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• BASIC RESEARCH •

The study between the dynamics and the X-ray anatomy and regularizing effect of gallbladder on bile duct sphincter of the dog

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Abstract

AIM: To study the relationship between the radiological anatomy and the dynamics on bile duct sphincter in bile draining and regulatory effect of gallbladder.

METHODS: Sixteen healthy dogs weighing 18 kg to 25 kg were divided randomly into control group and experimental group (cholecystectomy group). Cineradiography, manometry with perfusion, to effect of endogenous cholecystokinin and change of ultrastructure were employed.

RESULTS: According to finding of the choledochography and manometry, in control group the intraluminal basal pressure of cephalic cyclic smooth muscle of choledochal sphincter cCS was 9.0±2.0 mmHg and that of middle oblique smooth muscle of choledochal sphincter (mOS) was 16.8±0.5 mmHg, the intraluminal basal pressure of cCS segment was obviously lower than that of mOS ($P<0.01$) in the interval period of bile draining, but significant difference of intraluminal basal pressure of the mOS segment was not found between the interval period of bile draining (16.8±0.5 mmHg) and the bile flowing period (15.9±0.9 mmHg) ($P>0.05$). The motility of cCS was mainly characterized by rhythmically concentric contraction, just as motility of cCS bile juice was pumped into the mOS segment in control group. And motility of mOS segment showed mainly diastolic and systolic activity of autonomically longitudinal peristalsis. There was spasmodic state in cCS and mOS segment and reaction to endogenous cholecystokinin was debased after cholecystectomy. The change of ultrastructure of cCS portion showed mainly that the myofilaments of cell line in derangement and mitochondria is swelling.

CONCLUSION: During fasting, the cCS portion has a function as similar cardiac "pump" and it is main primary power source in bile draining, and mOS segment serves mainly as secondary power in bile draining. The existence of the intact gallbladder is one of the important factors in guaranteeing the functional coordination between the cCS and mOS of bile duct sphincter. There is dysfunction in the cCS and mOS with cholecystectomy.

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INTRODUCTION

The sphincter of Oddi regulates both bile and pancreatic juice flowing into the duodenum, and one of important feature is that the time of bile draining was delayed when the sphincter of Oddi dysfunction in postcholecystectomy. Obviously, this is relative to the abnormal dynamic change of choledochal sphincter in bile draining[1-7]. But the mechanism of sphincter of Oddi dysfunction remains speculative[8-19]. Up to now there was no report the relationship between the abnormal changes of bile draining and the functional anatomy of choledochal sphincter.

At the opening site of terminal bile duct there was a bundle of cyclic smooth muscles. Afterwards Ruger Oddi reported his results that this sphincter played a "valve"-like role in bile and pancreatic juice output. This bundle of muscles encysted the ampulla of Vater at the confluence of bile duct and pancreatic duct, thus was called ampulla sphincter or sphincter of Oddi. Boyden EA and Eichhorn EP, however, had also confirmed that, situated at the cephalic side of ampulla of Vater, in bile duct and in pancreatic duct there were two bundles of sphincter respectively which were independent to each other. The independent bile duct sphincter showed its own remarkable structural features that there was cyclic smooth muscle at the cephalic side portion, it was called cephalic cyclic segment of choledochal sphincter (cCS), and there was oblique and longitudinal smooth muscle following the cCS portion, it was called middle oblique smooth muscle segment of choledochal sphincter (mOS) because it was between in the cCS and classical SO. According to the above mentioned anatomical data, it seems that up to now the anatomical structures of sphincters involved in the studies of the function of sphincter of Oddi should include cCS, mOS and SO, which are referred to as the sphincter of Oddi. Obviously it is significantly different in concept and range from the classical sphincter of Oddi suggested by Rugero Oddi earlier. Based on the analysis of the anatomical characteristics, cCS and mOS are considered as the chief constitutive part of bile duct sphincter, thus it is suggested that the physiological role of cCS and mOS in regulating the bile flow is different from that of the classical sphincter of Oddi in this semi-enclosed hydrostatic system. In order to this objective, the methods of cholangiography, pressure measurement by perfusion, and microscopic observation were employed in this research primarily to observe the radiological anatomy of cCS and mOS, before and or after cholecystectomy, the morphologic features during bile draining, and the histological changes of cCS and mOS. The functional features of Ccs, mOS and its role in bile draining were investigated to find out the regulatory factors that affected the function of cCS and mOS.

MATERIALS AND METHODS

Experimental instruments and animal model

Unicameral manometry Teflon catheter with an 0.8 mm internal diameter and 1.7 mm outer diameter (Cook Co, USA), PT-16M pressure sensor (external pressure transducer, Shanghai, China), RM-6200C polygraph recorder (Chengdu, China), WZ-50 trace perfusion apparatus (Zhejiang, China) were used to

record pressures. Sixteen healthy hybrid dogs (Weighing 18-25 kg) raised in Shaanxi were randomly classified as control group and experimental group. The cholecystectomy were undertaken under they had received intraperitoneal injection with amobarbital, then they were fed for 4-6 weeks in experimental dogs.

Manometry and cholangiography

Anaesthesia was introduced with ketamine (100 mg/h). The operation was performed through thorax-abdomen-combined incision while autonomous respirator was being used to control animals' respiration. The cystic ducts of the experimental dogs were ligated. A vertical incision was then made on the proximal choledochus in order to insert the manometry catheter. Cholangiography was performed with 30 % meglumine diatrizoate injected through the manometry catheter (based on the calibration of developing in secondary branch of intrahepatic bile duct), and the bile excretion at portion of bile duct sphincter was recorded by cineradiography at the rate of 25 width/Sec. The intraluminal pressures at the portion of cCS and mOS were measured after the completion of contrast radiography.

The catheter that had been inserted into bile duct was introduced into duodenum again and measured the pressures in duodenal lumen. The manometric catheter system (the compliance of this system was low) was infused with 0.85 % NaCl solution at a flow rate of 25 ml/h, while the velocity of recording paper was 60 mm/min. The curves of changes in intraluminal pressures in the duodenum, the mOS and cCS portion of the bile duct sphincter were recorded respectively for 5 min. The intraluminal pressure in the duodenum was calibrated as zero basal level of pressure. In addition, a Teflon catheter was inserted into the stoma opening of stomach wall, with its top being placed in duodenal lumen for next experiment.

Observational parameters

Manometric parameters The numbers of the mOS segment contraction per min were regarded as the mOS contractile frequency (mOSCF). The difference between the diastolic pressure at the mOS portion and the duodenal intraluminal pressure was considered as the mOS basal pressure (mOSBP), and the difference between the contractile wave peak and its diastolic period intraluminal pressure as the mOS contractile amplitude (mOSCA). The difference between the cCS and the duodenal intraluminal pressure was classified as the cCS basal pressure (cCSBP).

Maximal inner diameter of bile duct and contrast draining time The maximal inner diameter of bile duct during cholangiography period was referred as the maximal inner diameter of choledochus, which was corrected by the magnification of contrast duct diameter. The biliary draining time (BDT) was referred as the time between the period when contrast medium completely filled the extrahepatic bile duct and the period when it completely disappeared. And the time in which biliary flows in choledochus was between the period when the bile duct sphincter began to drain bile and the period when it stopped draining bile. The time interval between the two biliary draining times was regarded as the interval of biliary draining.

Pathological examination

The intact choledochal sphincter segment of bile duct was fixed with 2.5 % glutaral, then with 1 % osmium acid, and finally embedded with epoxy resin after dehydration with 95 % alcohol. The ultra-thin section of the sample was sliced and stained with plumbum acid citrate. Then the observation was done under JEM-2000EX electromicroscope. Two dogs were involved in both the control and experimental groups.

Statistical analysis

The *"t"* test was used to evaluate the results. A *P* value less than or equal to 0.05 was regarded as significant.

RESULTS

The diameter of bile duct

The maximal diameter of bile duct was 3.5-4.5 mm in controls, and that of experimental group was 4.7-7.5 mm, the average diameter of bile duct was 6.1±1.3 mm in experimental group in 46 days and 58 days. There was significant cantly difference between the control and the experimental group ($P<0.01$). There were no stones and obstruction in the dilatants bile duct.

The contrast results in the control group

During interval period of bile draining, the mOS was in a state of shutting up, thus the terminal end of cCS portion shaped like "pestle", while the distal end of bile duct showed a cyclic notch which was the radiological marker of the initial part of cCS. With the concentric contraction of cCS segment, the bile was pumped into the mOS segment. The mOS segment appeared to be a narrow, slender lumen. An uneven caliber could be seen in peristalsis contraction, and at the same time the bile was squeezed into the duodenum (Figure 1). 10 min after 20 ml of 33.3 % $MgSO_4$ was injected through the catheter placed in duodenum, there was no significant change in the shape of cCS segment, but while the mOS lumen was significantly dilated in 3 fold, compared with that before the injection, there was no significant contraction and peristalsis in the mOS segment.

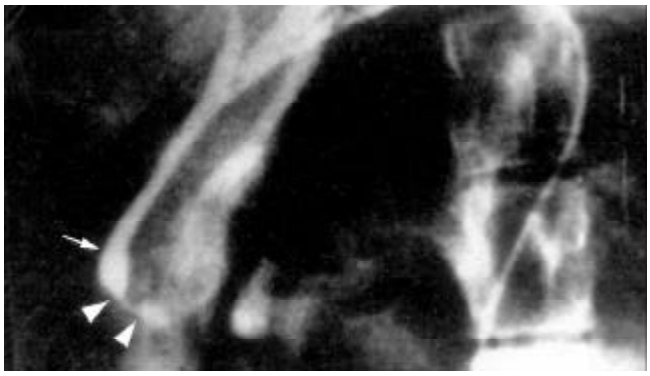

Figure 1 During bile draining in control group. It was showed that the mOS portion was in a peristaltic movement (↑→▲), and the narrow distal segment (▲→▲) was portion of the mOS and SO segment of bile duct. Between the end of choledochus and the cCS portion was demarcated by in notch (↑).

Image in the experimental group

During the bile draining period, between the distal end of bile duct, and cCS portion, there was a remarkable notch which appeared to be in a "infundibulum" shape at the cCS portion in connection with mOS segment. There was no significant contraction in the form of the spastic cCS segment and no significant peristaltic movement of the mOS segment, and lumen of the mOS segment appeared to be a narrow lumen as a "thin line", to last until the bile draining period ended (Figure 2). 10 min after the bile duct was injected with 20 ml of 33.3 % $MgSO_4$ through the intestinal tract, and significant change did not demonstrated in the diameter of cCS part and the diameter of mOS segment.

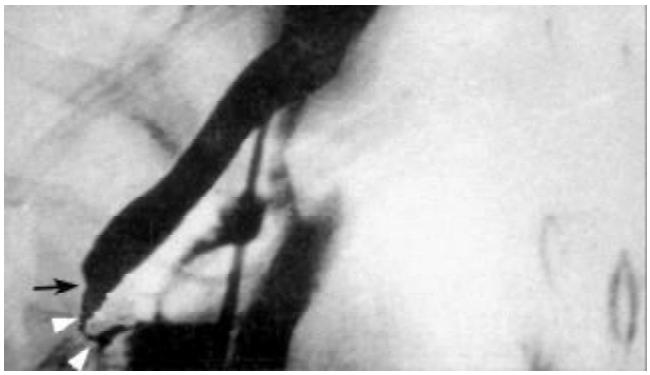

Figure 2 In experimental group of bile drainage. During bile draining the remarkable notch to keep up still in between the choledochus and the cCS portion, and it appeared to be in an "infundibulum" shape at the cCS portion and there was no significant contraction in the form of spastic cCS portion of bile duct and no significant peristelsis movement and there appeared to be a narrow lumen as a "thin line", to last until the bile draining period ended at the mOS segment. Infusion of 33.3% $MgSO_4$ after, no significant change was seen in the diameter of cCS partion (↑→▲) and mOS segment (▲→▲) of bile duct.

Manometric results

The pressure of cCS and mOS segments in the control and experimental groups (Table 1).

Table 1 The pressures of cCS and mOS segments before $MgSO_4$ infusion in interval period of bile draining (mmHg)

Group	cCSBP	mOSBP
Control (n=7)	9.0±2.0[a]	16.8±0.5[b]
Study (n=7)	14.0±2.0	14.7±0.7

[a]P<0.01, t=6.195; [b]P<0.05, t=2.717. *vs* the study group.

It is indicated that the cCSBP of control and experimental groups were lower than the mOSBP, which suggested that there was a retrograde pressure gradient between cCS and mOS segments in interval period of the bile draining. Although mOSBP in the study group was lower than that in the controls before infused $MgSO_4$, but the pressures of cCS segment in the study group were significantly higher than those in the controls (P<0.05), suggesting that the cCS and the mOS segment was in state of spastic contraction in the study group.

The pressure of mOS in the control Manometric results and reaction of mOS to 33.3 % $MgSO_4$ infusion in the control group (Table 2) and pressure curve of mOS (Figure 3,4).

Table 2 The manometric results of mOS segment before and after $MgSO_4$ infusion in the controls ($\bar{x}\pm s$)

	mOSBP (mmHg)	mOSCA (mmHg)	mOSCF (No/min)	BDT (min)
Before Infusion (n=7)	16.8±0.5	21.9±0.9	15.2±0.7	17.1±0.9
After Infusion (n=7)	15.7±0.9[a]	15.1±2.1[b]	11.4±0.3[c]	10.8±1.1[d]

[a]P<0.05, t=2.651; [b]P<0.01, t=7.344; [c]P<0.01, t=35.155; [d]P<0.01, t=33.375.*vs* before $MgSO_4$ infusion.

It is showed that the high-pressure zone of the sphincters of bile duct was mainly located at mOS segment, and the resistance and contractile frequencies of mOS were significantly reduced by endogenous cholecystokinin (CCK) while the intact gallbladder remained. (Table 2 and Figures 3,4).

In addition, it was founded, that there was no significantly different between the mOSBP in interval period of bile draining (16.8±0.07 mmHg), and the mOSBP in bile draining period (15.9±0.7 mmHg) in control group (P>0.05).

Manometric results and reaction of mOS segment to $MgSO_4$ infusion in the experimental group The pressure curves and the changes in pressures of mOS segment before and after $MgSO_4$ infusion are shown in Table 3 and Figures 5,6.

Table 3 The manometric results of mOS segment before and after $MgSO_4$ infusion in the study group ($\bar{x}\pm s$)

	mOSBP (mmHg)	mOSCA (mmHg)	mOSCF (No/min)	BDT (min)
Before Infusion (n=7)	14.7±0.7	14.2±1.3	15.9±0.7	27.0±3.4
After Infusion (n=7)	14.3±1.3	14.0±1.4	15.1±0.7	26.3±2.3

There were no significant differences in each parameter before and after infusion in the experimental group (P>0.05). This indicated that the sensitivity of mOS segment to endogenous CCK decreased after cholecystectomy, and that the diastolic and systolic movements of mOS segment were damaged, resulting in the elevation of resistance in bile draining. (Figures 5,6).

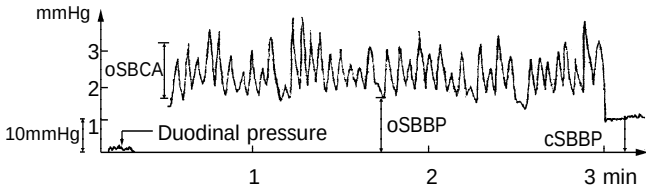

Figure 3 Pressure curves of the cCS and mOS portion and duodenum in control group. There is high pressure zone and rythmical contractile movement was appeared in the mOS portion of bile duct and pressure of the cCS portion of bile duct is lower than pressure of the mOS and the SO portion of bile duct.

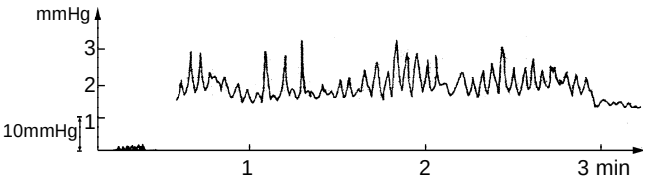

Figure 4 Reaction to the injection of 33.3 % $MgSO_4$ in control group. 10 min after 20 ml of 33.3 % $MgSO_4$ was injected through the catheter placed in duodenum, the pressure of mOS segment of bile duct is decreased, compared that before the injection, and unregular pressure curves was appeared in the mOS segment of bile duct.

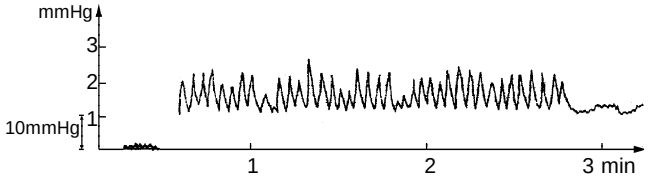

Figure 5 A pressure curves before $MgSO_4$ solution infusion in

the study group. Signs of the pressure curves is similar to the control group in the mOS segment of bile duct.

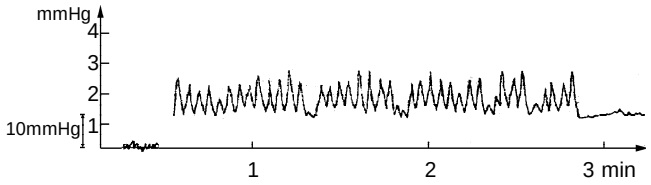

Figure 6 A pressure curves ofter $MgSO_4$ solution infusion in the study group. Signs of the pressure curves is similar to the pressure curves before $MgSO_4$ solution infusion.

Microscopic results of histopathology of the cCS portion

The results of the transection of cCS portion in the controls are showed in Figure 7.

The results of the transection of cCS portion in the study group: The light microscope results showed no the degeneration of muscular fibers of cCS, mOS portion and infiltration of inflammatory cells. Under the electromicroscope, the changes of smooth muscular cells are showed in Figure 8.

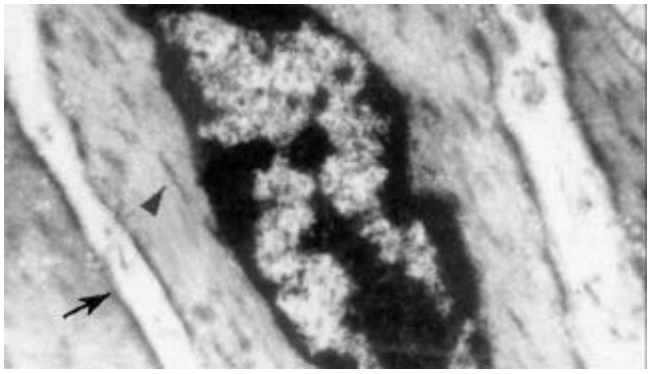

Figure 7 The figure is a transection of cCS portion of bile duct in the control group. It is showed that the smooth muscular cell membrane (↑) was flat, the myofilament and dense body appeared to be longitudinal arrangement in parallel to the long axis of smooth muscular cell and the dense body like spindles (▲). The structure of the mitochondrion was normal, which evenly distributed itself among the cytoplasm.

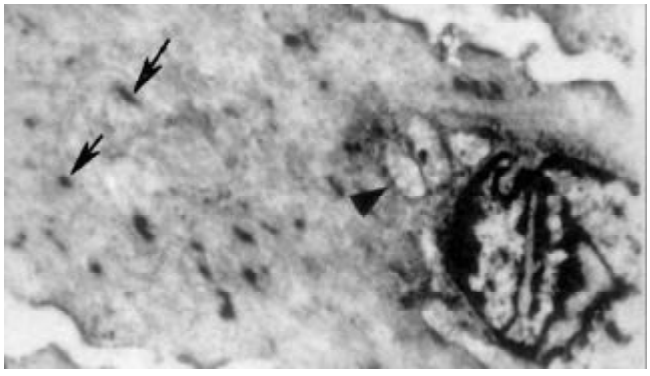

Figure 8 The figures is a transection of cCS portion of bile duct in experimental group. Under the electronmicroscope the cell membrane twisted like billows, and the myofilament density was not even, shaping like "whirl". The dense body showed derangement and various shapes (↑). The mitochondrions clustered at the end of the nucleus, and vacuolation (▲) was seen.

DISCUSSION

Evaluation of infused catheter manometry as a method of functional analysis of bile duct sphincter

The manometry with ERCP, which began in 1970s, has been widely used in functional evaluation and experimental studies of bile duct sphincter[20,21]. Based on the manifestation of manometry, Venu and Sherman suggested that the lesions of bile duct sphincter could be classified as functional and structural lesions. It is reported that the functional disturbances of bile duct sphincter are further classified in four types[22-26]: sphincter spasm, high-frequency contraction, abnormally directory contraction and abnormal response to CCK based on the results of manometry. Combined with the observations of clinically therapeutic effect, it is now generally accepted that the directory manometry with infused catheter is a golden criterion in evaluating the function of bile duct sphincter.

Dodds firstly reported the manometry of inner pressure of esophagus. He believed that the accuracy of infused manometry with catheter was negatively correlated with the compliance of catheter, but positively with the speed of infused fluid. In order to increase the accuracy of manometry, the catheter used must be characterized with less elasticity and thick wall. As far as the speed of infused fluid is concerned, Some people believed that it was suitable to have a speed of 0.25-0.6 ml/min[27-29]. The physical character of catheter and the speed of infused fluid employed in this study meet the above criteria, and manometric results obtained can objectively reflect the characteristic changes in pressures of CS segment in dogs.

The anatomical and functional study of CS

Eichhorn and Barraya confirmed in their study on the bile duct sphincter in dogs that there were successively from cephalic to distal ends of bile duct sphincter the cyclic sphincter (cCS), oblique and longitudinal sphincter (mOS) and classic SO (a strong cyclic sphincter encysting the terminal opening of bile duct). There is no anatomical definite boundary between the classic SO and mOS, but their arrangements show the remarkable differences. Because the anatomical structure and distributive position of the cCS and mOS segments are different from classical SO, there would be differences in their functions. Up to now, however, there has been no report on the functional features of the cCS and mOS segments.

The bile is a kind of important digestive fluid in the digestion of fatty substances. Dodds reported that 75 % bile secreted by liver is stored in the gallbladder, then being drained into the duodenum after alternating with the bile which already remains in the gallbladder, and the rest of it (25 %) directly flows into the duodenum through the bile duct sphincter. Eating causes the gallbladder contracting and results a large quantity of bile draining into duodenum to digest food within a short time. Only a small quantity of bile from the duct is directly drained into duodenum through the bile duct sphincter during the fasting period. Obviously, they are two different processes in bile draining. Only when the function of bile duct sphincter remains intact and coordinative, two different processes of bile draining can be successfully completed.

Nowadays there are arguments about the mechanism of bile duct sphincter in bile draining[30-37]. Toouli believed that the intramural type of choledochal sphincter, only plays a role of a "valve" in bile draining. Some people reported that the SO takes an active part in bile draining, and the power in bile draining comes from the spontaneous peristalsis contraction of bile duct sphincter. Scott, however, explained that the SO acts as a power source in bile draining while SO contracts moderately, and as a "valve" while contracting strongly. But our research results have confirmed that during fasting the lumen of mOS segment is not uniform in caliber. It can be

determined based on the study on the physiological function of smooth muscle that peristalsis-like diastolic and systolic motions are apparently not the patterns of characteristic manifestation of motions of cCS segment. Compared and analyzed with the manometric results, the peristaltic motility can only originate from the high-pressure area of bile duct sphincter, where the mOS segment of bile duct locates. It is further demonstrated by the manometric results in this study that cCS segment is a low-pressure lumen (9.0±2.0 mmHg), than that the pressure are of the mOS segment (16.8±0.5 mmHg), during the interval period of bile draining, and there is apparently a retrograde pressure gradient between cCS portion and mOS segment. It is apparent that the existing of high-pressure area in mOS segment is beneficial for preventing from the reflux of duodenal fluid, and even at the bile draining period the pressure in mOS segment does not decrease significantly, obviously, it is that the retrograde pressure gradient between the cCS segment and the mOS segment form the resistance in bile draining. But it is showed by cholangiography that cCS segment reveals concentric contraction in bile draining in the controls when fasting period, and its lumenal volume reduces, resulting in the bile being "pressed" into mOS segment. With the peristaltic contraction of mOS segment, the bile filled in mOS segment ejects like "squeezed milk" into the duodenum. Obviously in order to overcome the resistance in bile draining cCS segmen should play a role of similar cardiac "pump" in the process of changing the retrograde pressure gradient, that prevented reflux of duodenal juice, into a positive pressure gradient during bile draining. It is just because of the different roles of cCS and mOS segments play in bile draining, that the bile duct sphincter takes not only a part in inhibiting the reflux of duodenal fluid as a "valve", but also a part in regulating the stability of pressure in bile duct.

Effect of gallbladder to the movement of cCS and mOS segments

It is suggested that the functional coordination of cCS portion and mOS segment is closely related to whether the gallbladder is intact or not. It is showed by cholangiography that cCS segment has apparently dilative and contractile functions, while the peristaltic motion exists in the mOS segment that appears to be in a functional high pressure zone during the process of bile draining in the controls. But in the experimental group, cCS and mOS segments are constantly, and the notch remains still at the inferior extremity of bile duct and the lumen of mOS segment appears narrow like a "line". After infusion with $MgSO_4$, the notch at the inferior extremity of bile duct doesn' t disappear, and the "line"-shaped narrow lumen of the mOS segment shows neither significant dilation nor apparent peristaltic motion, and it showed that the cCS and the mOS segment are in the state of spasm. Grace has also confirmed that there was a decline of the sensitivity of the bile duct sphincter to the endogenous CCK after cholecystectomy. Tokunaga and his men has discovered that, with a concentration of 1 $\mu mol \cdot L^{-1}$, 0.11±0.03 gm of CCK-8 is needed to relax the cyclic muscle stripe of bile duct sphincter, but with the same concentration, only 0.02±0.01 gm of CCK-8 can relax the mOS segment. It seems to suggest from the above results that mOS segment is very sensitive to CCK-8 than that of the cCS, and its functional regulation is closely related to the content of endogenous cholecystokinin. In this study the results obtained from the choledochography confirm that Tokunaga Y' s viewpoint is right. Our results indicate that the functional regulation between the cCS and mOS segment is manifested in intact gallbladder. Further, our results showed that there is a significant change in spatial structure of smooth muscle cells of bile duct sphincter: the morphological manifestation of which is that the cell membrane is like billows, and myofilaments line in derangement and twist like "whirlpool". The form and size of the attachment points of corresponding myofilaments-dense bodies, are different and lose their behaviors of normal fusiform arrangement in parallel to the long axis of cells. There have been no reports about its pathological significance. If the changes are considered, this change in spatial structure of cytoskeleton may be related to the strong contraction and dragging of the myofilaments. The spastic state of cCS segment and the reduced range of concentric contraction, furthermore, will unavoidably result in decreasing in its bile draining volume. Although the basal pressure in mOS segment during bile draining somewhat decreases, the resistance produced by mOS segment in bile draining cannot be completely overcome by the motility obtained from contraction of cCS segment in bile draining, this may mostly be the important cause that the bile cannot drain smoothly from the bile duct and the time for emptying the contrast medium is elongated in the experimental group. The direct result is that the bile flow slows down and the relative stasis exists, and the bile duct is dilated.

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