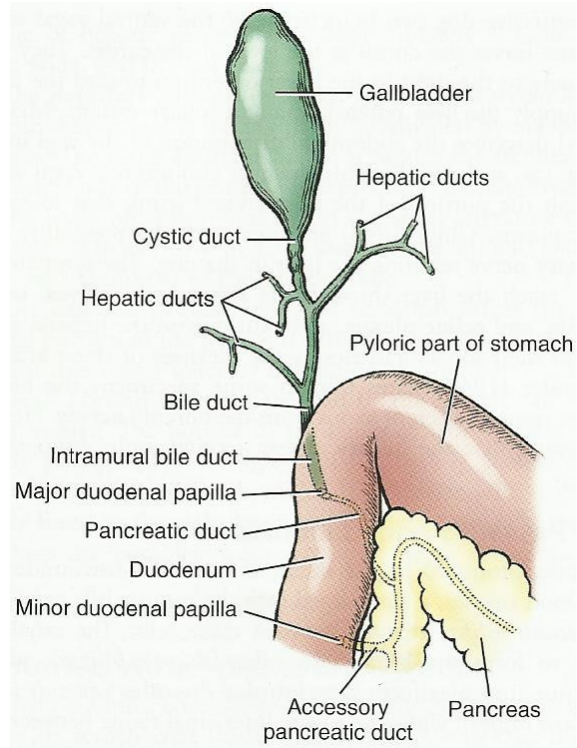
Figure 2.2   Bile, hepatic, and pancreatic ducts

Miller's Anatomy of the Dog[14]
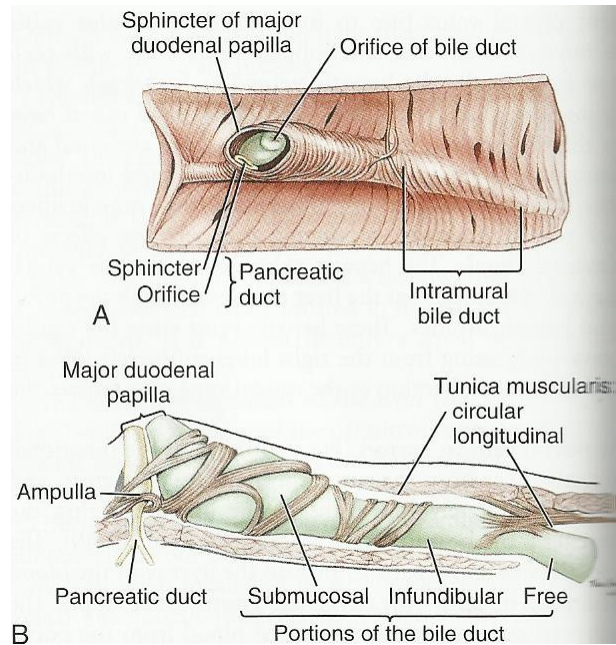
Figure 2.3   Intramural course of the bile duct

Miller's Anatomy of the Dog[14]

The gallbladder is a thin walled structure located in a fossa between the quadrate
and right medial lobes of the liver. (Figure 2.1) The cranial end of the gallbladder is
termed the fundus, the middle portion is the body, and the distal, narrower portion is the
neck, which joins the cystic duct.[14] The main function of the gallbladder is to store and
concentrate bile. The gallbladder also absorbs lipid-soluble compounds.[14] The
gallbladder can accommodate a volume of approximately 1 milliliter per kilogram of
body weight.[17] The vagus nerve supplies the parasympathetic innervation to the
gallbladder musculature causing it to contract and the duodenal sphincter to relax,
allowing emptying.[14, 18] The splanchnic nerves provide sympathetic innervation to the
gallbladder, allowing it to relax.[18] Increased intra-abdominal pressure secondary to
inspiration causes the majority of pressure changes within the gallbladder.[14] The
gallbladder fills continuously with bile through hepatic secretion and passive gallbladder

distention and is a low pressure system.[16] The left branch of the proper hepatic artery provides the blood supply to the gallbladder and bile duct.[14] The gallbladder is not an essential organ to the dog and is absent in some species including the horse and rat.[15]

Bile is composed of bile acids or salts, bile pigments, cholesterol, lecithin, and inorganic salts.[18] Bile acids are formed from cholesterol.[19] Bile acids function to emulsify dietary lipids and to solubilize byproducts of fat digestion.[19] They are produced in the smooth endoplasmic reticulum of the hepatocytes, and as they are secreted, break down phospholipids and cholesterol from the cell membrane.[19] Phospholipids, cholesterol, and bile acids all form the functional component of bile, which is key in the digestion and absorption of fats.[19, 20] Bile acids also stimulate the release of intestinal lipases that are responsible for absorption of fat soluble vitamins such as vitamin D.[18]

Bile pigments are another component of bile, with bilirubin being the main bile pigment, giving bile its characteristic green color.[19] Bile pigments do not aid in digestive function but facilitate excretion of waste products.[19] Bilirubin is produced during enzymatic cleavage of hemoglobin from normal red blood cells and is derived from the degradation of heme moiety.[16, 19-21] Heme is enzymatically cleaved by heme oxygenase and forms biliverdin, which is then reduced to bilirubin by biliverdin reductase.[21] Bilirubin is hydrophobic, meaning that it can only be transported in the blood when it is bound to albumin.[21] Unconjugated bilirubin is soluble in plasma due to its strong affinity for albumin.[16] Once conjugated, bilirubin is excreted into the bile. In the small intestine, conjugated bilirubin is converted to urobilinogen which is then excreted in the feces.[21] Only a small percentage of urobilinogen is absorbed and excreted renally.[21]

When fat is ingested and reaches the duodenum, discrete endocrine cells in the gastrointestinal tract are stimulated to release cholecystokinin, which stimulates contraction of the gallbladder and relaxes the sphincter surrounding the bile duct at the opening of the major duodenal papilla (this sphincter is referred to the *Sphincter of Oddi* in some veterinary texts) allowing stored bile from the gallbladder to flow into the duodenum.[1, 18, 19] Bile acids are then absorbed by the ileum and transported via the portal vein back to the liver where they are absorbed by the hepatocytes.[19] This circulatory flow of bile from the liver to intestine to portal blood and back to the liver and intestines is termed enterohepatic circulation.[19, 20] This positive feedback system is initiated through gallbladder contraction and thus initiates additional bile synthesis by the hepatocytes.[19, 20] This feedback system is important as bile is composed of 90% recirculated bile salts, which are necessary for lipid absorption from the small intestine.[18]

Hepatobiliary Disease

There are many disease processes that can affect the hepatobiliary system. Clinical signs associated with these diseases are often nonspecific but can include lethargy, vomiting, diarrhea, pyrexia, anorexia, icterus, abdominal pain, or ascites.[1, 17, 18, 22] Physical examination findings can also be nonspecific but may reveal icteric mucus membranes, a painful abdomen, or pyrexia. Pain may be localized to the cranial abdomen on the right side if the patient has biliary disease secondary to pancreatitis or pancreatic neoplasia.[18] Common abnormalities seen on a complete blood count include a stress leukogram or a neutrophilic leukocytosis with a left shift, which is most commonly seen with rupture of the biliary tract, or non-regenerative anemia due to chronic disease.[17] Serum chemistry profiles with hepatobiliary disease can include increased alanine

aminotransferase (ALT), increased serum alkaline phosphatase (ALP), increased gamma-glutamyl transpeptidase (GGT), hyperbilirubinemia, and hypercholesterolemia. If the patient is septic, hypoalbuminemia and hypoglycemia may also be seen.[17] Patients with a biliary obstruction may have hyperbilirubinuria on urinalysis. Clotting times can also be prolonged when absorption of fat soluble vitamin K is impaired, leading to reduced hepatic synthesis of vitamin K-dependent coagulation factors.[1] Pre- and post-prandial bile acids are used to test liver function and can be abnormal due to liver failure or obstruction of the biliary system. Pre- and post-ammonia challenge of blood ammonia levels are abnormal due to liver failure but are not affected by biliary disease.

Obstructive diseases of the hepatobiliary system

Extrahepatic biliary obstruction can be caused by an obstruction of the cystic or bile duct lumen, obstruction of the major duodenal papillae, or extraluminal compression of the cystic or bile duct.[1] Some causes of extrahepatic biliary obstruction include pancreatitis, neoplasia (including neoplasia of the gallbladder, bile ducts, pancreas, gastrointestinal tract, or lymph nodes), cholelithiasis, choledocholithiasis, cholecystitis, abscesses, granulomas, or fibrosis secondary to trauma.[17, 18, 21, 23] Intraluminal obstruction can be caused by cholelithiasis, biliary sludge or gallbladder mucocele, or parasitic infections.[1, 17, 24]

Pancreatic disease is the most common cause of extrahepatic biliary obstruction in dogs.[21, 24] Pancreatitis is an inflammatory condition of the pancreas that can result in inflamed tissues, abscesses, or cysts that can cause compression of the adjacent bile duct. It can also cause scar tissue to form in or around the bile duct.[21] Ultrasound is used most often to aid in the diagnosis of pancreatitis and extrahepatic biliary obstruction secondary

to pancreatitis. Following obstruction, dilated cystic and bile ducts are seen initially followed by the extrahepatic ducts and then intrahepatic ducts. It takes 5 to7 days post-obstruction to see dilated intrahepatic ducts.[25] Treatment of the obstruction usually consists of medically managing the pancreatitis. Early detection and management of pancreatic abscesses or necrosis has been shown to improve survival.[26] In severe or chronic cases, surgical intervention, such as cholecystoduodenostomy, cholecysostomy, cholecystectomy, or cholecystojejunostomy, may be needed.[18, 26, 27] Mortality rates in dogs that undergo biliary tract surgery range from 50% to 100%.[26, 27] Pancreatic neoplasia, such as pancreatic adenocarcinoma, can also cause an extrahepatic obstruction of the bile ducts. Treatment is often unrewarding, as most pancreatic neoplasms are malignant, and the prognosis is generally poor.[21] Pancreatic abscesses, cysts, and granulomas are less common causes of biliary obstruction.[18, 21]

Primary hepatobiliary tumors are rare and account for 0.6% to 1.5% of all canine neoplasms.[17, 28] The two types of primary bilious tumors are biliary cystadenoma and biliary adenocarcinoma. [17, 28] Biliary cystadenomas occur most frequently in older cats and are rare in the dog.[17] They are typically located in the intrahepatic bile ducts and can be single or multifocal and involve one or more hepatic lobes.[17] Biliary carcinomas account for 22% to 41% of all malignant liver tumors in the canine.[28] They most commonly occur in the intrahepatic ducts and very rarely occur in the gallbladder itself.[17, 28] Biliary carcinomas are slow growing tumors and are initially locally aggressive. Biliary carcinomas are often advanced or metastasized at the time of diagnosis due to a lack of clinical signs early in the course of disease.[17] Ultrasound is the most common imaging modality used for diagnosis of these tumors. However, a biopsy is the only way

to obtain a definitive diagnosis.[17] Treatment of hepatobiliary tumors is determined by the type of tumor and its location.

Cholelithiasis, or stone formation in the gallbladder, is one of the more recognized diseases of the gallbladder, although it still occurs rather infrequently in dogs and the etiology is unknown.[17, 23] It occurs most frequently in miniature schnauzers and miniature poodles.[17] It has also been shown that older female dogs are predisposed to cholelithiasis.[17] Choleliths vary in size and composition, with cholesterol, bilirubin, and calcium all being reported as components of stones.[17, 18, 23] Abnormalities that may lead to cholelithiasis include gallbladder dyskinesia, hypercholesterolemia, hypertriglyceridemia, hyperbilirubinemia, endocrine disease, and transport defects in the gallbladder.[17]

Choleliths can cause an obstruction of the biliary tract or inflammation of the liver or biliary tract that can eventually lead to gallbladder or biliary rupture and subsequent bile peritonitis.[18] Many times, however, choleliths are found incidentally in dogs at the time of necropsy. Choledocholithiasis occurs when stones form in the bile duct. These stones are either primary or secondary, with primary stones developing in the bile duct and secondary stones developing in the gallbladder and later passing into the bile duct. A definitive diagnosis of cholelithiasis or choledocholithiasis is usually made with abdominal ultrasound. Treatment for cholelithiasis and choledocholithiasis depends on the severity of clinical signs. Most patients with stones are asymptomatic. [17] Medical therapy consists of dissolution of the stones or providing supportive care until the stone(s) pass.[17] If the stones are causing complete obstruction, surgical intervention is the treatment of choice. The type of surgery depends on the location of the obstruction.[17]

A gallbladder mucocele is defined as an abnormal accumulation of inspissated mucus that causes distention of the gallbladder.[26, 29-31] As the mucocele expands, it stretches the gallbladder wall and disrupts the flow of bile leading to pressure necrosis of the wall.[17] Gallbladder mucoceles are characterized histologically by hyperplasia of mucus-secreting cells in the gallbladder mucosa, and it has been suggested that the mucocele results from dysfunction of these cells.[32, 33] The exact cause of this dysfunction is unknown, but it is thought to be multifactorial.[32]

Factors that have been shown to predispose dogs to mucoceles include dyslipidemias, decreased motility of the gallbladder, endocrine diseases, such as hyperadrenocorticism and hypothyroidism, and exogenous steroid administration.[17, 30, 34, 33, 35] It has also been shown that extrahepatic biliary obstruction does not play a primary role in the formation of gallbladder mucoceles in dogs as it does in humans.[32] Older patients are more likely to form a mucocele with the median age being 10 years.[17] Medium-sized breeds are most commonly affected, particularly the cocker spaniel, Shetland sheepdog, and miniature schnauzer.[30, 32, 33] Complications associated with gallbladder mucoceles include bile peritonitis secondary to rupture, extrahepatic bile duct obstruction, cholecystitis, necrotizing cholecystitis, and pancreatitis.[17, 22]

The diagnosis of a gallbladder mucocele is most often made with ultrasound, due to its characteristic kiwi-like appearance.[17, 33] Findings on ultrasound that have been shown to correlate with a gallbladder rupture include discontinuity of the gallbladder wall, hyperechoic fat in the cranial abdomen, free abdominal fluid, and striated, echogenic material located outside of the gallbladder lumen.[22, 32, 33] The sensitivity for diagnosing a gallbladder rupture with ultrasound ranges from 86-94.4%.[22, 32, 33] In a

study of 45 dogs that evaluated ultrasonographic findings associated with gallbladder rupture, ultrasound was shown to have a specificity of 44.4% for identifying gallbladder rupture.[22] This may be due to the fact that it can be difficult to detect a rent in the gallbladder wall in the absence of an extruding mucocele or mucocele free in the peritoneal cavity.[22] A clinical challenge with the imaging modalities currently available is determining whether or not surgical therapy of a gallbladder mucocele is warranted when a rent in the gallbladder wall is not definitively identified with ultrasound.

Nonobstructive diseases of the hepatobiliary system

Nonobstructive diseases of the hepatobiliary tract include cholecystitis, necrotizing cholecystitis, bacterial cholangiohepatitis/cholangitis, emphysematous cholecystitis, choleliths, parasites, neoplasia, or congenital anomalies.[17] Several of these disease processes can eventually lead to biliary obstruction.

Cholecystitis is inflammation of the gallbladder and bile ducts. It is commonly caused by migration of bacteria from the small intestine through the bile duct or by hematogenous spread of bacteria.[17] Factors that can predispose to cholecystitis include cholelithiasis, gallbladder mucoceles, bile stasis, ascending biliary tract infection, or biliary neoplasia.[17, 23] Clinical signs associated with cholecystitis can include anorexia, vomiting, abdominal pain, and fever.[17] Laboratory findings are variable. Ultrasound is considered the gold standard in dogs for diagnosing cholecystitis.[17] Treatment of cholecystitis depends on the severity of the disease but usually consists of medical or surgical management.

Necrotizing cholecystitis occurs when a bacterial infection causes necrosis of the gallbladder wall, leading to gallbladder rupture and secondary bile peritonitis.[17, 21, 23]

Three classes of necrotizing cholecystitis have been described. Class I includes necrotizing cholecystitis without gallbladder rupture.[17] Class II occurs with acute necrotizing cholecystitis with gallbladder rupture and bile peritonitis, and Class III includes chronic cholecystitis with cholecystic and omental adhesions with or without fistulas.[17]

Bacterial cholangitis and cholangiohepatitis occur when infection from the biliary tree ascends into the liver. These conditions occur more frequently in cats than in dogs.[36-38] Shetland sheepdogs have a higher incidence of these diseases than other dog breeds.[17] Infection usually occurs secondary to other circumstances including patients receiving immunosuppressive therapy, patients with hyperadrenocorticism or diabetes mellitus, biliary stasis, septicemia, decreased hepatic blood supply, or necrosis of hepatic tissue.[23] Bacterial cholangitis and cholangiohepatitis are rarely reported in dogs.[38] Diagnostic imaging with cholangitis and cholangiohepatitis usually consists of abdominal radiography and ultrasound and is often non-specific.[38]

Emphysematous cystitis occurs when gas-producing bacteria infiltrate the gallbladder and cause gas to fill the gallbladder lumen or invade the gallbladder wall. It is typically associated with animals with diabetes mellitus but can be seen in any animal.[17] This condition can be diagnosed using radiography or ultrasound. On radiographs, a round to ovoid gas opacity structure may be seen superimposed over the liver in the cranioventral portion of the abdomen.[17] Ultrasound displays a gas interface in the area of the gallbladder with distal acoustic shadowing.[17] Surgical intervention is the treatment of choice for this disease.

Biliary parasites are rare and are more commonly seen in cats than in dogs.[18] Biliary trematodes, such as *Platynosomum concinnum,* can cause a partial or complete obstruction of the biliary tract or secondary cirrhosis and hepatic lipidosis.[1, 18] Hepatobiliary disease associated with trematode infection has been primarily recognized in Florida and Hawaii.[18] Clinical signs of biliary parasites depends on the degree of liver injury and biliary obstruction but can include weight loss, vomiting, or anorexia.[17] Eosinophilia may be present on a complete blood count and elevated liver values can be seen on the serum chemistry panel.[17] Abdominal radiographs are usually normal, and abdominal ultrasound demonstrates dilated bile ducts if the patient is obstructed. A definitive diagnosis can be reached by aspirating and performing cytology on the bile or by performing a biopsy of the liver.[17]

Current Modalities Available for Imaging the Hepatobiliary System

Diagnostic imaging is an integral part in the diagnosis of hepatobiliary diseases. Modalities available for imaging of the hepatobiliary system include radiography, ultrasonography, computed tomography, magnetic resonance imaging, and nuclear scintigraphy. Positive contrast agents used with several of these imaging modalities can also be very useful in diagnosing hepatobiliary disease. Some examples of these studies include cholangiography combined with radiography, endoscopic retrograde cholangiopancreatography, and percutaneous transhepatic cholangiography. Magnetic resonance cholangiopancreatography is also a very useful imaging technique that does not require the use of contrast media. Many of these techniques have been used in humans for quite some time now and are being or have been adapted for use in companion animals.[17] These techniques will eventually change the way we diagnose and

treat biliary disease.[17] Each modality or technique has its own advantages and

disadvantages.

Radiography

Abdominal radiography is widely available and is recommended in dogs

suspected of having hepatobiliary disease. However, radiography is a fairly insensitive

method of diagnosing hepatobiliary disease.[36] Radiography also exposes the patient to

ionizing radiation. Radiographic signs associated with hepatobiliary disease can include

but are not limited to masses or irregular liver margins, hepatomegaly, decreased serosal

detail secondary to peritoneal effusion, radiopaque choleliths or choledocholiths,

emphysema of the gallbladder or gallbladder wall or mineralization of the gallbladder

wall.[17, 39] Most biliary stones do not contain sufficient calcium to be seen

radiographically.[17]

Ultrasonography

Ultrasound allows for a detailed examination of the architecture of the

hepatobiliary system including the liver, gallbladder, bile ducts, and hepatic vasculature.

It is widely used and available, non-invasive, and is currently considered the diagnostic

modality of choice when looking for causes of hepatobiliary disease in small animals.[17]

Common ultrasonographic findings associated with biliary disease include

choleliths/choledocholiths, thickening of the gallbladder wall, gallbladder sludge or

mucocele, biliary tree dilation or obstruction, or pericholocystic fluid.[17, 39]

One disadvantage of ultrasound is that it provides inferior images of the

peripheral and intrahepatic bile ducts, which are only seen when dilated, when compared

with other modalities.[2-4, 6] Dilation of the bile ducts may be evident as early as 24 to 48

hours following obstruction.[16, 29] Intrahepatic duct dilation may be identified with

ultrasound 5 to 7 days following complete obstruction.[16, 29] Gas in the gastrointestinal

tract can also limit ultrasonographic evaluation of biliary structures in some dogs. Mild

structural abnormalities or functional disturbances may not be detected with ultrasound.[2]

Ultrasound also has a low sensitivity and specificity for diagnosing inflammatory

conditions such as cholangitis and pancreatitis, where ultrasound findings have been

shown to correlate poorly with the histological diagnosis.[37]

Computed tomography (CT)

The gallbladder is readily seen on an abdominal CT with and without the use of

non-biliary specific iodinated contrast due to its shape and density. The size and location

of the gallbladder can vary depending on the amount of bile present within the

gallbladder lumen.[40] The gallbladder wall is not typically seen as a distinct structure

from the gallbladder contents because the wall and contents are the same density. The

bile ducts are not seen on CT unless they are dilated due to obstruction or contain mineral

dense calculi.[40] Dilated bile ducts are characterized as tortuous, non-enhancing tubular

structures that are hypodense (dark) to surrounding parenchyma.[40] Mineral dense calculi

can be seen in the gallbladder or bile ducts on CT. Non-biliary specific iodinated contrast

does not cause enhancement of the gallbladder or bile ducts. Modern CT scanners along

with the use of a biliary-specific iodinated contrast can provide high quality images of the

biliary system. This topic along with the topic of CT will be discussed in greater detail

later in the chapter.

Magnetic resonance imaging (MRI)

The use of MRI as a diagnostic tool in veterinary medicine has increased over the past few years. Its high contrast resolution allows soft tissue pathology to be characterized very sensitively due to its detection of subtle shifts in cellular water and protons.[37, 39] MRI allows for detection of inflammatory processes of the hepatobiliary system and pancreas due to changes in signal intensity as well as contrast enhancement.[37] The gallbladder is seen on MRI as a discrete, semicircular T2 hyperintense structure.[41] On a T2 weighted sequence, fluids are bright when compared to surrounding tissues. The gallbladder is fluid filled (bile), which allows it be clearly seen on this sequence. Hyperintense means that a structure is brighter than its surrounding tissues, and hypointense means that it is darker than surrounding tissues. The bile ducts may be evaluated by using various imaging planes, such as transverse, sagittal, or dorsal planes.[41] A disadvantage of MRI is its long data acquisition time, which leads to prolonged anesthetic episodes in small animals. MRI provides only morphological information without any functional information. It is also costly with limited availability.

Nuclear scintigraphy

Hepatobiliary scintigraphy is used most often in dogs for diagnosing biliary obstructions that cannot be confirmed by ultrasound.[1, 42] It involves the intravenous injection of a radiolabeled isotope, most commonly technetium-labeled iminodiacetic acid analogues (^{99m}Tc-IDA), followed by scintigraphic imaging with a gamma camera over the course of three hours to determine if the isotope is taken up by the liver, excreted into the biliary tract, or expelled into the intestines.[42, 43] In a normal canine patient, radioactivity should be observed in the gastrointestinal lumen within three hours of

isotope administration.[1, 42] If it is not observed in the intestines within three hours, a diagnosis of a complete extrahepatic biliary obstruction can be made.[1, 42] Imaging may be extended beyond three hours, and delayed imaging (24 to 48 hours) is recommended to confirm lack of intestinal activity.[1, 42] Other scintigraphic findings seen with a complete chronic biliary obstruction include a subnormal hepatic extraction fraction (the portion of isotope removed from the plasma as it circulates through the liver), a prolonged clearance half-life (the time it takes for half of the isotope to be excreted from the hepatocytes into the biliary tract), and an inability to see the biliary tree.[42] Partial extrahepatic biliary obstructions are characterized by normal hepatic extraction fractions and prolonged clearance half-life and cannot be ruled out or confirmed on the basis of radioactivity in the intestines.[42]

Hepatobiliary scintigraphy is non-invasive and sensitive in diagnosing biliary obstruction.[1] However, the need for radioisotopes and expensive equipment has limited the availability of this modality to mainly select referral institutions. Due to the low resolution of scintigraphy, identification of the level of the biliary obstruction is not always possible, and the technique does expose the operator to ionizing radiation.[1] Also, there are short term restrictions on patient handling following administration of radioisotopes that can further delay surgery if needed.[1] Scintigraphy also exposes the patient to ionizing radiation.

Conventional cholangiography

Contrast agents are used in veterinary medicine to improve the visibility of certain anatomic structures. The two types of radiographic contrast used are positive and negative contrast. Positive contrast agents have a high anatomic number causing them to

be more opaque than surrounding tissues on radiographs. Negative contrast agents are

gases that have a lower density causing them to be radiolucent. The two main types of

positive contrast agents used in human and veterinary medicine are barium and iodine.

Barium is used primarily in studies of the gastrointestinal tract. Iodinated contrast agents

are used for many types of studies including myelography, urogenital studies, and

vascular studies. Most standard iodinated contrast agents are administered intravenously

and are excreted renally through glomerular filtration due to the fact that they are water

soluble and not heavily protein bound. Biliary specific iodinated contrast agents are

transported in the blood bound to albumin and are taken up specifically by the

hepatocytes.[44] It is excreted in the same fashion as bile, through the bile ducts and into

the small intestine. Biliary specific contrast agents cause the liver, gallbladder, and bile

ducts to opacify. A small amount of biliary contrast is excreted renally.[44]

Cholangiography combines radiography with the use of an oral or intravenous

biliary specific iodinated contrast. Cholangiography has been used in combination with

conventional radiography in dogs over the years, and it provides good opacification of the

gallbladder and bile ducts in most patients.[45] In some patients, nonopacification of the

gallbladder occurs for no apparent reason.[45] In others, causes of nonopacification of the

gallbladder in patients that are properly prepared (fasted for 12 hours prior to the study)

and given a sufficient dose of contrast include vomiting of the oral contrast or

subcutaneous injection of an intravenous contrast agent, gastrointestinal disorders

preventing proper absorption of oral contrast agents, hepatic dysfunction causing

decreased excretion of contrast material into bile, hyperbilirubinemia, or disorders of the

gallbladder preventing concentration.[45] Due to the availability and superiority of cross-

sectional imaging modalities (CT and MRI) and other interventional techniques, conventional cholangiography is seldom used today in humans or animals.[12]

Endoscopic retrograde cholangiopancreatography (ERCP)

Endoscopic retrograde cholangiopancreatography (ERCP) combines the use of endoscopy, fluoroscopy, and iodinated contrast media to image the biliary and pancreatic duct systems.[3, 7] It is performed by passing an endoscope into the duodenum, locating the major duodenal papilla, and then passing a catheter filled with iodinated contrast media into the papilla.[2] The contrast media is then injected into the papilla until the bile ducts and the gallbladder are completely filled.[2] This procedure is repeated with the accessory pancreatic duct by way of the minor duodenal papilla.[2] Fluoroscopy allows for visualization of the catheter as well as visualization of the bile ducts and gallbladder once they are opacified with contrast.

In the past, ERCP was considered the gold standard in humans for diagnosing hepatobiliary disease.[6, 46, 47] However, in some institutions, magnetic resonance cholangiopancreatography has become the initial diagnostic imaging tool, with ERCP being reserved for therapeutic intervention.[6, 46, 47] ERCP has been performed in healthy dogs and cats and in dogs with chronic gastrointestinal problems.[2, 3, 7] Due to its high resolution, ERCP provides excellent delineation of the bile ducts and can also be used for therapeutic treatment, although, it has been described as technically difficult in small animals.[2, 6, 7] Disadvantages of ERCP are that it is very invasive to the patient (complication rates up to 5% in humans), exposes the patient to ionizing radiation, is costly, and is not widely available.[6, 47]

Percutaneous transhepatic cholangiography (PTC)

Percutaneous transhepatic cholangiography (PTC) is a technique involving ultrasound guided injection of iodinated contrast directly into the gallbladder, which allows for direct visualization of the gallbladder and biliary tract.[1] Abdominal radiographs are obtained immediately, at 45 minutes, 2 hours, and 24 hours after injection.[1] Opacification of the gallbladder and bile ducts as well as the duodenum usually indicates patency. However, high pressure from contrast injection could falsely generate patency in obstructed patients.[1] PTC has a high sensitivity and specificity for diagnosing biliary obstruction in dogs.[1] However, because this technique is invasive with potential complications including bile peritonitis, gallbladder rupture, or hepatic hemorrhage, it is not often used in clinical patients.[1]

Magnetic resonance cholangiopancreatography (MRCP)

Magnetic resonance cholangiopancreatography (MRCP) is a well recognized technique in humans for examining the biliary and pancreatic systems.[33] It has also been demonstrated in cats.[6, 25] MRCP is noninvasive and provides a detailed map of the biliary tree and pancreatic duct without the use of ionizing radiation or contrast media.[6, 25] Slow moving fluids, such as bile, are hyperintense (bright) on heavily T2 weighted sequences, allowing them to be easily seen against the hypointense (dark) background of surrounding tissues.[6, 25, 34] It has been shown to provide accurate detail of biliary calculi, malignant obstructions, variants in biliary anatomy, and post-surgical alterations of the biliary tract in humans.[34] MRCP combined with conventional MR sequences provides complete anatomic imaging of the biliary system, as well as the liver and the pancreas.[25]

The goal of MRCP is to generate images that resemble those obtained in more invasive procedures, such as endoscopic retrograde cholangiopancreatography.[29]

Some disadvantages of MRCP are that it can be costly and has limited availability. It also requires prolonged anesthetic times in small animals. MRCP can be prone to artifact and provides little information on biliary kinetics and function.[7] MRCP can also be inconclusive if air is present in the biliary system following surgery.[48]

Multi-Slice Computed Tomographic Cholangiography (MSCTC)

Over the past 40 years, CT scanners, and their imaging capabilities and image quality have improved tremendously.[49] Due to this improvement, the use of CT in clinical practice has experienced enormous growth.[49] CT allows for sectional or slice-oriented imaging of a patient, making anatomic localization of abnormalities more accurate than with conventional radiography.[39] CT also has excellent contrast resolution, which refers to the ability to discriminate different tissues composed of different substances and display them with different shades of gray or brightness in an image. [39]

Single-slice versus multi-slice or multi-detector CT scanners

Four generations of CT scanners have been described in the literature. The first generation scanner only scanned the head and used a pencil-like x-ray beam and a single detector.[49, 50] The tube detector movements were linear and rotary, which was termed "translate-rotate motion."[49, 50] A typical CT scan with this scanner took 25-30 minutes and only provided a single slice of data.[50] The second generation scanner employed the same "translate-rotate motion" but increased the rate of acquisition time by incorporating a fan-shaped x-ray beam and multiple detectors.[50] This design allowed more data to be

acquired in a shorter amount of time. In the 1970s, a third generation scanner was introduced that completely eliminated the translate motion and employed a "rotate-rotate" motion.[50] This meant the both the x-ray tube and the detectors rotated around the patient, which led to much shorter acquisition times. The third generation scanner is still the most widely used CT scanner today.[49, 50] Fourth generation scanners were mainly designed to combat an artifact produced by the third generation scanners called "ring artifact."[49] Ring artifact occurs when the CT detectors are not properly calibrated with one another.[49] When this happens, the detectors record incorrect data in every projection leading to this information being reconstructed as a ring on the image.[50] This ring makes it difficult to see the underlying anatomy on the image. The fourth generation scanner employs the "rotate-stationary" movement, which consists of a rotating x-ray tube but a stationary detector array.[49] These scanners are significantly more costly than the third generation scanners and more difficult to maintain, and algorithms have now been developed to combat the ring artifact in the third generation scanners, negating the need for a fourth generation scanner.[49]

Most single slice and all multi-slice CT scanners are third generation scanners.[51] The primary difference between single slice and multi-slice scanners is the design of the detector arrays.[51] Single-slice detector arrays are one dimensional and consist of a large number (usually >750) of detector elements that are in a single row across the irradiated slice to intercept the x-ray.[51] With multi-slice CT, each single-slice detector element is divided into small detector elements that form a two-dimensional array and multiple parallel rows of detectors [51] The amount of data or slices that can be collected

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simultaneously with multi-slice CT scanners depends on the number of detectors. This number ranges from a 4-slice scanner to a 64-slice scanner.

Another difference between single and multi-slice scanners is the relationship between slice thickness and x-ray beam width.[51] With single-slice CT, the slice thickness is pre-determined by the x-ray beam collimation design.[51] In the slice thickness direction, the detectors are monolithic, meaning that the single elements are long enough to intercept the entire x-ray fanbeam width.[51] Multi-slice CT slice thickness, however, is determined by the width of the detector rather than the x-ray beam collimation.[51] This means that multi-slice CT scanners can acquire much thinner slices than single-slice CT scanners, which in turn, allows for generation of high quality three-dimensional reconstructions.[51] When imaging the biliary system, conventional or single-slice CT, is often inadequate for evaluating the biliary tract or detecting low density calculi because its resolution, or image detail, is inferior for demonstrating smaller structures like the bile ducts.[52] Multi-slice CT is superior in that it allows for rapid acquisition of large data sets and has high spatial resolution (greater ability to discern small objects adjacent to each other).[9, 52, 53]

Multi-slice computed tomographic cholangiography (MSCTC)

The high diagnostic accuracy of MSCT in human medicine has been demonstrated in the fields of thoracic, cardiac, and cardiovascular imaging.[9] MSCT has also been shown to be valuable in veterinary medicine in regards to the adrenal glands, hepatic portal vasculature, and intestines.[10] The combination of multi-slice CT with cholangiography has also been shown to be very helpful in the diagnosis of hepatobiliary disease, for pre-operative planning, and for evaluation of post-operative complications in

human medicine.[48, 52, 54-61] Multi-slice CT cholangiography (MSCTC) is non-invasive and involves intravenous administration of a biliary specific contrast agent followed by MSCT imaging, which is then usually re-formatted into two-dimensional and three-dimensional reconstructions. The most common reconstructions used include maximum intensity projections (MIP), shaded surface display (SSD), and multiplanar reconstructions (MPR). MIPs are commonly used in human medicine for three dimensional reconstruction of CT angiograms because they allow for separation of high attenuation enhancing vessels from lower density surrounding soft tissue structures.[62] In relation to the bile ducts, MIPs are good at detecting intraluminal calculi because they allow contrast-filled structures to be evaluated in relation to densities of other surrounding structures.[56] SSDs provide a realistic three-dimensional reconstruction of the surface of structures while obscuring intraluminal structures.[56] SSDS are used in human imaging primarily for evaluating for vascular disease, such as aneurysms. MPRs are created by combining a series of successive transverse images and formatting them into a larger image in a different orientation, such as a sagittal or dorsal plane.[63] This type of reconstruction provides a two-dimensional reconstruction of a specific area of the body which helps to enhance the viewing of the complete anatomic picture.[56]

MSCTC also provides functional information regarding hepatocyte excretion, and if it is normal, provides detailed images of the bile ducts, including the intrahepatic ducts.[12] In post-cholecystectomy human patients, MSCTC can allow differentiation between normal post-surgical dilation and pathologic biliary obstruction.[8] In non-obstructed post-cholecystectomy patients, contrast material should be seen in the duodenum in less than 25 minutes.[8] Delayed passage of contrast media indicates

functional or anatomical abnormalities.[8] In humans, when compared to MR

cholangiography, CTC is better for determining the degree of biliary obstruction.[8] MR

cholangiography may show dilation of the bile ducts in an obstruction but will not

differentiate between a complete versus a partial obstruction.[8] With CTC, in cases of

complete obstruction, there will be a lack of enhancement of the dilated intrahepatic ducts

and liver parenchyma.[8]

As with most imaging modalities, MSCTC does have some disadvantages.

MSCTC exposes the patient to ionizing radiation. There may be side effects associated

with iodinated contrast material, although they are rarely reported in humans and dogs

and are usually mild.[12, 64, 65] The side effects will be discussed in further detail under the

heading biliary contrast media. Humans and dogs with poor hepatobiliary function,

specifically conditions associated with elevated plasma bilirubin, have unreliable

excretion of biliary contrast, which can lead to non-diagnostic or poor quality CT

cholangiography studies.[1, 12, 48, 54, 66-70] In humans, a serum bilirubin of greater than

2.0mg/deciliters (dL) is a good predictor of poor contrast excretion.[12, 68, 69] However,

even in hyperbilirubinemic patients it has been shown that although the biliary tract is not

optimally enhanced, it is still possible to obtain a diagnostic CTC study to detect

abnormalities such as dilation or obstruction of the bile ducts.[48, 68] Other studies in

humans have shown that slowly infusing a biliary specific contrast agent over several

hours as opposed to a single intravenous injection may allow for increased density of the

bile ducts in patients with high bilirubin levels (greater than 1.1mg/dL).[48, 69] Good

contrast enhancement of the biliary tree can also be obtained by increasing the dose of

contrast material in human patients with bilirubin levels greater than 1.5 times normal

and then waiting 2-2.5 hours after contrast administration to perform the CT scan.[54]

Several studies evaluating the effect of bilirubin on biliary iodipamide (Cholografin®)

excretion in dogs suggest that the contrast dose should be increased in hyperbilirubinemic

patients in order to obtain adequate opacification of the biliary structures, and that a

prolonged infusion or decrease in contrast dose is not indicated.[66, 67, 71] Although there

has been mixed success with MSCTC in human patients with bilirubin levels greater than

2 mg/dL, several studies have shown that diagnostic studies could be performed in some

patients with bilirubin levels as high as 9.3mg/dL.[48, 54, 68, 69] To the author's knowledge,

no studies have been performed using MSCTC in dogs with hyperbilirubinemia.

Indications for performing MSCTC in humans include

cholelithiasis/choledocholithiasis, anomalous conditions of the bile ducts, unexplained

upper abdominal pain, dilation of biliary ducts on ultrasound, neoplasia of the liver,

biliary tract, and associated structures, biliary tract rupture and stricture, and pre-and

post-surgical planning.[5, 6,8,11,13] Indications for imaging the canine biliary tract are similar

and include but are not limited to cholelithiasis or choledocholithiasis, cholecystitis,

gallbladder mucoceles, neoplasia of the liver and/or biliary tract, or extra-hepatic biliary

tract rupture or obstruction.[1-4] Many of these diseases are only accurately characterized

in advanced stages or at post-mortem due to the fact that clinical signs are often absent or

non-specific early in the disease process. Earlier diagnosis of these diseases is important,

and a sensitive, non-invasive method for imaging the biliary tract and determining biliary

excretory function, such as MSCTC, could be beneficial.

Biliary Contrast Media

The use of cholangiography in the dog came about in the 1920s when halogenated phthaleins were discovered.[45] It was found that these compounds were excreted primarily by the hepatocytes and were concentrated up to eight to ten fold in the gallbladder.[45] These contrast agents were given orally or intravenously and produced good opacification of the gallbladder but not the bile duct on radiographs.[12,72] In the 1940s and 1950s, several biliary specific contrast agents were introduced in Germany including iodoalphionic acid and sodium iodipamide, which greatly improved the quality of the cholecystogram and increased the safety of the technique.[12] Iodipamide methylglucamine became available in 1955 in the United States and is still in use today under the trade name Cholografin®, and is the only FDA approved biliary specific contrast agent available in the United States.[12] In the 1970s, other biliary specific contrast agents were developed including meglumine iotroxate or Biliscopin®.[12] Several studies have been performed over the years comparing some of the different biliary contrast agents.[65, 73] The major difference between biliary specific iodinated contrast agents and standard iodinated contrast agents is their method of excretion. Standard contrast agents are primarily renally excreted while biliary agents are absorbed by the hepatocytes, excreted through the bile into the intestines, and eliminated in feces. Standard iodinated contrast agents highlight the vascular system and the kidneys, while biliary contrast agents highlight the liver, gallbladder, and bile ducts. (Figure 2.4)
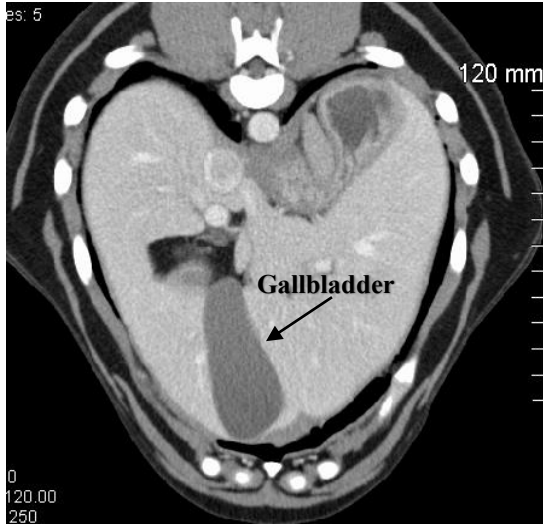
The gallbladder does not opacify with standard iodinated contrast media
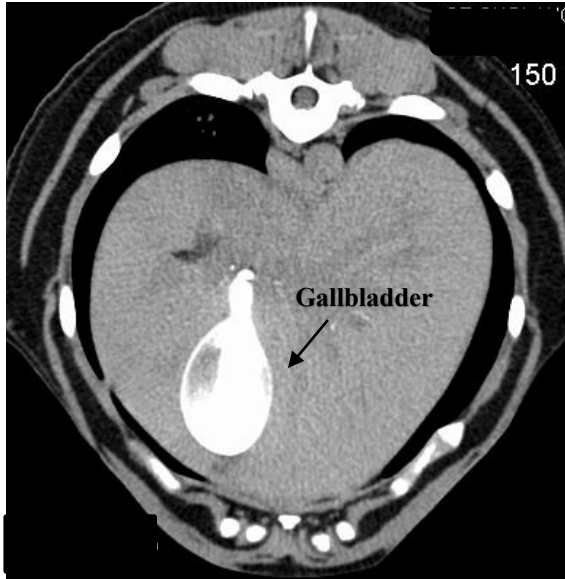
Figure 2.4   Standard Iodinated Contrast versus Biliary Specific Iodinated Contrast

Opacification of the gallbladder, cystic duct, bile duct, and intrahepatic ducts with biliary specific contrast media

Iodipamide meglumine (Cholografin®)

Cholografin® is a biliary specific iodinated contrast agent used for intravenous

cholangiography and cholecystography. The chemical makeup of Cholografin® includes

two substituted benzoic acids linked by a polymethylene chain.[74] Each milliliter (mL) of

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Cholografin® contains 520 milligrams (mg) iodipamide meglumine, 0.91mg sodium, and 257mg organically bound iodine.[75] When administered intravenously, Cholografin® is carried to the liver and rapidly secreted. Based on studies in people, it should appear in the bile within 10 to 15 minutes following injection allowing for visualization of the hepatic and bile ducts.[75] The biliary ducts should be visible 25 minutes following injection with maximum filling reached by 2 to 2 ½ hours.[75] Ninety percent of the contrast is eliminated through the feces without passing through the enterohepatic circulation.[75] The remaining ten percent of the intravenous dose is excreted through the kidneys.[75] Cholografin® is indicated in humans for intravenous cholangiography in acute abdominal conditions, in patients with symptoms following cholecystectomy and in patients unable to take oral contrast media or absorb contrast media from the gastrointestinal tract.[75] Cholografin® is contraindicated in patients who are dehydrated, who have a hypersensitivity to salts of iodipamide, or who exhibit sensitivity when given a test dose or in patients with severe liver or renal impairment.[75]

The published dosing in humans is 20 mL for adults and 0.3 to 0.6 mL/kilogram (kg) of body weight for infants and children.[75] A standard dose for dogs has not yet been established, although 0.6mL/kg and 0.9mL/kg of Cholografin® have been shown to provide good opacification of the biliary system when used with conventional radiography.[45]

Adverse effects of Cholografin® reported in humans include mild transient symptoms following rapid injection such as restlessness, sensations of warmth, sneezing, perspiration, salivation, flushing, pressure in the upper abdomen, dizziness, nausea, vomiting, chills, fever, headache, or tremors.[75] These symptoms will resolve once the

injection is completed.[75] Swollen eyelids, laryngospasm, respiratory difficulties, hypotension, tachycardia and cyanosis are rarely reported.[75] Hypersensitivity reactions may also occur and in very rare instances, anaphylactoid reactions may be seen.[75] In one study, 2,034 injections of Cholografin® were given intravenously during cholangiography over an eight year period and no anaphylactoid reactions occurred.[12] In the same study, it was noted that the incidence of mild adverse reactions increased when the injection was give rapidly.[12] Cholografin® has been administered to dogs in multiple studies with side effects rarely reported.

As stated above, Cholografin® is the only biliary specific contrast agent available in the United States. It has been used in multiple conventional radiography cholangiography studies in dogs and cats.

Meglumine iotroxate (Biliscopin®)

Biliscopin® is also a biliary specific iodinated contrast agent used for intravenous cholangiography and cholecystography. Each mL of Biliscopin® contains 105mg of meglumine iotroxate, 370mg sodium chloride, 10mg sodium calcium edetate, and 40mg sodium bicarbonate.[76] Each 100mL bottle of Biliscopin® contains 5 grams of iodine.[76] The chemical makeup of Biliscopin® is similar to Cholografin® in that it is a dimeric molecule and contains two substituted benzoic acids linked by a polymethylene chain.[65] The only differences are that Biliscopin® has a longer polymethylene chain and oxygen has been incorporated into the link.[65] Biliscopin® is excreted in the same manner as Cholografin® through the bile, and visualization of the bile ducts usually occurs in humans 30-60 minutes after administration.[76] Biliscopin is labeled for infusion in humans to be administered over a period of 30 minutes to 60 minutes.[76]

Contraindications for administering Biliscopin® in humans are similar to those of Cholografin® and include dehydration, severe cardiovascular compromise, hypersensitivity to iodine-containing contrast media, thyrotoxicosis, severely impaired liver or kidney function, and monoclonal IgM gammopathy.[76] Side effects associated with Biliscopin® in humans are also similar to Cholografin®. They are usually mild and transient and include hypersensitivity reactions, vomiting, nausea, abdominal pain, arrhythmias, respiratory distress, seizures, temporary acute renal failure, and anaphylactoid reactions.[76] The overall reaction rate of Biliscopin® is low, with one study reporting an adverse reaction rate of 1% out of 1,061 injections of Biliscopin®.[12] Little has been reported on the safety of Biliscopin® in dogs. A study specifically testing the safety of Biliscopin® in cats showed it is safe to use in normal cats and that Biliscopin® produces the same contrast effect in cats as it does in humans.[77] This study also stated that Biliscopin® is more favorable than other biliary contrast agents due to its rapid secretion into the bile, its effect on duct dilation, and because it is relatively non-toxic.[77] A study comparing different biliary contrast agents stated that Biliscopin® had a faster rate of bile excretion in dogs when compared to Cholografin®.[65]

CHAPTER III

CHOLANGIOGRAPHY USING 64-MULTI-DETECTOR ROW COMPUTED

TOMOGRAPHY IN NORMAL DOGS

Introduction

Hepatobiliary diseases are often difficult to diagnose due to non-specific clinical

signs that do not manifest until the late stages of disease. Diagnostic imaging plays an

important role in the diagnosis of these diseases. Current imaging modalities and

techniques available for biliary imaging in small animals include radiography,

ultrasonography, computed tomography, nuclear scintigraphy, cholangiography

combined with radiography, magnetic resonance cholangiopancreatography, endoscopic

retrograde cholangiography, and percutaneous transhepatic cholangiography.[3-6]

Radiography is often insensitive and non-specific for diagnosing hepatobiliary disease.

Ultrasound is non-invasive and readily available but provides inferior images of the

peripheral and intrahepatic bile ducts when compared with other modalities.[2-4, 6] Gas in

the gastrointestinal tract can limit ultrasonographic evaluation of biliary structures in

some dogs. Ultrasound is also user dependent and evaluating the biliary system requires

a skilled ultrasonographer. Nuclear scintigraphy is used in dogs for diagnosing biliary

obstructions. It is non-invasive, but requires the use of expensive equipment and

radioisotopes and has limited availability. Commonly used advanced biliary imaging

techniques in humans include percutaneous transhepatic cholangiography (PTC) and

endoscopic retrograde cholangiography (ERCP), which are considered the current gold standards.[6, 48] Both of these techniques provide excellent visualization of the bile ducts, but are very invasive and costly.[1-2, 6] In small animals, ERCP has also been reported to be technically demanding.[3-5] Magnetic resonance cholangiopancreatography is widely used in human medicine for evaluating the hepatobiliary system. It is non-invasive but can be prone to artifact, provides no functional information, has limited availability, and is costly.[1-2, 7 48]

Multi-slice computed tomography (MSCT) enables rapid acquisition of multiphase data sets that can be reconstructed into detailed three-dimensional images.[2, 10] In veterinary medicine, MSCT has been shown to be valuable in evaluating abdominal structures.[10, 78] This modality combined with cholangiography (intravenous injection of a biliary specific contrast agent) allows for acquisition of high quality images of the biliary system that can be reconstructed into three dimensional images. These three-dimensional reconstructions have been helpful in humans in assessing for intraluminal calculi, biliary obstructions, and ductal stenosis, due to the fact that they provide a more global and detailed view of the biliary anatomy.[56] Multi-slice computed tomographic cholangiography (MSCTC) is non-invasive, provides information regarding biliary kinetics and function, and has high spatial and contrast resolution.[1-2, 7-10] MSCTC using a 64-slice scanner has been performed successfully in normal pigs but has not yet been reported in the dog.[1]

Indications for performing MSCTC in humans include but are not limited to cholelithiasis or choledocholithiasis, anomalous conditions of the bile ducts, unexplained upper abdominal pain, dilation of biliary ducts detected on ultrasound, neoplasia of

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hepatobiliary structures, biliary tract rupture or stricture, and pre-and post-surgical planning .[1,2,7,9-11] Indications for imaging the canine biliary tract are similar and include but are not limited to cholelithiasis or choledocholithiasis, cholecystitis, gallbladder mucoceles, neoplasia of hepatobiliary structures, or extra-hepatic biliary tract rupture or obstruction.[3-6]

The purposes of this study were to determine the feasibility of MSCTC in normal dogs and to describe the normal cross-sectional and three-dimensional biliary anatomy. Our goal was to demonstrate the best technique for performing high-resolution CTC with regards to the type of contrast media used, contrast dose and optimal time to imaging after injection of the contrast agent.

Materials and Methods

Sample population

The study population consisted of eight healthy adult purpose bred hounds and hound mixes. The dogs were deemed healthy based on physical examination, complete blood counts, serum chemistry profiles, and urinalyses. Ultrasound of the hepatobiliary system was also performed on each animal by the author using a BioSound Esaote MyLab50[a] ultrasound machine and a microconvex probe with available frequencies ranging from 5-8 MHz as well as a linear probe with available frequencies ranging from 7.5-12 MHz. All procedures were approved by the Mississippi State University Institutional Animal Care and Use Committee.

Computed tomographic cholangiography

All dogs were fasted 12 hours prior to imaging to optimize image quality and to decrease the potential for complications associated with sedation. Water was not restricted. An 18-22 gauge over the needle catheter was placed in the cephalic vein. Each dog was sedated with butorphanol[b] (0.2mg/kg intramuscular (IM) or intravenous (IV)) and dexmedetomidine[c] (5µg/kg IM or IV). Sedation was re-dosed one time per dog if needed. Subjects were placed in dorsal recumbency for imaging and placed in the gantry head first. CTC was performed using a 64-slice, multi-row GE Lightspeed scanner[d]. The following scanning parameters were used for all CT imaging: 0.625 mm slice thickness, 0.5 seconds per rotation, 5 mm collimation, a pitch of 1, tube potential of 120kV, and tube current of 300 mA. The imaging field of view extended from the apex of the heart, caudally to the level of the left renal hilus. Noncontrast images of the abdomen were obtained prior to the administration of contrast.

Cholografin[®e] (iodipamide meglumine) and Biliscopin[®f] (meglumine iotroxate) were the biliary specific contrast agents used. Two contrast groups were formed, with four dogs receiving Cholografin[®] and four dogs receiving Biliscopin[®]. Of the four dogs in each group, two were intravenously administered a contrast dose of 0.5mL/kg and two were intravenously administered 1mL/kg. Each dog was scanned for sixty minutes at 0, 5, 10, 15, 20, 30, 45, and 60 minutes.

Image analysis

All CT images were reviewed on a designated picture archiving and communication system (PACS)[g] work station. All images were evaluated for any variations outside of the normal biliary anatomy. For all post-contrast images, multiple

reconstructions were performed, including multiplanar reconstructions (MPR), maximum intensity projections (MIP), and shaded surface display (SSD). These images were evaluated to determine which reconstructions provided the most useful information. The presence or absence of contrast in the lumen of the duodenum was also noted. If contrast was present in the lumen of the duodenum, the time it was initially seen following contrast administration was noted .Visibility scores were assigned to each biliary structure including the dorsal and ventral portions of the gallbladder, cystic duct, common bile duct, left and right first order intrahepatic ducts, second order intrahepatic ducts, and third order intrahepatic ducts for each time interval (0, 5, 10, 15, 30, 45, and 60 minutes). Visibility was scored on a scale of 1 to 4 (1=structure not seen, 2=structure faintly seen, 3=structure seen but not in its entirety, and 4=entire structure seen). The maximum diameters of the proximal and distal portions of the common bile duct, the cystic duct, and the viewable intrahepatic ducts were measured for each time interval on transverse images. The time to maximum visibility score and time to maximum bile duct diameter were recorded as well as the maximum visibility score and maximum diameter for each structure.

Statistical analysis

Descriptive statistics (mean, standard deviation, minimum, and maximum) were calculated using PROC TABULATE in SAS for Windows 9.3[h]. Histograms were used to visually assess if the measured outcomes were normally distributed using PROC UNIVARIATE in SAS for Windows 9.3. The distributions of the outcome measures were not normally distributed. Accordingly, a non-parametric method, Wilcoxon Rank Sum test, using PROC NPAR1WAY in SAS for Windows 9.3 was used to assess the

effect of contrast media and the effect of dose on each of the outcomes. Differences in the time to maximum visibility score, time to maximum bile duct diameter, maximum visibility score, and maximum bile duct diameter measured were assessed between the two contrast media and between the two doses in eight separate models for each of the structures. Differences in time to maximum visibility of contrast media in the duodenum were also assessed for the different contrast media and doses. An alpha level of 0.05 was used to determine statistical significance for all methods.

Results

The time to maximum visibility score with regards to choice of contrast media was not significantly different in the dorsal and ventral aspects of the gallbladder (p>0.829) (Table 3.1), but it was significantly different for the cystic duct (p=0.029), proximal bile duct (p=0.029), distal bile duct (p=0.029), first order intrahepatic ducts (p=0.029), second order intrahepatic ducts (p=0.029), and third order intrahepatic ducts (p=0.057) in that the time to the maximum visibility score was longer for Cholografin® than for Biliscopin® (Table 3.1). The time to maximum duct diameter in regards to contrast media choice was significantly different for the cystic duct (p=0.057) with the maximum diameter being reached faster with Biliscopin® than Cholografin® (Table 3.2). The choice of contrast media was not significantly different with regards to the time to maximum duct diameter for the bile duct and intrahepatic ducts (p>0.086) (Table 3.2). The dose of contrast had no significant effects on the time to maximum visibility score for any of the biliary structures (p>0.142) (Table 3.3). Differences in the time to maximum bile duct diameter due to dose were also not significant in any of the bile ducts (p>0.085) (Table 3.4). The choice of contrast media had no significant effect on the

maximum visibility score (p>0.429) or the maximum diameter of each bile duct (p>0.143) (Tables 3.5 and 3.6). The dose also had no significant effect on the maximum visibility score (p>0.714) or the maximum diameter (p>0.143) (Tables 3.7 and 3.8). There was a significant difference between the two contrast agents and the time to contrast seen in the duodenum (p=0.057) (Table 3.1). There was not a significant difference with regards to dose in the time it took for contrast to reach the lumen of the duodenum (p=1.000) (Table 3.3). Contrast was seen the lumen of the duodenum in five out of the eight dogs. Contrast was seen in the duodenum in all four of the dogs administered Biliscopin[®] with time to contrast seen in the lumen ranging from 15 to 45 minutes. Contrast was seen in the duodenal lumen in one dog administered Cholografin[®] at 45 minutes. No adverse reactions to the contrast media were noted. No variation from normal anatomy described in the veterinary textbooks was seen in any of the dogs.

Table 3.1 Time to Maximum Visibility Score by Contrast Media

		Contrast Media							
	Biliscopin®				Cholografin®				
	Time to Maximum Visibility Score				Time to Maximum Visibility Score				
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure										
VENT GB	4	37.50	8.66	30.00	45.00	4	36.50	19.47	20.00	60.00
DORS GB	4	52.50	8.66	45.00	60.00	4	46.25	9.46	40.00	60.00
CD	4	8.75	2.50	5.00	10.00	4	32.50	14.46	19.00	45.00
PROX BD	4	6.25	2.50	5.00	10.00	4	35.25	11.84	21.00	45.00
DIS BD	4	11.25	2.50	10.00	15.00	4	40.50	15.29	26.00	60.00
1st OD	4	8.75	4.79	5.00	15.00	4	40.00	7.07	30.00	45.00
2nd OD	4	20.00	12.25	5.00	30.00	4	46.75	11.64	32.00	60.00
3rd OD	4	12.50	11.90	5.00	30.00	4	41.75	22.19	15.00	60.00
TCINDUO	4	21.25	16.01	10.00	45.00	4	56.25	7.50	45.00	60.00

VENT GB= ventral gallbladder, DORS GB= dorsal gallbladder, CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st OD= 1st order intrahepatic ducts, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, TCINDUO= time to contrast seen in the lumen of the duodenum, N=number of observation StdDev= standard deviation, Min= minimum, Max= maximum, Time= minutes

Table 3.2   Time to Maximum Duct Diameter by Contrast Media

	Contrast Media								
	Biliscopin®				Cholografin®				
	Time to Maximum Duct Diameter				Time to Maximum Duct Diameter				
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure									
CD	4	15.00	10.00	10.00	30.00	4	52.50	15.00	30.00	60.00
PROX BD	4	21.25	25.94	5.00	60.00	4	52.50	8.66	45.00	60.00
DIS BD	4	52.50	8.66	45.00	60.00	4	56.25	7.50	45.00	60.00
1st ODR	4	28.75	18.87	10.00	45.00	4	48.75	14.36	30.00	60.00
1st ODL	4	28.75	22.50	10.00	60.00	4	49.25	13.50	32.00	60.00
2nd OD	4	22.50	18.48	5.00	45.00	4	52.50	8.66	45.00	60.00
3rd OD	4	30.00	12.25	15.00	45.00	3	40.67	16.77	30.00	60.00

CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st ODR= right 1st order intrahepatic duct, 1st ODL= left 1st order intrahepatic duct, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, N= number of observation, StdDev= standard deviation, Min= minimum, Max= maximum Time= minutes, Duct diameter- measured in millimeters

Table 3.3   Time to Maximum Visibility Score by Dose

	Dose								
	0.5mL/kg				1mL/kg				
	Time to Maximum Visibility Score				Time to Maximum Visibility Score				
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure										
VENT GB	4	39.00	17.15	21.00	60.00	4	35.00	12.25	20.00	45.00
DORS GB	4	55.00	10.00	40.00	60.00	4	43.75	2.50	40.00	45.00
CD	4	21.50	16.50	10.00	45.00	4	19.75	17.80	5.00	45.00
PROX BD	4	20.25	17.80	5.00	45.00	4	21.25	19.74	5.00	45.00
DIS BD	4	27.75	22.51	10.00	60.00	4	24.00	17.15	10.00	45.00
1st OD	4	27.50	17.56	10.00	45.00	4	21.25	19.74	5.00	45.00
2nd OD	4	35.00	15.81	15.00	50.00	4	31.75	22.49	5.00	60.00
3rd OD	4	28.75	22.50	10.00	60.00	4	25.50	26.29	5.00	60.00
TCINDUO	4	41.25	18.87	15.00	60.00	4	36.25	27.50	10.00	60.00

VENT GB= ventral gallbladder, DORS GB= dorsal gallbladder, CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st OD= 1st order intrahepatic ducts, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, TCINDUO= time to contrast seen in the lumen of the duodenum, N= number of observation, StdDev= standard deviation, Min= minimum, Max= maximum, Time= minutes

Table 3.4   Time to Maximum Duct Diameter by Dose

	Dose									
	0.5mL/kg					1mL/kg				
	Time to Maximum Duct Diameter					Time to Maximum Duct Diameter				
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure										
CD	4	27.50	23.63	10.00	60.00	4	40.00	24.49	10.00	60.00
PROX BD	4	46.25	27.50	5.00	60.00	4	27.50	20.21	10.00	45.00
DIS BD	4	52.50	8.66	45.00	60.00	4	56.25	7.50	45.00	60.00
1st ODR	4	25.00	15.81	10.00	45.00	4	52.50	8.66	45.00	60.00
1st ODL	4	40.50	24.24	10.00	60.00	4	37.50	19.36	15.00	60.00
2nd OD	4	45.00	12.25	30.00	60.00	4	30.00	26.77	5.00	60.00
3rd OD	4	30.50	1.00	30.00	32.00	3	40.00	22.91	15.00	60.00

CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st ODR= right 1st order intrahepatic duct, 1st ODL= left 1st order intrahepatic duct, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, N= number of observation, StdDev= standard deviation, Min= minimum, Max= maximum Time= minutes, Duct diameter- measured in millimeters

Table 3.5   Maximum Visibility Score by Contrast Media

	Contrast Media									
	Biliscopin®					Cholografin®				
	Maximum Visibility Score					Maximum Visibility Score				
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure										
VENT GB	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
DORS GB	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
CD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
PROX BD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
DIS BD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
1st OD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
2nd OD	4	4.00	0.00	4.00	4.00	4	3.50	0.58	3.00	4.00
3rd OD	4	2.50	0.58	2.00	3.00	4	2.50	1.00	2.00	4.00

VENT GB= ventral gallbladder, DORS GB= dorsal gallbladder, CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st OD= 1st order intrahepatic ducts, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, N= number of observation, StdDev= standard deviation, Min= minimum, Max= maximum

Table 3.6   Maximum Bile Duct Diameter by Contrast Media

	Contrast Media								
	Biliscopin®				Cholografin®				
	Maximum Duct Diameter				Maximum Duct Diameter				
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure										
CD	4	3.93	0.87	3.00	5.10	4	4.13	0.67	3.50	4.80
PROX BD	4	3.30	0.84	2.60	4.50	4	3.80	1.54	2.40	5.70
DIS BD	4	3.35	0.44	3.10	4.00	4	4.38	1.34	2.60	5.60
1st ODR	4	2.03	0.56	1.50	2.80	4	2.70	0.57	2.00	3.30
1st ODL	4	2.03	0.26	1.80	2.30	4	2.05	0.35	1.70	2.40
2nd OD	4	2.03	0.36	1.70	2.50	4	1.99	0.55	1.40	2.70
3rd OD	4	1.45	0.19	1.20	1.60	3	1.81	0.48	1.40	2.34

CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st ODR= right 1st order intrahepatic duct, 1st ODL= left 1st order intrahepatic duct, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, N= number of observation, StdDev= standard deviation, Min=minimum, Max= maximum, Duct diameter- measured in millimeters

Table 3.7   Maximum Visibility Score by Dose

	Dose								
	0.5mL/kg					1mL/kg			
	Maximum Visibility Score					Maximum Visibility Score			
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure									
VENT GB	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
DORS GB	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
CD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
PROX BD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
DIS BD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
1st OD	4	4.00	0.00	4.00	4.00	4	4.00	0.00	4.00	4.00
2nd OD	4	3.75	0.50	3.00	4.00	4	3.75	0.50	3.00	4.00
3rd OD	4	2.75	0.96	2.00	4.00	4	2.25	0.50	2.00	3.00

VENT GB= ventral gallbladder, DORS GB= dorsal gallbladder, CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st OD= 1st order intrahepatic ducts, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, N= number of observation, StdDev= standard deviation, Min= minimum, Max= maximum

Table 3.8   Maximum Duct Diameter Measured by Dose

	Dose								
	0.5mL/kg					1mL/kg			
	Maximum Duct Diameter					Maximum Duct Diameter			
	N	Mean	StdDev	Min	Max	N	Mean	StdDev	Min	Max
Structure										
CD	4	3.98	0.57	3.50	4.80	4	4.08	0.95	3.00	5.10
PROX BD	4	3.15	0.90	2.40	4.40	4	3.95	1.42	2.70	5.70
DIS BD	4	3.60	1.35	2.60	5.60	4	4.13	0.82	3.20	5.20
1st ODR	4	2.45	0.84	1.50	3.30	4	2.28	0.46	1.80	2.80
1st ODL	4	2.03	0.26	1.80	2.30	4	2.05	0.35	1.70	2.40
2nd OD	4	2.27	0.41	1.80	2.70	4	1.75	0.29	1.40	2.10
3rd OD	4	1.76	0.41	1.40	2.34	3	1.40	0.20	1.20	1.60

CD= cystic duct, PROX BD= proximal bile duct, DIS BD= distal bile duct, 1st ODR= right 1st order intrahepatic duct, 1st ODL= left 1st order intrahepatic duct, 2nd OD= 2nd order intrahepatic ducts, 3rd OD= 3rd order intrahepatic ducts, N= number of observation, StdDev= standard deviation, Min=minimum, Max= maximum, Duct diameter- measured in millimeters

Dorsal

R   **L**
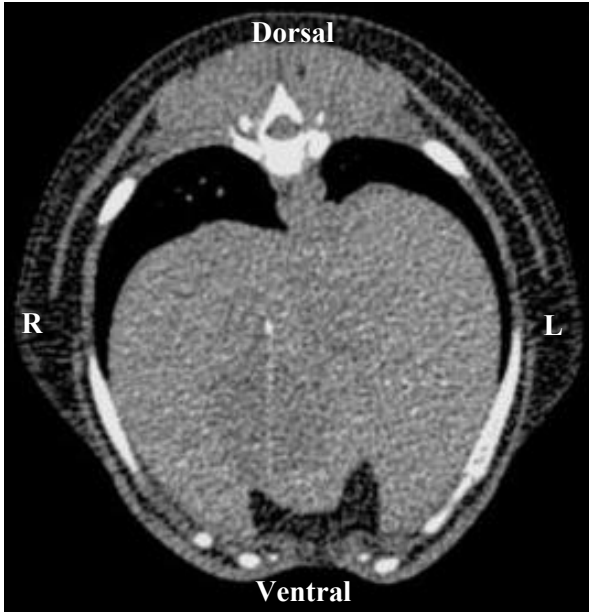
Ventral
5 minutes
All transverse images have the same directional orientation

15 minutes

Figure 3.1   Cholografin® (0.5mL/kg) at 5, 15, 30, 45, and 60 Minutes Post Contrast
Injection

30 minutes

45 minutes

Figure 3.1 (Continued)
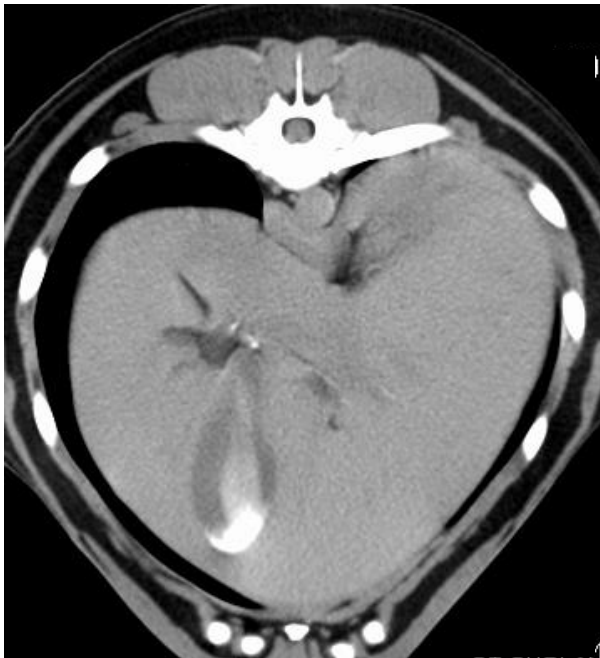
60 minutes

60 minutes

Figure 3.1 (Continued)
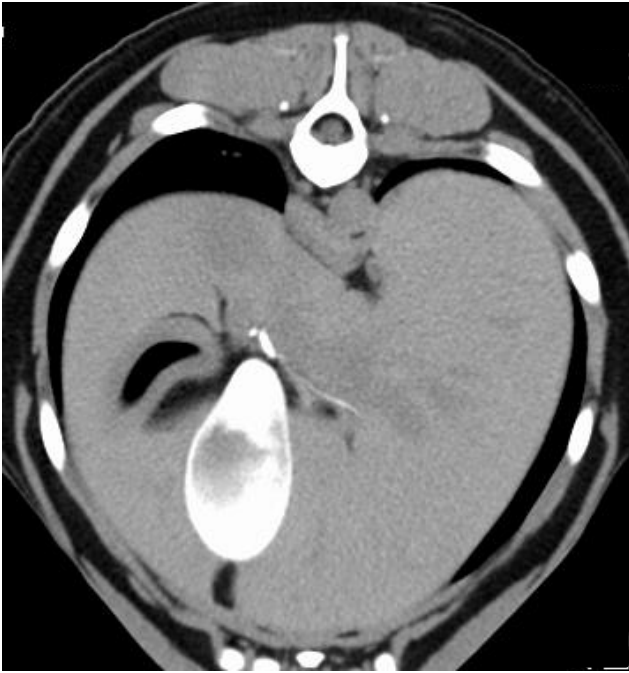
5 minutes

15 minutes

Figure 3.2   Cholografin® (1mL/kg) at 5, 15, 30, 45, and 60 Minutes Post Contrast Injection
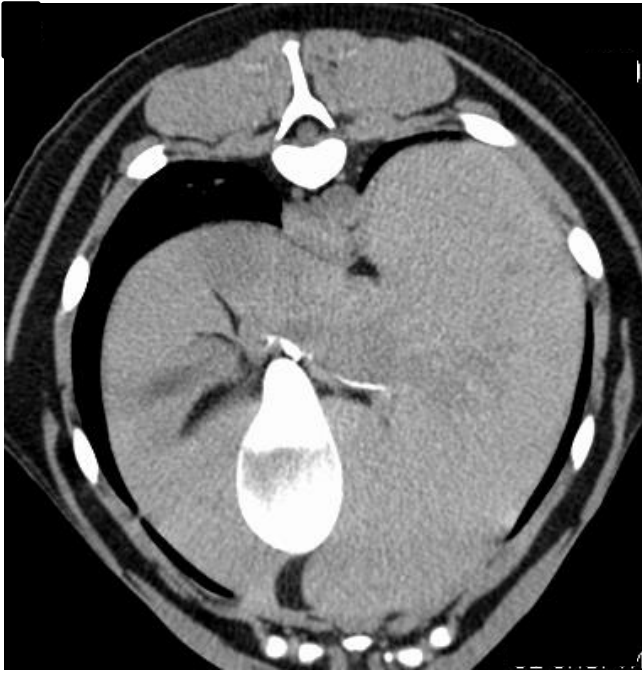
30 minutes

45 minutes

Figure 3.2 (Continued)

60 minutes

60 minutes

Figure 3.2 (Continued)

5 minutes

15 minutes

Figure 3.3   Biliscopin® (0.5 mL/kg) at 5, 15, 30, 45, and 60 Minutes Post Contrast Injection

30 minutes
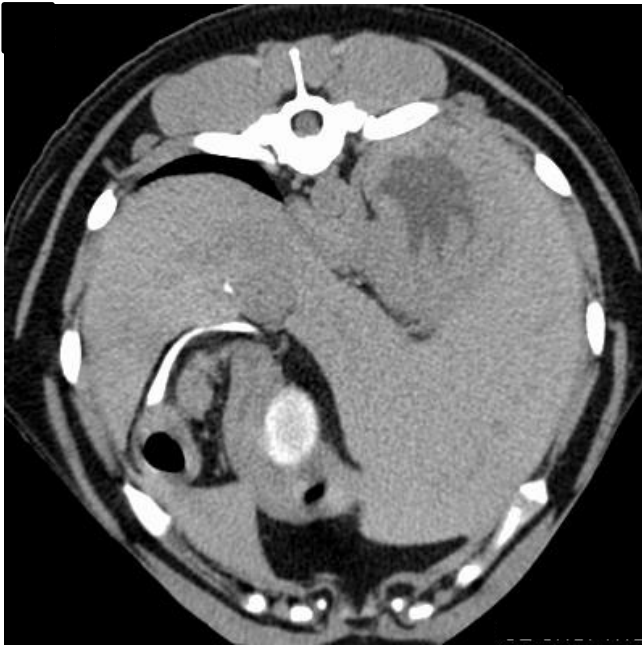

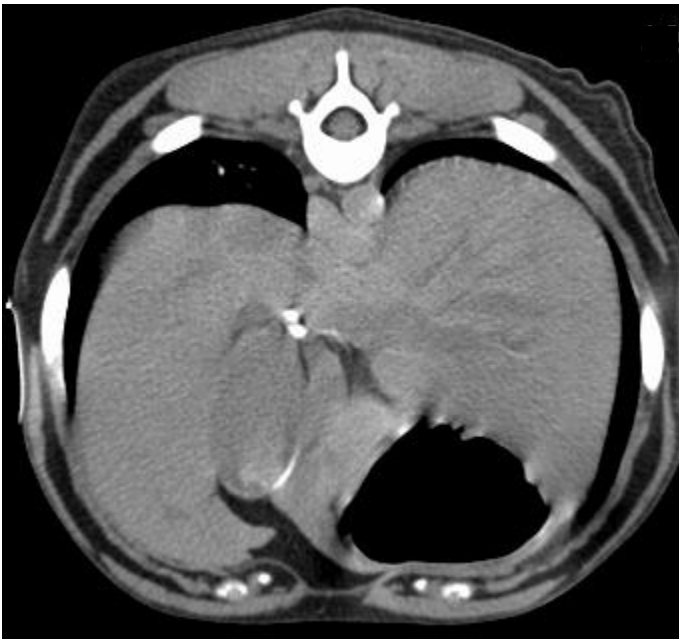**45 minutes**

Figure 3.3 (Continued)

60 minutes
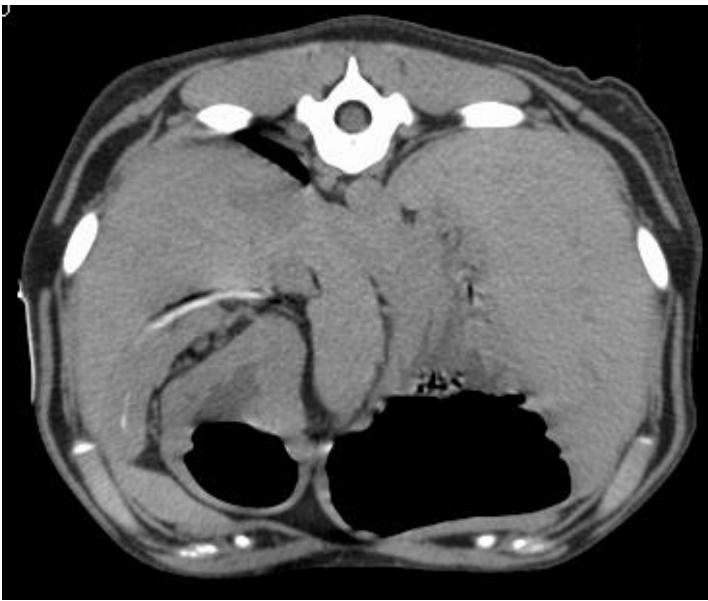
60 minutes

Figure 3.3 (Continued)

5 minutes
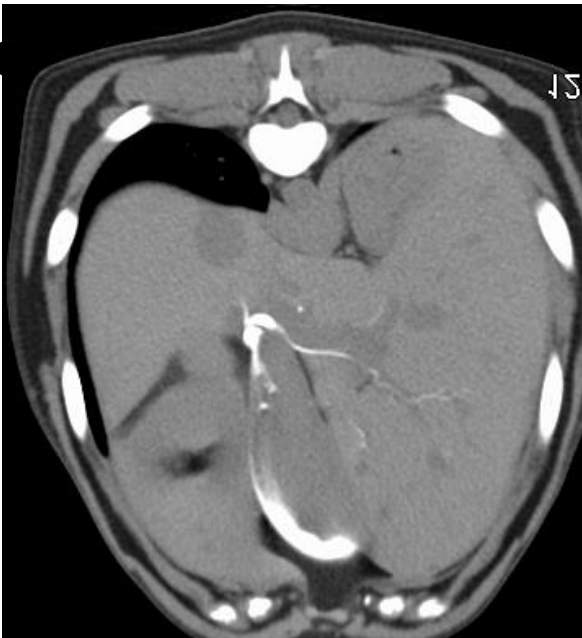
15 minutes
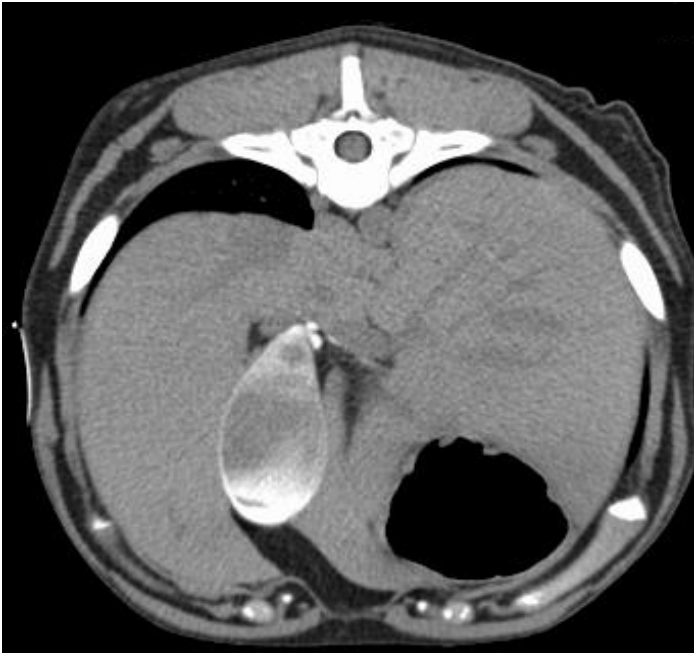
Figure 3.4 Biliscopin® (1mL/kg) at 5, 15, 30, 45, and 60 Minutes Post Contrast Injection

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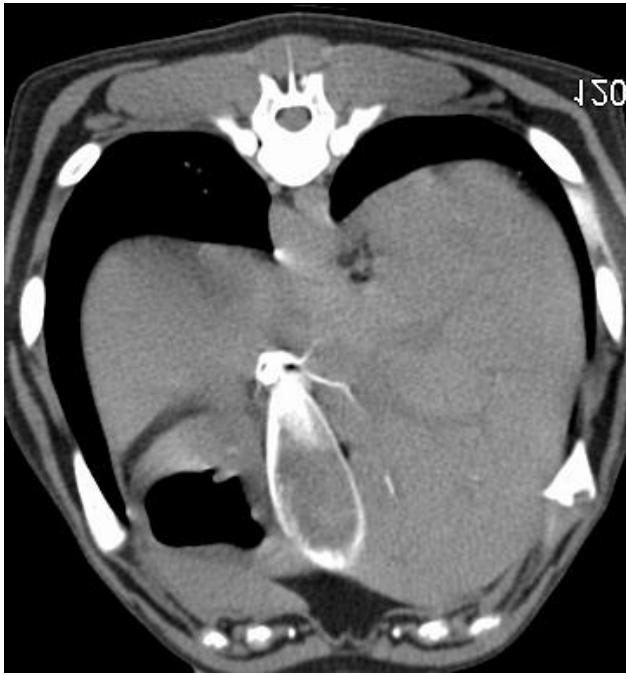
30 minutes

45 minutes

Figure 3.4 (Continued)

60 minutes
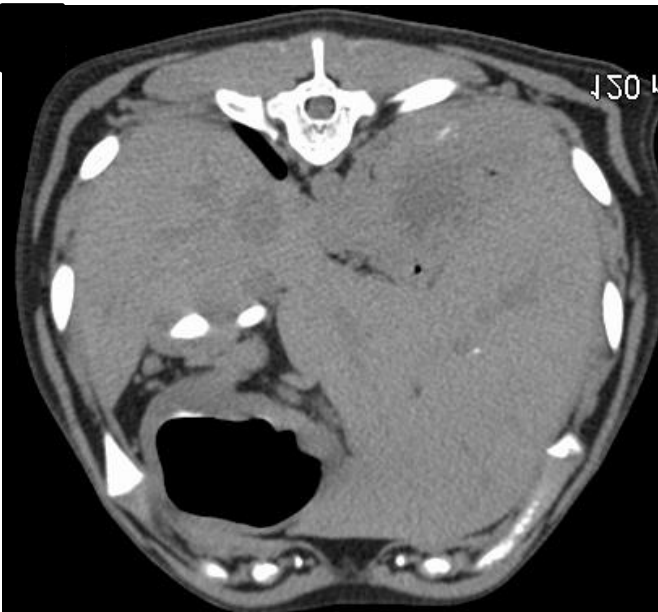
60 minutes

Figure 3.4 (Continued)

Cholografin® (0.5mL/kg)
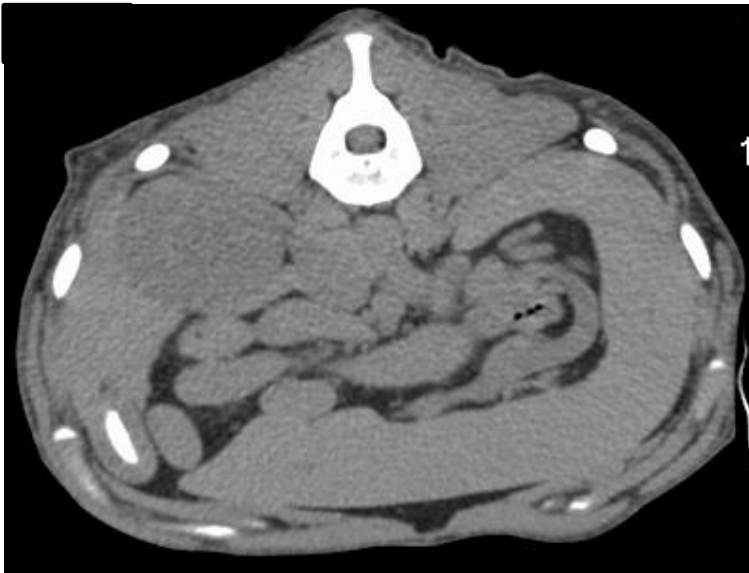
Biliscopin® (0.5 mL/kg)

Figure 3.5   Duodenal Luminal Contrast with Cholografin® and Biliscopin®
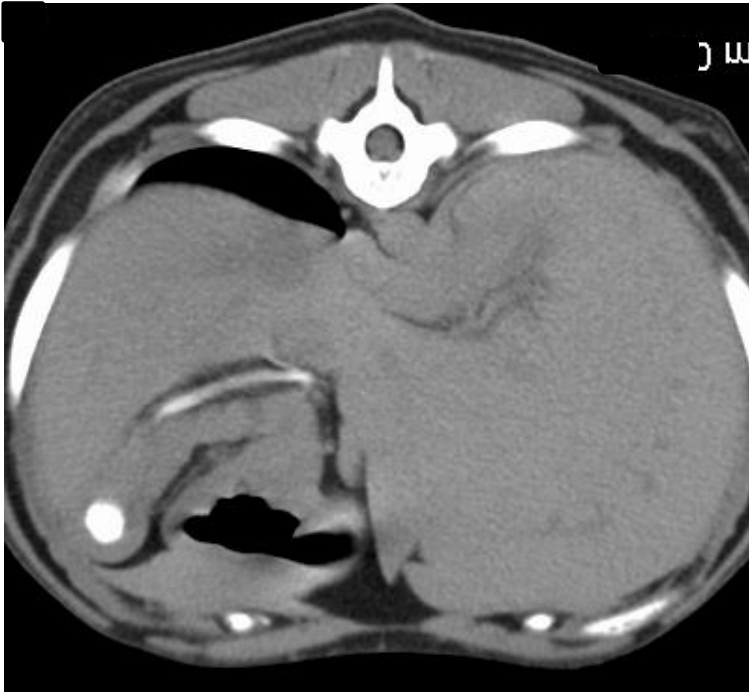
Biliscopin® (1mL/kg)

Figure 3.5 (Continued)

Sagittal Reconstruction Biliscopin (1 mL/kg)
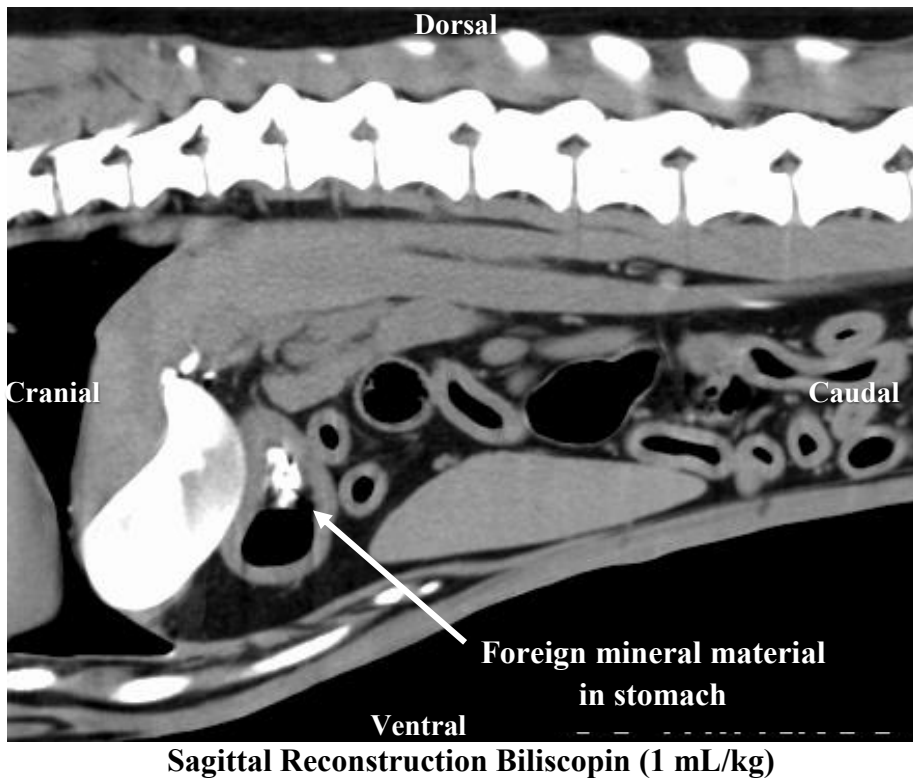
Figure 3.6   Multiplanar Reconstructions (MPR)

Dorsal Reconstruction Biliscopin® (1mL/kg)

Figure 3.6 (Continued)
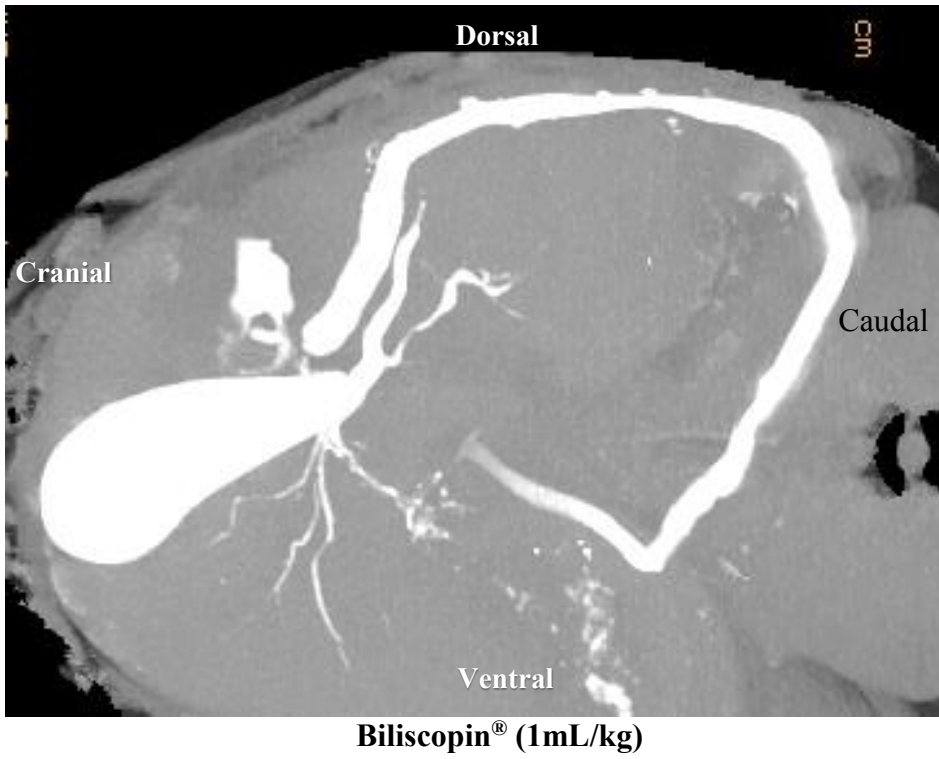
Biliscopin® (1mL/kg)

Figure 3.7   Maximum Intensity Projections (MPR)

Cholografin® (1mL/kg)

Figure 3.7 (Continued)

Biliscopin® (1mL/kg)

Cholografin® (1mL/kg)

Figure 3.8   Shaded Surface Displays

Discussion

Advantages of MSCTC include that it is non-invasive, it can be performed with injectable sedation in dogs, it can provide functional information about the biliary system, and it can provide detailed cross-sectional and three-dimensional images of biliary anatomy. This procedure has been shown to be diagnostically relevant and helpful in multiple human studies involving hepatobiliary disease as well as pre- and post-operative hepatobiliary surgical cases.[48, 52, 54-57, 59-61, 69] Pre-operatively, it has been used in humans for detection of stones or other causes of biliary obstruction and in visualizing the biliary anatomy to evaluate for any anatomic variations that could increase the risk of ductal injuries.[60, 61] Post-operatively, it has been used to evaluate for leakage and stricture at the surgical site. Our study established that MSCTC is feasible in the normal dog and produces high quality images of the biliary anatomy.

Multiple contrast dosing ranges and techniques have been studied and used in humans for MSCTC. The majority of human studies report good results using an infusion of biliary contrast over a range of 5 to 60 minutes prior to CT imaging, reporting scan delay times from 5 minutes to 75 minutes.[8, 9, 11, 47, 79, 80] In a MSCTC study performed on normal pigs, an infusion of Biliscopin® was administered over 20 minutes and the pigs were then scanned every two minutes for 34 minutes.[6] The authors reported the optimum imaging time for visualization of the biliary system was 10 to 34 minutes.[6] A cholangiography study combined with CT performed in normal dogs under general anesthesia compared three different doses (1 mL/kg, 1.5 mL/kg, and 2 mL/kg) of Biliscopin® administered as infusions over 10 minutes.[81] Computed tomographic imaging was performed immediately after contrast injection and then repeated every 10

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minutes.[81] They reported that the 1 mL/kg dose was insufficient for visualizing the

biliary system and that the 2 mL/kg dose was the most optimal for visualizing the bile

ducts.[81] They also reported that the most optimal time to image the biliary system is 20

to 40 minutes following a 10 minute infusion of the 2 mL/kg dose of Biliscopin®.[81] In

our study, we based our dosing choices on doses used in previous conventional

cholangiography studies that were shown to produce good opacification of the biliary

tract in dogs.[45, 71, 82] We chose to administer a bolus injection over a constant rate

infusion because Cholografin® is labeled as a single dose injection agent, and we felt that

it would be more practical in an animal that was sedated and would save time in a clinical

setting.[45, 82] The infusion method has been reported to decrease the severity side effects

in humans; however, little has been reported on the adverse effects of biliary specific

contrast in dogs. No adverse effects from the contrast were seen in any of the dogs used

in our study. The infusion method could be studied in normal dogs or dogs with

hepatobiliary disease in the future using MSCTC.

Our data showed that the contrast dose made no difference in the time to

maximum visibility, time to maximum duct diameter, maximum visibility score, or

maximum duct diameter. There was a statistical difference in the type of contrast media

used, however, with Biliscopin® providing a faster time to maximum visibility score in

almost all structures and a faster time to maximum duct diameter in the cystic duct. This

correlates with previous studies in dogs and cats in which Biliscopin® had a faster

excretion rate than other contrast agents and a strong dilating effect on the bile ducts.[65, 77]

The type of contrast media had no effect on the maximum visibility score or maximum

bile duct diameter. It did, however, have an effect on contrast entering the lumen of the

duodenum as contrast was seen in the duodenum in all four dogs that were administered Biliscopin® and only one dog that was administered Cholografin®.

Subjectively, Biliscopin® provided superior images of the biliary structures based on the homogeneity of the ducts and a faster rate of bile duct opacification than Cholografin®. The higher dose of 1mL/kg subjectively provided better quality images of the bile ducts than the lower dose of 0.5mL/kg in all dogs. It was determined that the most optimal time to scan a patient following injection of Cholografin® was 60 minutes. At 60 minutes, the gallbladder, cystic and bile ducts, and first, second, and most of the third order intrahepatic ducts were opacified and seen clearly. The optimal time to image the bile ducts following Biliscopin® administration occurred between 15 to 30 minutes in all four dogs. The opacification of the entire gallbladder, however, was best seen at 60 minutes in patients administered Biliscopin®.

High quality two-dimensional and three-dimensional reconstructions were performed in each dog and included multiplanar reconstructions, maximum intensity projections, and shaded surface display. All of the reconstructions were helpful in evaluating the normal biliary anatomy. Subjectively, the shaded surface display images provided the best quality images of all of the biliary structures. They provided the best global viewing of the entire biliary tree and individual structures.

In our original study design, we planned to use only one type of contrast and two different doses. Initially, we chose Cholografin® as our biliary specific contrast agent, given that it was the only one available in the United States. We originally planned to scan all eight dogs using this contrast agent. However, halfway through our data collection, Cholografin® became commercially unavailable and we did not have enough

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contrast to complete the project. As we were unsure when Cholografin® would be available, we decided to complete the project using an alternative contrast agent still commercially available outside of the United States. We chose Biliscopin® (meglumine iotroxate) as our replacement contrast to complete the study.

Due to the change of contrast midway through the project, we were also had to reconfigure the dose groups. Of the four dogs in each contrast group, two received the lower dose of contrast (0.5mL/kg) and two received the higher dose of contrast (1mL/kg). This unfortunately decreased our sample size of eight dogs to four dogs in each contrast group. We recognize our small sample size is a limitation of the study. There may have been more differences detected between the two dose groups if the sample population had been higher. While, there was no statistically significant difference between the two dose groups with regards to the time to maximum visibility and duct diameter as well as the maximum visibility scores and maximum bile duct diameters, the higher dose provided subjectively better quality images. The lack of statistically significant difference may have been due to our visibility scoring system not having enough discernment. If our scoring system had consisted of a wider range of numbers, such as 3.1 or 4.5 versus just 3 and 4, we may have detected more statistically significant differences between the two dose groups. More work is needed to determine if the dose of contrast affects the visibility of biliary structures and the duct diameters. Difficulty in measuring structures of such a small magnitude with our available work station may have also skewed some of the statistics with regards to duct diameter. Regardless of the limitations of our study, we were still able to clearly demonstrate that MSCTC is feasible in normal dogs.

Hyperbilirubinemia has been described as a limitation for performing cholangiography with radiography and MSCT. In humans and dogs with poor hepatobiliary function, elevated plasma bilirubin is associated with unreliable excretion of biliary contrast causing non-diagnostic or poor quality CT cholangiography studies.[12, 48, 54, 66-71, 83] In humans, a serum bilirubin of greater than 2.0mg/deciliters (dL) is a good predictor of poor contrast excretion.[12, 68, 69] However, even in hyperbilirubinemic patients it has been shown that, although the biliary tract is not optimally enhanced, it is still possible to obtain a diagnostic CTC study to detect abnormalities such as dilation or obstruction of the bile ducts.[48, 68] Other studies in humans have shown that slowly infusing a biliary specific contrast agent over several hours as opposed to a single intravenous injection may allow for increased density of the bile ducts in patients with high bilirubin levels (greater than 1.1mg/dL).[48, 69] Good contrast enhancement of the biliary tree can also be obtained by increasing the dose of contrast material in human patients with bilirubin levels greater than 1.5 times normal and then waiting 2-2.5 hours after contrast administration to perform the CT scan.[54] Several studies evaluating the effect of bilirubin on biliary iodipamide (Cholografin®) excretion in dogs suggest that the contrast dose can be increased in hyperbilirubinemic patients to obtain adequate opacification of the biliary structures and that a prolonged infusion or decrease in contrast dose is not indicated.[66, 67, 71] Although there has been mixed success with multi-slice CTC in human patients with bilirubin levels greater than 2 mg/dL, several studies have shown that diagnostic studies can still be performed in some patients with bilirubin levels as high as 9.3mg/dL.[48, 54, 68, 69] To the author's knowledge, no studies have been

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performed using MSCTC in dogs with elevated bilirubin, and this could be a potential

focus for future studies.

Endnotes

[a] Biosound MyLab 50, Esaote North America, Inc., Indianapolis, IN

[b] Butorphanol, Hospira, Inc., Lake Forrest, IL

[c] Dexmedetomidine, Hospira Inc., Lake Forrest, IL

[d] GE Lightspeed, GE Medical Systems, Waukesha, WI

[e] Cholografin®, Bracco Diagnostics, Princeton, New Jersey

[f] Biliscopin®, Bayer Group, Berlin, Germany

[g] Picture Archiving System (PACS), McKesson, Richmond, BC, Canada

[h] SAS for Windows® version 9.3, SAS Institute Inc., Cary, NC

CHAPTER IV

CONCLUSION

Our study demonstrated the feasibility of MSCTC in normal dogs. The key advantages that make MSCTC ideal for imaging the hepatobiliary system in dogs are that it is non-invasive, it provides high quality two and three dimensional images of the biliary anatomy, it provides functional information regarding biliary kinetics, and it can be performed under sedation. The biliary specific contrast agents we used provided excellent opacification of the gallbladder and bile ducts. Biliscopin® proved to be superior to Cholografin® by providing subjectively better quality images of the biliary anatomy in a shorter amount of time. However, both contrast agents produced high quality images of the hepatobiliary system and could be used with MSCT to obtain a diagnostic quality study. At this time, Cholografin® is still unavailable but is scheduled to be released at some point this year.

In our study, no statistically significant differences were seen between the doses of contrast used. However, subjectively, the higher dose of 1mL/kg produced better quality images of the hepatobiliary system. Studies have been performed in dogs in the past using conventional cholangiography investigating different doses of contrast to administer to see which provides the best images of the hepatobiliary system. Some studies used infusions of different doses while others used a single bolus injection. Future work investigating different dosages and/or infusion rates of biliary specific

contrast agents to determine which method of administration provides the best images could be performed with MSCTC in normal dogs and in dogs with hepatobiliary disease.

The optimal time to image following contrast injection was shown to be 60 minutes with Cholografin[®]. With Biliscopin[®], the best time to image the bile ducts following contrast injection was 15 to 30 minutes, and the best time to image the gallbladder was 60 minutes. Optimal imaging times in dogs using cholangiography with radiography were reported to be 30 minutes following injection of Cholografin[®] for the cystic and hepatic ducts and 90 to 120 minutes for the gallbladder.[45] A study in pigs reported that the optimal imaging time following infusion of Biliscopin[®] over 20 minutes was 10 to 34 minutes.[6] Based on our study, the optimal time to image after contrast injection is dependent on the type of contrast agent used.

One of the purposes of this study was to serve as a platform for subsequent performance of MSCTC in dogs with hepatobiliary disease. Hepatobiliary disease is being diagnosed more commonly in small animals due to advances in imaging. Ultrasound is currently considered the gold standard for imaging the hepatobiliary tract in dogs.[26, 33] When compared to MSCTC, however, ultrasound is inferior for demonstrating the peripheral and intrahepatic bile ducts.[1, 2, 5] MSCTC produces detailed, high resolution images of all of the biliary anatomy. Future work in dogs with hepatobiliary disease using MSCTC could demonstrate if this technique would provide us with any additional diagnostic information that could not be obtained with the more commonly used imaging modalities.

Clinical situations in which MSCTC could be beneficial in the dog include determining conformation or exact location of a suspected biliary obstruction, looking for

invasion of or metastasis to the bile ducts with a hepatic mass, or a suspected gallbladder rupture that cannot be proven on ultrasound. Other indications for performing MSCTC in the dog include cholelithiasis or choledocholithiasis, cholecystitis, gallbladder mucoceles, neoplasia of the hepatobiliary structures, or extra-hepatic biliary tract rupture or obstruction.[1-3] Although this study was limited to hounds and hound mixes, MSCTC should be feasible in all breeds given that the anatomy is relatively the same in all dogs. MSCTC could also be investigated in dogs with hyperbilirubinemia, as it has been labeled a limitation of conventional cholangiography studies in the past. It would be clinically important to know how high the bilirubin has to be for MSCTC to be non-diagnostic. Evaluation of the rate of excretion of biliary contrast in dogs with hepatobiliary disease or with hyperbilirubinemia could also be further studied as well as the effect of cholecystokinin on biliary contrast excretion. Further investigation of MSCTC in dogs with hepatobiliary disease could aid in the earlier diagnosis and treatment of these diseases in the future.

A current limitation to the feasibility of this technique becoming widely available is the fact that very few veterinary or referral hospitals have 64-multi-slice CT scanners. However, many veterinary hospitals now have some type of multi-slice scanner. This technique could be performed using different types of multi-slice scanners to see what type of image quality could be obtained from each one. The images obtained by performing this technique could also be used as an aid for teaching cross-sectional and three-dimensional biliary anatomy to veterinary students and radiology interns and residents.

Based on our findings, future work in dogs with hepatobiliary disease using MSCTC will include the following recommendations: Cholografin® used at 1mL/kg with a post-injection scan time of 60 minutes for optimum biliary tract visualization or Biliscopin® used at 1 mL/kg with a post-injection scan time of 30 minutes for optimal bile duct visualization and 60 minutes for optimum gallbladder visualization.

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