Effect of Sphincteroplasty on Gallbladder Function and Bile Composition

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The effect of sphincteroplasty on bile concentration and composition and on gallbladder function was investigated in the dog. Gallbladder and hepatic bile samples were analyzed for cholesterol, phospholipid (lecithin), bile salt concentration and individual bile salt content. Motor function was studied by cholecystokinin-cholecystography with changes in gallbladder volume computed from the radiographs. All bile samples were cultured and at the conclusion of the experiments, the gallbladders were histologically examined. Sphincteroplasty did not alter biliary cholesterol concentration but the concentration of lecithin and bile salts decreased in gallbladder bile and increased in hepatic bile ($p < .001$). These changes depict a trend toward greater lithogenicity for gallbladder bile and lesser lithogenicity for hepatic bile. Postoperative analysis of individual bile salts in gallbladder bile showed an increase in monohydroxy and dihydroxy bile salts and a decrease in trihydroxy bile salts ($p < .001$). This tendency has been shown to be conducive to gallstone formation. The concentrating ability of the gallbladder was partially eliminated by sphincteroplasty but gallbladder filling and motor response to stimulation by cholecystokinin was not affected. All gallbladders demonstrated histologic changes of chronic inflammation and all developed a significant bacterial flora following sphincteroplasty. It is concluded that cholecystectomy should always be performed following transduodenal sphincteroplasty not because of any resultant abnormality of motor function, as has previously been held, but because of the resultant abnormality of gallbladder pathophysiology.

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SPHINCTEROPLASTY, IN CONTRAST to sphincterotomy, is a procedure in which the terminal constrictive mechanism of the common bile duct is completely and permanently eliminated. This is accomplished by an extended incision through the full thickness of the sphincteric muscle, common bile duct and duodenal wall followed by mucosal suture approximation. In the initial description of the operation, Jones and Smith[7] recommended that the gallbladder be removed routinely when sphincteroplasty is performed because destruction of the sphincteric mechanism would result in the inability of the gallbladder to fill and, therefore, function. However, no good clinical or experimental evidence has been offered to support this premise. In fact, Lempke[14] showed by oral cholecystography that patients maintained normal gallbladder function during the first three weeks following sphincterotomy when resistance to bile flow in the common duct had been shown to be minimal.[5] Moreover, experimental evidence suggests that gallbladder filling is not dependent on an intact sphincteric musculature but rather may be a function of the vascular dynamics of the ductal epithelium in the terminal common bile duct.[20]

In order to investigate this problem we studied gallbladder function after sphincteroplasty by analyzing the two major aspects of gallbladder physiology: 1) its ability to contract and empty in response to appropriate stimuli, and 2) its ability to concentrate and alter bile. In addition we endeavored to determine whether sphincter ablation created a potentially pathologic condition in the gallbladder.

Materials and Methods

Operative Procedures

Experiments were performed on six adult mongrel dogs, 22–26 kg, under sterile conditions using intravenous pentobarbital sodium anesthesia. The animals were fasted 18 hours prior to operation. At the initial procedure, the gallbladder was evacuated by needle aspiration and this represented the control gallbladder bile for each animal. A transduodenal sphincteroplasty was then performed according to the technique described on Jones,[10] with the length of the completed sphincteroplasty varying from 15 to 25 mm depending on the length of the intramural portion of the common bile duct. The common hepatic duct was intubated retrograde through the sphincteroplasty with a 6 F ureteral catheter, and hepatic bile obtained over a one hour drainage period. A Thomas cannula was then placed in the duodenum centered over the sphincteroplasty and brought out through the anterior abdominal wall.

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0003-4932/79/0300/0317 $00.75

TABLE 1. *Concentration of Bile Constituents (mean ± S.D.)*

	Cholesterol (m Mol/L)	Lecithin (m Mol/L)	Bile Salts (m Mol/L)	Total (m Mol/L)
Gallbladder bile				
Control	1.47 ± .24	45.5 ± 6.6	85.3 ± 11.3	132.3 ± 11.8
Postsphincteroplasty				
5 weeks	1.29 ± .20†	35.1 ± 7.4*	55.8 ± 6.6*	92.0 ± 11.3*
10 weeks	1.45 ± .43†	27.3 ± 6.3*	58.4 ± 9.4*	87.1 ± 10.2*
Hepatic bile				
Control	.81 ± .13	3.6 ± 1.2	14.7 ± 3.8	19.1 ± 3.7
Postsphincteroplasty				
5 weeks	.45 ± .18*	13.0 ± 5.6	27.6 ± 5.5*	41.1 ± 5.0*
10 weeks	.44 ± .02*	9.1 ± 1.5	29.1 ± 4.2*	38.7 ± 4.8*

* $p < .001$. † Not significant.

Bile Analysis

At five and 10 weeks postsphincteroplasty, each dog was re-explored under light pentobarbital anesthesia and a sample of gallbladder bile obtained for analysis. During the same operation, an aliquot of hepatic bile was obtained by direct intubation of the common hepatic duct via the Thomas cannula.

Gallbladder and hepatic bile samples were all cultured aerobically and anaerobically and analyzed for cholesterol, phospholipid (lecithin) and bile salt concentrations. Cholesterol and bile salt concentrations were determined by gas-liquid chromatography and lecithin concentration by colormetric analysis according to modified techniques described by Rubulis.[17]

Radiographic Procedures

Cholecystokinin-cholecystography was performed on each dog presphincteroplasty, five and ten weeks postsphincteroplasty. All roentgenograms were obtained on fasted anesthetized animals in the right lateral position with a vertical beam. Cholografin (52% meglumine iodopamide), 0.6 cc/kg, was given intravenously over ten minutes and opacification of the gallbladder generally occurred after one hour. An infusion of cholografin, 0.2 cc/kg in 20 cc normal saline, was then begun at a rate of 1 cc/min in order to maintain gallbladder opacification during subsequent cholecystokinin induced contraction.[6] Cholecystokinin (CCK-PZ; GIH, Karolinska Instit.) 1.0 Ivy unit/kg, was injected intravenously as a bolus, and radiographs taken at zero, three, six, nine, 15 and 20 minutes. Gallbladder volume was computed from the radiographs by the method of Siffert de Paula e Silva[19] and expressed as a percentage of the control gallbladder volume prior to cholecystokinin administration.

Retrograde cholangiography was performed at ten weeks postsphincteroplasty to document free reflux of contrast from the duodenum into the common bile duct and thus confirm the adequacy of the sphincteroplasty. This was carried out in the fasted anesthetized dog by gravity infusion of 40% Micropaque into the duodenum via the Thomas cannula with roentgenograms taken between one and two hours later.

Histologic Studies

Once the final bile samples were obtained and radiographic procedures completed ten weeks postsphincteroplasty, the animals were sacrificed and the gallbladders removed for histologic examination.

Results

Bile Analysis

The results of the lipid analyses of gallbladder and hepatic bile are shown on Table 1. Gallbladder bile preoperatively was seven times more concentrated than hepatic bile and although the gallbladder retained its ability to concentrate bile after sphincteroplasty, the difference in concentration was only about two times ($p < .001$). This change was brought about not only by a reduced concentrating ability of the gallbladder for lecithin and bile salts but a tendency of the liver to produce a more concentrated hepatic bile. The mean concentration of both lecithin and total bile salts in gallbladder bile decreased approximately 35% postsphincteroplasty while the mean concentration of these constituents in hepatic bile more than doubled ($p < .001$). Concurrently, mean cholesterol concentration was essentially unchanged in gallbladder bile but decreased approximately 50% in hepatic bile. These biliary lipid changes if expressed in millimols percent portray a decrease in the lithogenic ratio* and thus a trend toward greater lithogenicity for gallbladder bile and an increase in the lithogenic ratio and thus a trend toward less lithogenicity for hepatic bile. Despite this trend gall-

* lithogenic ratio $= \frac{[\text{lecithin}] + [\text{bile salts}]}{[\text{cholesterol}]}$

TABLE 2. *Bile Salt Concentration (mean ± S.D.)*

	Cholate (mg %)	Desoxycholate (mg %)	Chenodesoxycholate (mg %)	Lithocholate (mg %)
Gallbladder bile				
Control	2654 ± 556	410 ± 117	153 ± 40	9.3 ± 4.6
Postsphincteroplasty				
5 weeks	1327 ± 302*	691 ± 103*	156 ± 38†	56 ± 12.4*
10 weeks	1192 ± 296*	759 ± 112*	137 ± 16†	72 ± 20*
Hepatic bile				
Control	395 ± 70	56 ± 16	30 ± 6	6.8 ± 2.9
Postsphincteroplasty				
5 weeks	687 ± 125*	173 ± 40*	54 ± 17**	17.3 ± 6.9*
10 weeks	654 ± 111*	210 ± 33*	52 ± 11**	18.6 ± 5.0*

* $p < .001$. ** $p < .05$. † Not significant.

bladder cholesterol concentration as is characteristic of canine bile, remained within the micellar zone of the triangular coordinate plot of Admirand and Small.[1]

The change in mean concentration of individual bile salts in gallbladder and hepatic bile are shown in Table 2. Sphincteroplasty resulted in a decrease in both the concentration and proportion of the trihydroxy bile salt, cholate, and an increase in the dihydroxy salt, desoxycholate, and the monohydroxy salt, lithocholate in the gallbladder. Whereas preoperatively approximately 85% of the total bile salts present in the gallbladder consisted of cholate, postoperatively 55–60% of total bile salts was comprised of cholate ($p < .001$). This change was affected by an approximate 50% decrease in concentration of cholate with a proportionate increase in concentration of desoxycholate and a 6–7 fold increase in lithocholate. The concentration of chenodeoxycholate was essentially unchanged, however its proportionate content increased slightly. In hepatic bile, all four bile salt constituents increased two to three fold such that their proportionate concentrations remained about the same.

Cultures of all samples of gallbladder and hepatic bile presphincteroplasty had no bacterial growth. However, at both five and ten weeks postsphincteroplasty a significant aerobic and anaerobic bacterial flora had developed in the gallbladder of each dog. *E. Coli*, Klebsiella and enterococcus were the predominant aerobes recovered while Bacteroides, Clostridia and Peptostreptococcus predominated among the anaerobic organisms. Cultures of the hepatic bile yielded a bacterial flora similar to that found in the gallbladder bile.

Radiography

All of the dogs had opacification of the gallbladder on cholecystography postsphincteroplasty although two dogs had nonvisualization on a single occasion. One animal, failed to have gallbladder visualization at five weeks but at ten weeks had satisfactory opacification and the earlier failure was assumed to be due to a technical problem. The other dog had gallbladder opacification at five weeks but nonvisualization at ten weeks.

Resting gallbladder volume decreased in all dogs following sphincteroplasty averaging 52% of the preoperative volume at 10 weeks (Table 3). Volume was computed for each time period after cholecystokinin injection and demonstrated maximal gallbladder contraction at 6 to 9 minutes. Prior to sphincteroplasty mean volume at maximal gallbladder contraction was 58% of the resting volume. Following sphincteroplasty, gallbladder emptying in response to cholecystokinin was proportionately more complete with volume at maximal contraction averaging 45% of the resting volume at five weeks and 35% at ten weeks. Therefore, gallbladder filling did occur after sphincteroplasty and target organ responsiveness to hormonal stimulation remained intact.

The postoperative demonstration of free reflux of radiopaque contrast material into the duodenum confirmed the adequacy of the sphincteroplasty in all dogs. Plain radiographs taken five to ten weeks postoperatively also consistently showed air in the common bile duct and gallbladder.

Pathology

Gross examination of the gallbladders ten weeks postsphincteroplasty revealed minimal mural thickening

TABLE 3. *Gallbladder Volume in Response to Cholecystokinin (CCK) (mean ± S.D.)*

			Postsphincteroplasty			
	Control		5 Weeks		10 Weeks	
Time	Vol (ml)	%	Vol (ml)	%	Vol (ml)	%
0	35.7 ± 6.4	100	28.1 ± 5.1	100	18.8 ± 4.5	100
CCK + 3 min	24.9 ± 5.7	70	16.3 ± 2.5	58	10.8 ± 3.5	57
CCK + 6 min	22.7 ± 3.7	63	14.0 ± 2.7	50	8.4 ± 2.4	44
CCK + 9 min	20.7 ± 4.5	58	12.6 ± 2.2	45	6.6 ± 2.5	35
CCK + 15 min	23.0 ± 5.0	64	17.7 ± 3.5	62	8.6 ± 2.1	46
CCK + 20 min	26.2 ± 4.1	73	18.8 ± 3.9	67	8.9 ± 2.3	47

without evidence of acute inflammation. All of the gallbladders contained feculent smelling bile. A solitary soft, flat, rectangular and brown gallstone was found in one dog. Although the common bile duct appeared slightly dilated and thickened, all sphincteroplasties were widely patent with no evidence of stenosis. Microscopically, the gallbladder mucosal architecture was intact, but all had mucosal and submucosal infiltration by lymphocytes and plasma cells aggregated into follicles which lacked germinal centers. There was also slight to moderate chronic inflammation of the muscular and serosal layers.

Discussion

Historically sphincterotomy preceded sphincteroplasty for the treatment of recurrent pancreatitis. The operation attempted to minimize bile reflux into the pancreatic duct via the common channel formed by it with the common bile duct. Colp et al.[3] reported their early experience with this procedure when done in dogs through an endocholedochal approach using a sphincterotome. They found that in animals in whom they did not perform a cholecystectomy, severe cholecystitis and cholangitis usually developed. Citing these experimental results, Doubilet and Mulholland[4] concluded that destruction of the sphincter of Oddi led to complete loss of gallbladder function with compromise of filling. It was their belief that the gallbladder became an atonic diverticulum following sphincterotomy and therefore suggested that the gallbladder be removed whenever the sphincter of Oddi was destroyed.

In 1952 Jones and Smith[7] described transduodenal sphincteroplasty as a method for more completely and permanently destroying sphincteric function in the treatment of recurrent pancreatitis. Four patients were described who underwent sphincteroplasty but because normal gallbladders were found at operation, cholecystectomy was not performed. Three of these patients, had normal oral cholecystograms preoperatively but were found to have nonvisualization on repeat roentgenographic examination three to four months postoperatively. They did not report a followup on these patients and it is not known if the nonvisualized gallbladders subsequently became diseased producing symptoms necessitating cholecystectomy. However, from this clinical observation they advised that cholecystectomy always be performed when doing a sphincteroplasty regardless of whether the gallbladder is diseased. Subsequent reports by these same investigators have repeated this recommendation.[8–10]

Kleinert and Large[11,12] studied the effect of choledochoduodenostomy and choledochojejunostomy in producing biliary tract infections. After creating complete obstruction for three weeks by ligature and transection of the common bile duct, the greatly dilated common duct was anastomosed to the intestine and the gallbladder left *in situ*. The dogs that survived for long term evaluation all developed chronic inflammation of the gallbladder with mural thickening, lymph follicle formation in the mucosa, and cellular infiltration of all layers. Bile was found in all gallbladders but in each instance bacterial cultures yielded mixed pathogens and 67% of the gallbladders contained concretions. It was concluded from these experiments that since no obstruction was present, the chronic inflammatory changes were due to ascending infection secondary to reflux of contaminated duodenal contents. Large[13] also reported clinical instances of gallbladder pathology following transduodenal sphincterotomy or choledochojejunostomy which her termed "regurgitation cholecystitis." He echoed the opinions of Jones and Doubilet that the gallbladder should routinely be removed when the sphincter of Oddi has been destroyed or bypassed.

The importance of the role attributed to the common bile duct sphincter on gallbladder function, however, it not universally held. Lempke[14] showed that gallbladder function, as determined by oral cholecystography, may be preserved after sphincterotomy. Moreover, seven of eight patients he followed two years after destruction of the sphincter, developed no clinical evidence of cholecystitis. It was demonstrated by Eiseman[5] that sphincteric competence returns four to six weeks after sphincterotomy due to healing with scar tissue and sphincteric reconstitution and this may explain Lempke's findings. But in five of Lempke's patients oral cholecystography within four weeks postoperatively, when yield pressures in the common duct are still low, showed normal gallbladder opacification. He offered the explanation that this was due to the contribution of the duodenal wall musculature creating sufficient terminal common bile duct resistance to permit gallbladder filling and visualization on cholecystography. Whitaker[22] and Winkelstein[23] also concluded from their studies that gallbladder filling was more a consequence of the effect of the surrounding duodenal wall muscle on the intramural portion of the common bile duct rather than to the action of the ampullar sphincter. On the other hand, Tansy et al.[20] showed experimentally by meticulous dissection that neither the intrinsic or extrinsic terminal bile duct musculature was essential to gallbladder filling. They postulated that occlusion competence of the terminal common bile duct instead was related to the vascular dynamics of the ductal epithelium which accounted for gallbladder filling. Thus the problem remains unsettled.

Our experiments indicate that gallbladder filling continues to occur after complete elimination of muscular action on the distal common duct by sphincteroplasty

and the response of the gallbladder musculature to stimulation by cholecystokinin is normal. Moreover, the concentrating ability of the gallbladder is preserved after sphincteroplasty although less effectively compared to its preoperative ability. Nevertheless despite normal filling and motor function, the gallbladder becomes pathologic following sphincteroplasty. The histopathologic changes in the gallbladder seen in our study were similar to those described by Large[12] and the bile, which preoperatively was sterile, developed a significant bacterial flora postsphincteroplasty. Moreover, the data showed an increased lithogenicity of the gallbladder bile following sphincteroplasty brought about primarily by a decrease in the concentration of phospholipid and total bile salts. Normally the gallbladder mucosa in impermeable to lecithin, bile salts, and cholesterol but permeability properties have been shown to change during certain pathophysiologic conditions such as bacterial contamination of the bile.[2] This situation was found in the gallbladder of all our dogs following sphincteroplasty and could have led to selective reabsorption of bile salts and lecithin to account for the decrease in concentration of these constituents. Since a principal function of bile salts in bile is to maintain cholesterol in aqueous solution, a decrease in bile salt content would contribute to an increased potential for gallstone formation. Hepatic bile, on the other hand, showed an increased concentration of phospholipid and bile salts following sphincteroplasty and thus a trend toward decreased lithogenicity. These same changes in hepatic bile composition have been reported following cholecystectomy and are probably due to the same mechanism.[18]

Another effect of bacterial contamination of bile is the capability of dehydroxylation possessed by certain anaerobic bacterial which have yet to be identified.[15] This results in the conversion of cholate to desoxycholate yielding an increase of dihydroxy bile salts and a decrease of trihydroxy bile salts. Such was the case in our experiments which support the findings of Van der Linden[21] who showed that gallstones are associated with a relative increase in dihydroxy (or decrease in trihydroxy) bile salts.

Coincidence of events does not prove causality, but the data from this study would tend to suggest that the increased lithogenicity of the gallbladder bile may be a result of the substantial anaerobic bacterial flora present in these gallbladders after sphincteroplasty. Whether this colonization is due to stasis, despite a non-obstructed biliary tract and a normal response to exogenous cholecystokinin, cannot be determined from this study.

The canine model is not ideal for the study of biliary lipid pathophysiology since normally canine bile contains a very low concentration of cholesterol relative to bile salts and phospholipid.[6,16] Demonstration of an increase in lithogenicity of canine bile consequently is difficult, and we can only describe a trend in that direction. Nevertheless, it is 25 years since Jones and Smith first recommended cholecystectomy as an adjunctive procedure with transduodenal sphincteroplasty. Our study leads us to conclude that this is sound advice based on the resultant abnormality of gallbladder physiology rather than abnormality of motor function.

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